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ABSTRACTS

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Oral Free Paper Sessions

OFP-01 | Oral Free Paper Session Digestive Diseases Pathology - GI

OFP-01-001
Gastric polyps in familial adenomatous polyposis (FAP) Portuguese patients - the first Western cohort with Asian features
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Background & objectives: Chronic atrophic gastritis may contribute to the phenotype of gastric polyps in familial adenomatous polyposis (FAP). As the prevalence of Helicobacter-pylori infection in Portugal is up to 90%, we aim to characterize gastric polyps in a series of Portuguese patients.
Methods: Fifty-six FAP patients followed up at our hospital in High-Risk Consultation of Digestive Tumours, from 1992 to 2021 were retrospectively selected. Thirty-two patients were males (57.1%), and the medium age was 52 (range: 26-87). Clinicopathological features, with particular emphasis on periodic upper endoscopic examinations, were studied. IBM SPSS (Release 27.0) was used for statistical analysis.
Results: Our series encompassed 95 gastric polyps, including 53 (55.8%) fundic gland polyps (FGPs) without dysplasia (n=34) or with dysplasia (n=19) and 42 (44.2%) intestinal-type adenomas. Half of FAP patients (n=28, 50.0%) developed endoscopically visible gastric polyps, including FGPs in 12 patients (21.4%) and adenomas with or without FGPs in 16 patients (28.6%). Foveolar-type adenomas and pyloric gland adenomas were not identified in this series. Intestinal-type adenomas occurred predominantly in the distal stomach (62.5%, p=0.031), were larger than 7mm in 9/16 cases (56.3%, p=0.03), and were more frequently associated with duodenal adenomas (87.5%, p<0.001). Chronic atrophic gastritis and intestinal metaplasia was observed in the background mucosa in most cases (75.0%, p=0.009).
Conclusion: To our knowledge, this is the first Western series showing high prevalence of intestinal-type adenomas in FAP patients, comparable to Asian studies. Chronic atrophic gastritis/intestinal metaplasia are likely responsible for this difference, with risk of neoplastic transformation and management implications. Endoscopists should have a high degree of suspicion in FAP patients and low threshold to biopsy/excision of gastric polyps, particularly in patients with chronic atrophic gastritis/intestinal metaplasia, in those with distal gastric polyps with worrisome features (namely >7mm) and/or duodenal adenomas.

OFP-01-002
Road-mapping for gastric intestinal metaplasia
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Background & objectives: Uneven distribution of gastric intestinal metaplasia (GIM) may require mapping biopsies rather than random biopsies which may fail to reflect the extent of the lesions. We, hereby, evaluated the value of mapping in determining the extent and severity of IM.
Methods: Random biopsies (RB) obtained according to updated Sydney protocol and mapping biopsies (MB) taken from 6 different sites of corpus and antrum during surveillance were evaluated for the severity and extent of histologic parameters of gastritis, mainly focusing on GIM with atrophy in a cohort of 202 patients. Statistical analysis was performed using Wilcoxon test on SPSS version 22.
Results: Mean age of 202 patients (104 females, 86 males) was 61.78±11,5 years. Average time interval between RB and MB was 18 months. There were 98 cases with isolated antral IM and 75 cases with isolated corpus IM in RB while MB revealed IM in the corpus in 13 of 98 cases (13.26%) and antral IM in 23 of 75 (30.66%) cases. IM at both sites was observed in 17 (8.9%) RB and 31 (16.4%) MB which yielded a significant increase by an increment of 1.84 (p<0.05). Severity of antral IM significantly increased in MB in 28% of cases (p<0.05) while no such difference was found for corpus IM.
Conclusion: The results of the present study suggest that mapping with multiple biopsies improves the detection rate of IM both in the corpus and antrum, providing information for the extent and severity of the lesions. This approach also seems to be useful in cases with isolated antral IM in monitoring severity of IM as already demonstrated by MB taken from the antrum in our study. However, large prospective, randomized, multicentre studies comparing different follow-up strategies are necessary for a better roadmap.

OFP-01-003
Myths and facts: reflux oesophagitis vs eosinophilic oesophagitis
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Background & objectives: Basal cell hyperplasia and papillomatosis are non- discriminatory for eosinophilic oesophagitis (EoO) or reflux oesophagitis (RO). The aim here is to clarify the true incidence of these features in RO and EoO using morphometry to highlight their diagnostic significance.

Methods: A total of 543 RO and 59 EoO cases were re-evaluated for basal cell hyperplasia and papillomatosis using an ocular grid and basal cell thickness (BCT) and papillary height (PH) were measured on H&E stained sections of biopsies with the most severe histology. Data were evaluated using one sample t test on SPSS version 22. A $p<0.05$ was considered significant.
Results: EoO group (41 females, 17 males) had a significantly younger mean age of 15.25±13.9 ($p<0.001$) compared to RO (297 females, 246 males) with a mean age of 37.65±23.6. Papillomatosis was significantly more common in RO (85%) compared to EoO (55%) which showed basal cell hyperplasia (12.7% vs 100%) significantly more frequently. Morphometrically, BCT was 284 (25-250) and 153 (25-250) microns, PH was 209.75 (25-975) and 118.75 (0-325) in RO and EoO, respectively. The ratio of PH/epithelial thickness was significantly ($p<0.05$) higher (57%) in RO than EoO (39%). Although BCT was higher in RO the ratio was lower compared to EoO due to epithelial thickness which was much higher in RO.
Conclusion: Morphometric analysis allowed more accurate interpretation of papillomatosis and basal cell hyperplasia measured as BCT and PH with respect to epithelial thickness. Indeed, proportioning yielded better results in distinguishing RO from EoO. The results also showed that basal cell hyperplasia proved to be a constant feature of EoO besides eosinophilia. Papillomatosis on the other hand is less discriminatory as it can be present in both conditions, though more common in RO.

OFP-01-004
Clinical relevance of tumour response patterns in rectal cancer
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Background & objectives: Tumour regression grading (TRG) and tumour downstaging are standard methods for examination of pathological response after neoadjuvant chemoradiotherapy (CRT). However, different response patterns can be observed. We investigate these response patterns and their clinical relevance in rectal cancer.
Methods: The study included a test and a validation cohort consisting of post-CRT rectal cancer patients with adenocarcinoma n.o.s and response to the therapy. TRG was established according to both CAP and Dworak. Response patterns were scored based on the three-step flowchart by two independent observers and correlated with pathological features and outcome.
Results: The test and validation cohorts included 236 and 103 patients respectively. In both cohorts, the predominant response pattern was fragmentation (74% vs 66%) and the interobserver agreement was excellent ($k=0.85$). The fragmented pattern presented with a significantly higher pathological stage (TNM III/IV: 31% vs 20%; $p<0.001$), less tumour regression ($p=0.001$), a tendency towards less downstaging (downstaging: 45% vs 65%; $p=0.06$). The shrinkage pattern presented better overall survival (OS) ($p=0.049$) in the test cohort and longer recurrence-free survival (RFS) (HR 2.85, 95% CI 1.09-7.49, $p=0.033$) in the validation cohort. In the regression analysis of combined cohorts, pathological stage and Dworak TRG were independent prognostic factors of survival.
Conclusion: The heterogeneous nature of tumour response following CRT is reflected in different response patterns, which can be scored reproducibly. Fragmentation and shrinkage are the main response patterns in rectal cancer with a predominancy of the fragmented pattern. This pattern is associated with deeper invasion and positive lymph nodes. While not independently associated with outcome, knowledge of response pattern can guide future treatment decisions, in particular concerning local treatment.

OFP-01-005
Consultation rate and pathologist diagnostic rate in 6,020 oesophageal biopsy specimens
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Background & objectives: Institution level data analyses can supplement case reviews for quality assessment. The objective of this project was to characterize the pathology in all institutional oesophageal biopsies and assess consultation rate and variation of the pathologist diagnostic rate (PDR).
Methods: All in house oesophageal biopsy specimens (EBS) accession 2011-2020 were extracted, diagnostically categorized with a hierarchical string-matching algorithm (HSMA) and tabulated by pathologist with documented (informal and/or formal) consultations. HSMA categorizations were audited by reviewing 200 EBS reports. PDR was compared using funnel plots with 95%($p<0.05$) and 99.9%($p<0.001$) confidence intervals (CI) centred on the group median diagnostic rate.
Results: The cohort contained 6,020 EBS and the HSMA was 99% (198/200) accurate. These were 524(8.7%) malignant/tumour, 34(0.6%) suspicious (SUSP), 72(1.2%) high-grade dysplasia (HGD), 78(1.3%) low-grade dysplasia (LGD), 65(1.1%) indefinite for dysplasia (IFD). The malignant/tumour were 339(5.6%) adenocarcinoma (ADN), 162(2.7%) squamous carcinoma(SCC), and 23(0.4%) other tumour(OTH). The consultation rates were 22.7%, 15.4%, 34.8%, 61.8%, 56.9%, 25.6%, 24.6% for ADN/SCC/OTH/SUSP/HGD/LGD/IFD respectively, and 5.6% (339/6,020) for all EBS. Thirteen pathologists interpreted >150 EBS each (158-626) and together saw 5,243. The number of 95%/99.9% CI outliers were 3/1, 2/0, 1/0, 4/2, 4/4, 1/0, 5/4 for ADN/SCC/OTH/SUSP/HGD/LGD/IFD respectively. Intestinal metaplasia (IM) (818), eosinophilic esophagitis (EE)(293) and gastroesophageal reflux (GERD) (897) had 9/4, 3/1 and 12/7 outliers respectively.
Conclusion: The funnel plots demonstrated moderate to poor PDR similarity on malignant, pre-malignant and benign diagnoses. Reviews are most frequent at the benign-malignant interface. The relative rarity, and PDR variation support the recommendation for reviewing all HGD. Concordance for benign diagnoses (with the exception of EE) likely can be improved significantly. Observational data can be useful for quality assessment and for helping guide quality improvement efforts.

OFP-01-006
Endoscopic biopsies in the diagnosis of colorectal carcinoma – is it quantity or quality?
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Background & objectives: Endoscopic biopsy is required not only for definitive diagnosis of colorectal carcinoma (CRC), but also for additional molecular tests. Our aim was to evaluate the relationship between the number of biopsies taken and diagnostic accuracy in our hospital.
Methods: A search was performed on the departmental database for colonic biopsies obtained for suspected CRC between March and October 2021. Data was then retrieved from both endoscopy and pathology reports.
Results: In total 135 cases were identified and 68% of them had ≥6 biopsies taken. Initial biopsies were reported as invasive malignancy in 101(74.8%) and the remaining 34(29.4%) reported as

suspicious of malignancy (19), dysplasia (12) and normal/other(3). Of the 101 cases with confirmed CRC, 73.7% had ≥6 biopsies and 26.3% had <6 biopsies. Of the 34 cases without a definite diagnosis, 55.9% had ≥6 biopsies. Repeat procedure was required for diagnostic purposes in 10 cases, 4 of which already had ≥6 initial biopsies taken. For molecular testing, estimated tumour content was provided in 57% of confirmed cases. Cases with <6 or ≥6 biopsies had comparable tumour content of 37% and 38% respectively.
Conclusion: In the majority of cases, the number of biopsies taken for suspected CRC at our hospital is in line with ESGE recommendations. Our findings suggest that the quality of targeted biopsies is also relevant, as a definite diagnosis was achieved in more than quarter of cases with less than 6 initial biopsies. Furthermore, more than half of initial unconfirmed cases met the recommended number of 6. In addition, the number of biopsies taken does not appear to affect tumour content.

OFP-01-008

Epithelial-mesenchymal transition and α-SMA expression in the tumour microenvironment: role in tumour stroma composition and association with prognosis in colorectal cancer

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Background & objectives: The epithelial-mesenchymal transition is characterized by increased expression of mesenchymal markers and
plays an essential role in promoting tumour invasion and metastasis. We analysed the association between overall survival and α-SMA expression in colorectal cancer (CRC).
Methods: The TSR in colorectal adenocarcinoma was categorized into 2 groups: ≤50%- low stroma and >50%- high stroma. The immunohistochemical expression of α-SMA was observed in cancer cells (CCs) and cancer-associated fibroblasts (CAFs) present in different tumour areas: estimative stromal (ES), invasion front and desmoplastic stroma. α-SMa immunostaining >10% was defined as positive. The association between α-SMA expression and overall survival was evaluated.
Results: A total of 158 cases were analysed, with 54% of the tumours presenting stroma high. Positive immunostaining of α-SMA was detected, in CCs and CAFs, in 80.3% of cases. Stroma-high tumours showed increased expression of α-SMA. Cancer cells with expression of α-SMA were observed in 59.6% of cases. CAFs expressing α-SMA were found in 87.2% of the cases, higher positivity was observed predominantly in the ES and invasion front areas: 88.9% and 86.7% of cases, respectively. The positive immunostaining observed in CCs and CAFs present in the area of stromal estimation showed correspondence with death outcome. The high expression of α-SMA, in CAFs present in the invasion front and in the desmoplastic stroma, was associated with lower overall survival.
Conclusion: The α-SMA is a mesenchymal biomarker related to the epithelial-mesenchymal transition and is highly expressed in different tumour areas of the CRC, which are associated with a worse prognosis. Cancer cells and CAFs show high expression of α-SMA. The immunoexpression of this biomarker showed correspondence with the death outcome. In CRC, high expression of α-SMA in CAFs is associated with shorter overall survival.

OFP-01-009

Digital spatial profiling and proteomics identifies differences in biological phenotypes of tumour deposits and lymph node metastases in colorectal cancer

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Background & objectives: Both lymph node metastases (LNM) and tumour deposits (TD) are currently included in nodal staging of colorectal cancer (CRC). However, knowledge regarding the biological background of these biomarkers is lacking, which is essential in understanding their role in CRC spread.
Methods: Spatial profiling was performed on TD and LNM from 10 CRC patients using 1,800 RNA targets, and segmentation for tumour and tumour microenvironment (TME). From 10 other CRC patients, one TD and LNM were included for filter aided shotgun proteomics, identifying 5,578 differentially expressed proteins. Differences in RNA and protein expression were visualized using heatmaps, volcano plots, and enrichment analyses.
Results: Digital spatial profiling showed distinct transcriptome profiles between TD and LNM. The most significant results were found for the TME where TD showed a more tumour supportive environment (e.g., overexpression of SFRP2, COMP, THBS1, COL11A1, FN1) compared to LNM. Enrichment analyses showed enrichment of focal adhesion, proteoglycans in cancer, and ECM-receptor interaction in the TD ($p<0.05$), using the KEGG pathways, and the hallmark of epithelial mesenchymal transition ($p<0.05$), using the Molecular Signatures Databases (MSigDB). The proteomics analyses of 10 other CRC patients validated the transcriptome results from the digital spatial profiling, with largely overlapping expression profiles as well as similar enriched pathways.
Conclusion: This study shows that TD have a distinct and more invasive phenotype compared to LNM on both the RNA and protein level. The most pronounced differences were found in the TME, which was more pro-tumorigenic in TD. Furthermore, the hallmark of epithelial mesenchymal transition was enriched in TD compared to LNM. These results show that TD are biologically distinct from LNM and give insight into the heterogeneity of different modes of locoregional spread in CRC.

OFP-01-010

Extraappendiceal goblet cell carcinoid like amphicrine tumours of GI tract: a long known, not routinely used entity, associated with aggressive behaviour

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Background & objectives: Amphicrine tumours are a rare group of tumours in which single tumour cells coexist both epithelial and neuroendocrine differentiation. This entity is included in the 5th WHO classification of appendiceal tumours, but it is not included in other organ classifications.
Methods: Total of 24 gastrointestinal (GI) carcinomas showing amphicrine features reported between January,2016 and February,2022 were retrieved from pathology files. Cases that didn't express at least two neuroendocrine markers and whose appendix weren't examined for the primary tumour presence (histopathologically or radiologically) were excluded from the study. Twenty non-amphicrine GI-carcinomas reported at the same time interval were randomly selected to compare tumour stages.
Results: Of the 24 patients 13 were female and 11 were male; mean age was 59 (22 to 72 years). Tumour localizations were

as follows: 8 gastric-antrum, 2 gastric-cardia, 2 ampullary-duodenum, 10 ascending colon, 2 transvers colon. On microscopic examination of tumours the most prominent feature that attracted our attention was that majority of the cases (20 out of 24) formed at least focal crypt-like structures formed by signet ring-like cells in either myxoid(mostly) or desmoplastic stroma. Remaining 4 cases showed conventional intestinal carcinoma morphology with amphicrine immunophenotype. Another significant finding was the presence of multiple lymph node metastases and advanced stage disease in all of the cases, except for four cases.
Conclusion: Despite the fact that this entity is not included in the current WHO classification of GI organs other than appendix, they usually present in advanced stages and exhibit aggressive behaviour. In most, if not all, amphicrine tumours have characteristic morphologic clues (crypt-like structures formed by signet-ring-like cells) and clinical features(83% of the lower-GI cases on ascending colon). These clues can be defined clearly, and the terminology should be used in daily practice in order to assure an adequate therapy in a timely manner.

OFP-01-011
Mismatch repair protein and microsatellite instability status in gastric cancer: a comparative study between endoscopic biopsies and surgical specimens
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Background & objectives: Evaluation of mismatch repair protein (MMR) and microsatellite instability (MSI) status is of utmost importance for the management of gastric cancer (GC) patients. Aim: to assess if MMR/MSI-status in surgical specimens (SSs) may be predicted accurately in endoscopic biopsies (EBs).
Methods: One-hundred GC cases with EBs and respective SSs were selected retrospectively from two institutions between 2004 and 2015. Both EBs and SSs were evaluated for MMR-status by immunohistochemistry (IHC) and classified as MMR-proficient (MMRp) or deficient (MMRd). Cases were also classified for MSI-status by Idylla™ and Bethesda panel (five mononucleotide markers) as microsatellite stable (MSS) or unstable (MSI-high).
Results: Sixty-three patients were submitted to surgery alone, while 37 patients underwent neoadjuvant chemotherapy. In SSs, 64/100 cases (64%) were MMRp and 36/100 (36%) were MMRd by IHC; 72/100 (72%) were MSS and 28/100 (28%) were MSI-high by Idylla™. In SSs, no cases classified as MMRp were MSI-high, but 21/100 cases (21%) were reported as MMRd by IHC and MSS by Idylla™. MSI-status, evaluated by Idylla™, was concordant to the gold-standard Bethesda panel in 64/65 SSs (98.5%). When comparing EBs and SSs, only 5/100 cases (5%) were discordant by IHC (k=0.889%, sensitivity=88.9%, specificity=98.4%), while 14/100 cases (14%) were discordant by Idylla™ (k=0.620, sensitivity=60.1%, specificity=95.8%).
Conclusion: High concordance rate was found when comparing EBs and SSs for MMR-status by IHC, suggesting that we can rely on the immunohistochemical evaluation of EBs when assessing GC cases before surgery/neoadjuvant chemotherapy. The few discordant cases (n=5) may be explained by insufficient tumour sampling to account for GC heterogeneity (4/5 had ≤2 EBs), and/or neoadjuvant chemotherapy (used in 3/5 patients). Although Idylla™ reliably evaluated MSI-status in SSs, as compared to gold-standard, it doesn't seem to accurately identify MSI-status in EBs.
Funding: Bolsas de Investigação Luz Saúde, Portugal

OFP-01-012
Which is which? Autoimmune (*H. pylori*) gastritis
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Background & objectives: Pyloric metaplasia(PM) and neuroendocrine-cell hyperplasia(NCH) are common features of autoimmune gastritis(AIG), but are also seen in HP-gastritis leading to diagnostic difficulty. Co-ocurrence of two complicates their distinction. We aimed to evaluate features useful in the differential diagnosis when overlaps occur.
Methods: Total of 123 cases of gastritis comprising 77 AIG cases(group1) with normal/reactive antrum, 30 cases of HP-gastritis with concurrent atrophy and metaplasia in the corpus and antrum(group 2), and 16 cases with AIG-like changes in the corpus, and atrophy and/or IM in the antrum(group 3) were reevaluated for updated Sydney parameters, PM and NCH. Chi-square test was used for statistics.
Results: Though all cases in group1 and 3 had inflamed corpus, severe chronic inflammation was significantly (p=0.03) higher in group 1(71.4%) compared to group3(37%) while activity of group3(43.7%) was significantly higher (p<0.001) than group1(25,8%). Atrophy was significantly (p=0.026) higher in group2(86.6%) than group3 (50%) similar to IM (100% and 93,75 in groups 2 and 3, %, respectively). NCH was present in 80,5% of all cases and was significantly more common (p<0.001) in group3(100%) than group2(23.3%). PM, on the other hand, was seen in %77 of all cases and its frequency was significantly higher(p=0.002) in group1 (%85.7) compared to groups 2 and 3 (56.6%, 75%, respectively).
Conclusion: Inflammation, both active and chronic, not differing between HP-gastritis with(group3) or without(group2) features of AIG, suggest that overlaps do indeed exist. As expected, IM and atrophy were more severe in HP-gastritis compared to HP-gastritis with features of AIG in contrast to NCH and PM which were more predominantly observed in AIG or HP-gastritis with such features. These, taken together, support the idea of incorporating PM and/or NCH into the Sydney system of gastritis for accurate diagnosis, treatment of overlapping cases.

OFP-01-013
Systemic neutrophil-to-lymphocyte ratio in colorectal cancer: differences in systemic cytokine profile and immune effector cell populations
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Background & objectives: A raised pre-operative neutrophil-to-lymphocyte ratio (NLR) is correlated with poorer outcomes in colorectal cancer (CRC). We assessed the plasma cytokine profiles and immune effector cell populations of NLR<5 and NLR>5 groups in operable CRC to establish a mechanism for this.
Methods: Patients undergoing elective bowel resection for CRC were prospectively recruited. Preoperative plasma from 47 patients underwent cytokine analysis by multiplex fluid-phase immunoassay. A second group of 33 patients was recruited for flow

cytometric evaluation of full blood count for immune cell population assessment.
Results: The NLR>/=5 group showed significant depression of some T -cell subgroups, activated natural killer cells and eosinophils and significant elevation of memory B cells and neutrophils. Significant depression of the cytokines IL-2, IL-1β, IL-7, IL-13, basic FGF, IFN-γ and MIP-1α occurred in the NLR>/=5 group
Conclusion: The down regulation of IFN-γ, IL-2 and IL7, involved in immunoregulation in the NLR>5 group suggests the failure of a coherent, T-cell driven, Th1-polarised response to cancer. The pan-T cell lymphocytopaenia seen in the NLR>5 group demonstrates an inappropriate T-cell driven immune response to tumour. The increased neutrophilia seen in the NLR≥5 group may relate to tumour microenvironmental factors that make them pro-tumourigenic.
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OFP-01-014
An innovative artificial intelligence based application for the differentiation of invasive adenocarcinoma from pseudoinvasion in colorectal polyps
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Background & objectives: Dysplastic glands misplaced in the submucosa (pseudoinvasion) of colorectal polyps sometimes cannot be differentiated from invasive adenocarcinoma, even by expert pathologists. We are developing an innovative application to differentiate invasive adenocarcinoma from pseudoinvasion on whole-slide images (WSI).
Methods: Under low power (x2) magnification, we trained the algorithm to identify areas of interest (dysplastic glands) on WSI. Using our images and NCT-CRC-HE-100K datasets, we developed a combined non-patch and patch-based algorithm to identify 12 morphological categories in differentiating pseudoinvasion from invasive adenocarcinoma (true invasion). We used two models to aggregate the per-patch/area classification results into a final classification.
Results: Slides from 130 colon polyps (70 pseudoinvasion and 60 true invasion) were digitized. Low power detection successfully identified all areas of interest. The convolutional neural network (CNN) model achieved an overall accuracy of 98% in recognizing and classifying each area/patch into categories. Based on the 9 categories currently completed, the linear model and the 3-layer CNN model show accuracy rates of 83% and 88% respectively in the final classification (true versus pseudoinvasion).
Conclusion: Our AI based application mimics how pathologists work and has achieved reliable results with 9 of 12 categories used. We are confident that with the other 3 categories added into the algorithm, reliability will be increased. The algorithm will be validated using another 60 cases and diagnostic accuracy will be compared with expert GI pathologists blinded to the results. The application will be available on our website for pathologists to access worldwide (http://ai4path.ca/).
Funding: Ontario Molecular Pathology Research Network CPTRG Pathology Image Analysis Fund

OFP-01-015
MMR-deficient crypts detection by immunohistochemistry in normal colonic mucosa of patients with MMR deficient (dMMR)/MicroSatellite Instable (MSI) colorectal cancer: a helpful tool for the diagnosis of Lynch syndrome
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Background & objectives: The diagnosis of Lynch syndrome (LS) is challenging. We investigated whether the detection of MMR-deficient non-neoplastic intestinal crypts could be helpful in patients with inconclusive germline mutation studies of MMR genes (Lynch-like syndrome; LLS) or variants of uncertain significance (VUS).
Methods: We evaluated the expression of MMR proteins in non-neoplastic mucosa of colorectal cancers from patients with LS (n=15), including 7 with multiple CRCs (mRCCs), LLS (n=7) and VUS (n=7). Ten immunohistochemistry (IHC) slides were performed on 1 or 2 blocks of both adjacent (adj-muc) and distant (dist-muc) mucosa. A crypt ratio (number of dMMR crypts/total number of crypts) was determined.
Results: dMMR crypts were identified in 12/15 patients with LS (80%). dMMR crypts tended to be more frequently observed in dist-muc [11/15 (73%) vs 8/14 (57%), p=0.157], and in mRCC [7/7 (100%) vs 5/8 (63%), p=0.244]. The ratio of dMMR crypts was significantly higher in patients with mCRC [mCRC-ratio = 0.00337 vs non-mCRC-ratio = 0.0005 (p=0.003)]. A minimum number of n=8 IHC slides analysed in adj-muc and n=6 slides in dist-muc identified all patients with dMMR crypts and 66.7% and 91.7% respectively of all patients with LS. dMMR crypts were identified in 1/7 patients with LLS (14%) and in 4/7 patients with VUS (57%).
Conclusion: The detection of dMMR crypts, with a minimum number of 6 IHC slides in dist-muc, could be an integral part of the decision-making algorithm for the diagnosis of LS in patients with LLS or VUS.

OFP-01-016
Tumour budding is an independent prognostic factor in stage III colon cancer patients: a post-hoc analysis of the IDEA-France phase III trial (PRODIGE-GERCOR)
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Background & objectives: Tumour budding (Bd) is an emerging prognostic biomarker in colon cancer (CC). We explored further the significance of Bd for risk stratification by evaluating survival of stage III CC patients included in the IDEA-France phase III trial.
Methods: Bd was assessed on scanned HE-stained slides and scored by central review by the Bd criteria of the 2016 International Tumour Budding Consensus Conference (ITBCC2016) and classified as Bd1 (0-4 buds/0.785 mm2), Bd2 (5-9 buds), and Bd3 (≥10 buds) categories. Disease-free survival (DFS) and overall survival (OS) were analysed by log-rank test. Clinicopathologic features and Immunoscore® were correlated with Bd.
Results: Samples of 1048 CC patients were analysed. Overall, Bd1, Bd2, and Bd3 were observed in 39%, 28%, and 33% of CC, respectively. Bd2 and Bd3 were associated with vascular (P = .002) and

perineural invasions (P =.0009). The 3-year DFS and the 5-year OS rates for Bd (1 versus 2-3) was of 79.4% versus 67.2% (P=.001) and 89.2% versus 80.8% (P=.001), respectively. This was confirmed after adjustment for relevant clinicopathological features for DFS (HR, 1.41; 95% CI, 1.12 to 1.77; P =.003) and OS (HR, 1.65; 95% CI 1.22 to 2.22; P = .001). When combined with pTN stage and Immunoscore subgroups, Bd significantly improved disease prognostication.
Conclusion: Bd demonstrated its independent prognostic value for DFS and OS. Given these findings, Bd per the ITBCC 2016 should be mandatory in every pathology report in stage III CC patients. Bd and Immunoscore could play a complementary role in personalized healthcare in this setting.
Funding: We thank the GERCOR team, the PRODIGE investigators and the National Cancer Institute (INCa) for funding the trial.

OFP-02 | Joint Oral Free Paper Session Gynaecological Pathology / Cytopathology

OFP-02-001
Consensus based recommendations for the diagnosis of Serous Tubal Intraepithelial Carcinoma; an international Delphi study

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Background & objectives: Diagnosis of Serous Tubal Intraepithelial Carcinoma (STIC), a precursor lesion to high-grade serous carcinoma, has moderate reproducibility. We aim to inventory criteria for STIC diagnosis among gynaecopathologists and formulate consensus based recommendations.
Methods: We invited 70 gynaecopathologists to a 3 round Delphi study. The first round consisted of open ended questions concerning their diagnostic process. The answers of round 1 were used to formulate 64 statements. In the subsequent rounds, participants were asked to rate their level of agreement with these statements, using a 9-point Likert-scale, ranging from fully disagree to fully agree.
Results: Gynaecopathologists participating in this study (n=34, 49%) scored 64 statements, subdivided in topics: tissue handling, morphological criteria, immunohistochemical staining and reporting recommendations. Consensus was reached for 27/64 (42%) statements, such as: each fallopian tube has to have the fimbriated end fully embedded; nuclear pleomorphism, nuclear enlargement, high nuclear to cytoplasmatic ratio and nuclear hyperchromasia are morphological criteria that need to be present for diagnosing STIC; P53 and Ki67 staining only have to be performed in case a STIC is considered based on morphology; WT1, CyclinE, STMN1 and p16 have no added value in diagnosing STIC.
Conclusion: We describe current practices concerning STIC diagnostics among 34 gynaecopathologists and present a list of 27 recommendations based on consensus vote. Consistent and reproducible STIC diagnostics is important, as it holds prognostic value for individual patients. Moreover, it is a prerequisite to safely offer alternative risk reducing surgical interventions to women who are at an increased risk of ovarian carcinoma within the protection of a clinical trial. The recommendations from this study contribute to further standardization of the diagnostic process.
Funding: Funded by the Dutch Cancer Society (KWF Kankerbestrijding)

OFP-02-002
Endocervical endometrioid adenocarcinoma: clinicopathologic characterisation of a rare human papillomavirus-independent tumour type

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Background & objectives: Endocervical endometrioid adenocarcinoma (EEA) is a rare human papillomavirus (HPV)-independent tumour type included in the 2020 World Health Organization Classification of cervical adenocarcinoma. Due to its apparent rarity, this entity has been poorly characterised in the literature to date.
Methods: EEAs that fulfilled the following strict criteria were collected from multiple institutions: presence of confirmatory endometrioid features; surgically treated; exclusion of endometrial or ovarian origin; negative high risk HPV by in situ hybridization or polymerase chain reaction. Demographic, pathologic and follow up information, if available, was recorded for each case.
Results: There were 14 patients with a median age of 56 years (range 30-74 years). Endometriosis and areas of mesonephric(-like) differentiation were seen each in 2 cases (one tumour had both). 4/14 tumours demonstrated evident squamous differentiation/metaplasia. The median tumour size was 3.6 cm (4 tumours 2-3.9 cm and 6 tumours ≥ 4 cm, range 0.8 to 8.6 cm). All were at least stage IB1 (FIGO 2018). Initial nodal involvement was seen in 2/13 patients and recurrence (14 months, liver; 60 months, paraaortic nodes) in 2/11 patients (follow up median 46 months, range 2-192 months). Oestrogen receptor expression was at least focal in 13/14 tumours while all showed non-diffuse p16 expression.
Conclusion: This endeavour represents the largest reported series of EEA. Diligent sampling, comprehensive microscopic examination and ancillary studies for detection of HPV are essential to establish the correct diagnosis. Additional studies are needed to determine the molecular pathogenesis and optimal management for these neoplasms and to compare their clinicopathologic behaviour with other endocervical adenocarcinoma types.

OFP-02-003
QPOLE; a rapid, simple and cheap approach for POLE assessment in endometrial cancer by multiplex qPCR

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Background & objectives: Detection of pathogenic *POLE*-mutations in endometrial cancer is of prognostic and therapeutic importance. Currently, *POLE*-status is determined by DNA-sequencing, which is time-consuming, not widely available and expensive. We validated a rapid, low-cost quantitative polymerase-chain-reaction (qPCR) assay for pathogenic *POLE*-mutations; *QPOLE*.
Methods: Primer and fluorescence-labelled 5'-nuclease probe-sequences of pathogenic *POLE*-mutations within the *POLE* exonuclease domain were designed. Two multiplex mixes, *QPOLE*-frequent for the most occurring mutations (P286R, V411L, A456P, S459F) and *QPOLE*-rare for the rare variants (M295R, F367S, D368Y, L424I, P436R, M444K) were developed using DNA extracted from formalin-fixed paraffin-embedded tumour tissues from our extensive EC tumour tissue repository.
Results: Cut offs for *POLE*-wild type, -mutant and failed results were predefined based on 50 *POLE*-wild types and 7 *POLE*-mutant cases. For cases with values in the equivocal range between wild type and mutant, additional DNA-sequencing (i.e. Next Generation Sequencing (NGS)) is recommended. In our testing set of 227 cases

(71 *POLE*-mutated, 156 *POLE*-wild type), 20 samples (8.8%) fell in the equivocal range (10 *POLE*-mutant, 10 *POLE*-wildtype). Sensitivity and specificity for the combined *QPOLE* assays were 93.4% (95%CI 90.1-96.7%) and 100%. *QPOLE* combined with NGS for equivocal cases yields a final sensitivity of 94.4% (95%CI 91.6-97.2%), while maintaining a 100% specificity.
Conclusion: With this qPCR assay, *QPOLE*, we have developed a simple, faster, reliable and sensitive alternative for targeted NGS of all pathogenic somatic variants in the exonuclease domain of the *POLE*-gene. The simplicity of the design enables assessment of *POLE*-status within 4 hours, and will make universal low-cost *POLE*-testing available for all EC patients. An interlaboratory validation study to determine the assay's practical feasibility is ongoing; results are available at the time of the conference.

OFP-02-004
Molecular characterisation of endometrial carcinoma and prognostic risk group classification
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Background & objectives: Molecular classification of endometrial carcinoma (EC) has been recently incorporated into prognostic risk classification of endometrial carcinoma and should be integrated into conventional pathologic diagnosis.
Methods: We included EC cases diagnosed in our Department between September 2019 and March 2022. Clinicopathological features were retrieved from the electronic medical records of the patients. Molecular classification was performed by the TCGA surrogate testing immunohistochemical markers (p53, MLH1, PMS2, MSH2 and MSH6) and somatic mutation analysis of POLE. Prognostic risk group stratification was established according to ESGO-ESTRO-ESP 2021 guidelines.
Results: We found 92 patients with EC, 80 of which underwent surgery. Most cases were low-grade early stage endometrioid carcinomas (85%). According to the molecular classification, 25% EC showed mismatch repair deficiency (MMRd), 15% were p53abn (all high-grade, mostly at advanced stages), 6.5% showed a pathogenic POLE mutation, and 50% were of no specific molecular profile (NSMP). Three cases displayed more than one alteration ("multiple classifiers"). According to clinicopathological features, 38 cases were low-risk, 12 intermediate, 9 intermediate-high, 18 high-risk, and 2 advanced metastatic. After integrating molecular classification, a risk-group shift occurred in 3 patients (one p53abn from low to intermediate risk, and 2 POLEmut from high-intermediate to low-risk).
Conclusion: There is good correlation between molecular classification and histological subtypes: all p53abn tumours were high-grade carcinomas (43% presented at advanced stage), whereas POLEmut cases were mostly low-grade endometrioid carcinomas. Inclusion of this surrogate marker approach to the molecular-based classification is prognostically informative in low-, intermediate-, and high-risk endometrial carcinoma. Changes in prognostic risk group classification occur mainly in p53abn and POLEmut cases. According to current guidelines, molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumours.

OFP-02-005
Comparison of tumour infiltrating lymphocytes between endometrial carcinoma primary tumours and matched metastases
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Background & objectives: Tumour infiltrating lymphocytes (TILs) in endometrial carcinoma can stimulate anti-tumour immune response and have been shown to impact survival. In some tumour models decreased TILs in metastases was shown, but in metastatic/recurrent endometrial carcinoma limited data is available.
Methods: We studied a cohort of 39 primary endometrial endometrioid carcinomas and matched metastases, diagnosed between 2000 and 2013, at two Portuguese tertiary centers. Patient's clinical files and histological slides were retrospectively reviewed. The number of TILs per square millimeters was automatically determine using QuPath in 6 (primary) and 3 (metastasis) random fields for each case.
Results: The number of TILs in metastases had a significant, but weak, correlation with the number of TILs in primary tumours (rs=0.40, p=0.01). Metastases had a median of 238 TILs/mm2 (range:4,1871), with no difference between distant versus regional metastases, nor between lymph-node versus other sites (peritoneum, lung, bone). Primary tumours had a median of 262 TILs/mm2 (range:0,1013). Twenty metastases showed a decrease in the number of TILS compared to matched primary tumours, and 18 showed an increase. Variations in TILs numbers do not correlate with metastases site, grade or mitotic count. Even though not statistically significant, patients with higher number of TILs in metastasis had a better overall survival (HR:0.43, p=0.11).
Conclusion: The immune microenvironment in endometrial carcinoma metastases seems to be variable, either with an increase or decrease in TILs compared to primary tumours. Further studies with larger series are needed to confirm our findings and determine the factors underlying this variation.

OFP-02-006
DNA methylation analysis of endometrial carcinomas identifies molecularly and clinically distinct subgroups
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Background & objectives: DNA methylation analysis is an emerging approach with great potential to further our understanding of oncogenic mechanisms and assisting with tumour classification. In this study we set to characterize a group of endometrial carcinomas using their methylation profile.
Methods: We collected a series of molecularly profiled (using ProMisE) and clinically annotated endometrial carcinomas. Methylation analysis was done using the Illumina Infinium EPIC (850k) BeadChip with subsequent unsupervised clustering of the differentially methylated regions. Statistical analyses including two-tailed T-Tests, Chi-Squared tests, and Kaplan Meier survival analysis were done across various clinical and molecular variables.
Results: Our cohort (n=50) included 10 *POLE* mutated (*POLE*mut), 10 MMR-deficient (MMRd), 10 p53 abnormal (p53abn), and 20 with no specific molecular profile (NSMP). The unsupervised clustering analysis identified two major methylation groups (A and B), each with two subgroups (A1/2 and B1/2). Clusters A and B differed significantly in terms of molecular subtypes (p<0.001): cluster A only included NSMP and p53abn cases, while cluster B had high representation of MMR-deficient and *POLE*mut tumours. Deep myometrial invasion (stage IB), lower BMI, and beta-catenin expression were associated with cluster B (p=0.040, 0.009, and 0.037 respectively). Survival analysis

of sub-cluster B2 showed significantly better overall survival compared to the others three subgroups (p=0.040).
Conclusion: Endometrial carcinoma is a complex disease with a spectrum of different genomic and epigenetic alteration profiles. Our findings support that methylation analysis has the potential to predict molecular and clinical variables. Further analysis of the impact of specific differentially methylated regions on clinicopathologic variables is ongoing.
[1] Both authors contributed equally[2] Co-senior authors

OFP-02-007
Integrated clinicopathological and molecular analysis of endometrial carcinoma: prognostic impact of the new ESGO-ESTRO-ESP endometrial cancer risk classification
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Background & objectives: The ESGO/ESTRO/ESP committee has been recently proposed a new risk stratification system for endometrial cancer (EC) patients incorporating both clinicopathological and molecular characteristics. The study aims to compare the ESGO/ESTRO/ESP risk classification system with the previous 2016 risk classification.
Methods: The cohort included 187 consecutive patients with endometrial carcinoma. Immunohistochemistry (IHC) and Next-Generation Sequencing (NGS) were used to assign TCGA molecular EC subgroups: POLE mutant (POLE), mismatch repair deficient (MMRd), p53 mutant (p53abn), and no specific molecular profile (NSMP).
Results: TCGA class assignment of EC cohort: 7% POLE group, 31% MMRd group, 23.5% p53abn group, 38.5% NSMP group. In the 2020 risk classification system, 39.1% of patients were allocated to low risk compared with 22.6% in the 2016 risk classification system, mainly due to reclassification of patients previously classified especially as high-intermediate risk. The recent 2020 guidelines revealed a total of 61 patients (32,6%) with a change in risk group in relation to the 2016 classification system: the shift was due to p53abn, POLE alterations and lymph vascular invasion. The application of the 2020 risk stratification system shows Kaplan-Meier curves with a more significant difference between the groups throughout survival.
Conclusion: In our cohort, the application of the new 2020 risk classification integrating clinicopathological and molecular parameters provided a more accurate identification of low-risk and high-risk patients, potentially allowing a more specific selection for post-operative adjuvant therapy. Integrated molecular classification is a promising tool for a better therapeutic management of patients.

OFP-02-008
CCND1 amplification and cyclin D1 overexpression correlate with adverse outcome in vulvar squamous cell carcinoma
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Background & objectives: There is scarce evidence regarding the role of CCND1 amplification and protein overexpression in vulvar squamous cell carcinomas (VSCC). We aimed to 1) correlate cyclin D1 DNA amplification with protein overexpression and 2) correlate cyclin D1 overexpression with clinical prognosis.
Methods: Whole exome sequencing and cyclin D1 immunohistochemistry (IHC) were performed in 65 VSCC. Copy number alterations were predicted for the tumour-control pairs using ControlfreeC. The prognostic significance of cyclin D1 IHC overexpression and its correlation with clinical-pathological features was further assessed in a subset of 90 VSCC. Cyclin D1 was considered overexpressed when >50% of the tumour cells stained positive.
Results: A total of 18/65 (27.6%) VSCC showed amplifications in CCND1 and 26/65 (40.0%) showed strong cyclin D1 overexpression. A strong positive correlation between CCND1 amplification and cyclin D1 overexpression was found (p<0.001). Both CCND1 gains and cyclin D1 overexpression strongly correlated with worse disease-free survival (p<0.001 for each). Only cyclin D1 IHC overexpression had significant association with worse disease-specific survival (p<0.01).
In the cohort of 90 VSCC, tumours overexpressing cyclin D1 showed worse disease-specific and disease-free survival than cyclin D1-negative tumours (p<0.001 for each). Cyclin D1 overexpression correlated also with HPV-negative status (p<0.001), presence of p53 abnormalities (p<0.001) and advanced FIGO stage [III-IV vs. I-II] (p=0.02).
Conclusion: Our findings indicate that CCND1 is amplified and overexpressed in a significant proportion of VSCC, mostly in HPV-independent tumours. Cyclin D1 overexpression is strongly associated with adverse patient outcome (worse disease-specific and disease-free survival) and could be a useful tool for prognostic stratification. Innovative targeted therapies could be explored based on these findings.
Funding: Project "PI20/00368; Caracterización genómica de los carcinomas de vulva independientes de virus del papiloma humano y de sus precursores", funded by Instituto de Salud Carlos III and co-funded by the European Union (ERDF) "A way to make Europe". ISGlobal receives support from the Spanish Ministry of Science and Innovation through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program.

OFP-02-009
Worse disease-free survival for patients with vulvar squamous cell carcinoma arising on HSIL-like or VAAD/DEVIL lesions
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Background & objectives: A number of new precursors of Human Papillomavirus (HPV)-independent vulvar squamous cell carcinomas (VSCC) have been recently defined: vulvar acanthosis with altered differentiation (VAAD), differentiated exophytic intraepithelial lesions (DEVIL) and high-grade squamous intraepithelial (HSIL)-like lesions.
Methods: We assessed whether patients with HPV-independent VSCC had any clinico-pathological differences depending on the associated adjacent precursor. The study comprised 157 patients with HPV-independent VSCC surgically treated between 1975 and 2021. The skin adjacent to the tumour was histologically reviewed. The median follow-up was 69 months. Correlations with outcome were analysed using multivariable Cox regression and log-rank analysis.
Results: 50 patients (31.8%) showed differentiated VIN (dVIN), 49 patients (31.2%) showed adjacent inflammatory dermatosis, 25 (15.9%) had HSIL-like lesions, 9 (5.7%) showed VAAD or DEVIL and in 24 women (15.3%) no adjacent skin lesion was identified. Patients with HSIL-like and VAAD/DEVIL lesions showed impaired disease-free survival (higher

rates of relapse and/or persistence of disease) compared with other groups ($p<0.001$). In addition, despite no statistically significant, the tumour size of VSCC associated to HSIL-like lesions was smaller than of other groups ($p=0.17$). No differences in overall or disease-specific survival were identified among the six groups ($p=0.15$). None of the women with VAAD or DEVIL died of disease.

Conclusion: Our findings indicate higher risk of relapse or persistence of disease in patients with VSCC arising on HSIL-like or VAAD/DEVIL lesions. Closer surveillance after surgical resection of VSCC may be indicated for these cases.

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OFP-02-010

Reproducibility of low-volume lymph node metastasis assessment in endometrial cancer

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Background & objectives: Lymph node (LN) assessment is critical for staging of endometrial cancer (EC). Low volume metastasis (LVM), upstages patients, but early data suggests
some of these patients can be spared adjuvant treatment. So, accurate pathologic determination of LVM is critical.

Methods: Whole slide images (WSI) (3 H&E levels, 40 µm apart and 1 CK AE1/AE3 slide) of 11 pelvic sentinel lymph nodes (SLN) involved by LVM were reviewed by 9 pathologists from multiple institutions. Various parameters were assessed: number of foci, size of the largest focus, clusters versus scattered cell, site of involvement in the LN and extra-nodal extension.

Results: An international consortium of 9 pathologists were participated in this study. 9 out of 11 cases, ≥8 pathologists had complete agreement determining the type of involvement (MM vs ITC). In the remaining 2 cases, there was an even split in the designation of the involvement type. These two cases showed multiple scattered tumour foci with dispersed cells, making the accurate measurement and determination of the involvement type challenging. The largest focus measurements showed some disagreement in both micro-metastasis and ITC cases, with slightly higher variability in the ITC sub-group. Agreement in #foci/plane, pattern, and site of involvement were high.

Conclusion: Our study indicates an excellent interobserver agreement for the separation of ITCs and MM amongst an international group of gynaecologic pathologists using WSI. Problematic cases arise when tumour foci extend along a distance within a lymph node. Additional studies are needed to determine the impact of these findings and to formulate recommendations to address.

OFP-02-011

Evaluation of the implementation and diagnostic accuracy of the Paris classification for reporting urinary cytology in voided urine specimens: a cyto-histological correlation study in a high-volume cancer centre

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Background & objectives: The Paris classification was introduced for reporting urinary cytology, highlighting the need to focus on accurately identifying high-grade urothelial carcinoma (HGUC), and aiming to improve criteria, terminology and ultimately improving patient management.

Methods: To assess the overall implementation and diagnostic performance of the Paris classification for reporting urinary cytology. All urinary cytology reports from July 2018-December 2019 were collected (n=1240). Only voided urine samples were included (n=1180), of which 9.9% had histological confirmation. Risk of malignancy (ROM) was calculated. Diagnostic performance of urinary cytology was assessed, including sensitivity, specificity, PPV, NPV and accuracy.

Results: The median age of the study population was 69 years, and 71.2% were male. The Paris system categories were widely used (in 99.7% of reports). The distribution of categories was: 0.3% unsatisfactory, 90.5% negative for HGUC, 5.6% atypical urothelial cells (AUC), 1.6% suspicious for HGUC, 1.9% HGUC and 0.1% other malignancies. No diagnosis of low-grade urothelial neoplasia was given. ROM was 21.4% for negative for HGUC, 66.7% for AUC, 91.7% for suspicious for HGUC and 100% for HGUC. When using suspicious for HGUC as a cut-off, the diagnostic performance of urinary cytology in identifying HGUC was 46% sensitivity, 98% specificity, 96% PPV, 68% NPV and 74% accuracy.

Conclusion: Specificity of urinary cytology is very high. ROM for each category was in accordance with literature, except for AUC where ROM was slightly higher (66.7%). Sensitivity of voided urine specimens is known to be lower than that of instrumented specimens, explaining the lower sensitivity in our study. Study population characteristics (high-volume cancer centre with many patients treated with intra-vesical therapies) may explain part of our results. This pilot study motivated an interobserver variability study among three Cytopathologists, which is ongoing.

OFP-02-012

Application of a standardised terminology and nomenclature for respiratory cytology: experience from a large tertiary respiratory cancer centre

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Background & objectives: International cytopathology coding systems have a valuable role in facilitating report standardisation. A new international respiratory cytopathology coding system is currently being developed. Our institution has been coding all respiratory cytology specimens in a similar manner for over 10 years.

Methods: Specimens are coded as non-diagnostic (C1), benign (C2), atypical, favour reactive (C3), suspicious for malignancy (C4) or malignant (C5).

We calculated rates of diagnostic categories on our cohort over a two-year period by evaluating all endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), bronchial washing, bronchial brushing, bronchial lavage and sputum specimens performed at our institution using the laboratory information system.

Results: We assessed all aforementioned respiratory cytological specimens received at our institution in the years 2020 and 2021. In total, 1433 cytological specimens fulfilled the inclusion criteria and were analysed. Of these, 15.8 % (n=226) were coded as malignant (C5) and 1.47% (n=21) were coded as suspicious for malignancy (C4).

The calculated rates of diagnostic categories, bases on cytological findings, were as follows:

1. EBUS-TBNA (n=415): C1=8.7%, C2=54.7%, C3=2.4%, C4=1.4%, C5=32.8%.
2. Bronchial brushings (n=96): C1=1.0%, C2=49.0%, C3=8.3%, C4=3.1%, C5=38.5%.
3. Bronchial washings (n=486): C1=3.1%, C2=75.7%, C3=8.4%, C4=2.3%, C5=10.5%.
4. Bronchial lavages (n=429): C1=1.9%, C2=97.0%, C3=0.5%, C4=0.2%, C5=0.5%.
5. Sputum (n=7): C1=14.3%, C2=85.7%, C3=0.0%, C4=0.0%, C5=0.0%.

Conclusion: Coding systems are widely utilised in other areas of cytopathology, such as in thyroid and salivary gland specimens. The consistency and standardisation of reporting achieved from such systems provides greater clarity for the treating physician and facilitates clear communication of essential information.
We have been using a classification system analogous to the proposed new respiratory cytology classification system for approximately 10 years. This data provides indicative rates of cytological outcomes in a tertiary referral lung oncology centre.

OFP-02-013

A retrospective report-based review of 4,155 consecutive patients undergoing minimally invasive thoracic lymph node sampling

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Background & objectives: Endoscopic bronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) are minimally invasive strategies to assess thoracic lymph nodes. This project examined the pathology of patients from a regional thoracic surgery centre that underwent EBUS/EUS and (if applicable) lung cancer resection.
Methods: All EBUS/EUS specimens accessioned 2011-2020 were retrieved and linked via anonymized patient identifier to lung cancer resections with synoptic reports. Cases were automatically classified and grouped into mutually exclusive categories (malignant(MAL), suspicious(SUSP), insufficient(INSUF), benign(BEN)), based on the most recent specimens using a previously validated program. Data was stratified by location (station(ST)7, ST4R, ST4L, all other N2 ST(STN2others), all N1 ST(STN1all)).
Results: The cohort contained 4,155 patients with 10,922 EBUS/EUS specimens. Patients had 1 to 13 specimens and median number of specimens per patient was three. Patients with station MAL/number of patients(% MAL) was: ST7 750/3,407(22%), ST4R 816/2,844(29%), ST4L 293/1,504(20%), STN2others 283/668(42%), STN1all 381/1,264(30%). Overall, N2 MAL status/number of patients(%) was 1,399/3,992(35%) and multiple N2 stations/STN2others were involved in 604 of 1,399(43%) patients. 829(20%) patients went for lung cancer resection; 47 had two surgeries and two had three surgeries. Nodal stage by most recent surgical specimen was 20 (patients) pNX, 563 pN0, 175 pN1 and 71 pN2. 469 of 4,155 patients (11%) had granulomatous inflammation in 838 EBUS/EUS specimens.
Conclusion: EBUS/EUS is used for lung cancer staging, sarcoidosis and other indications. Patients with N2 positivity frequently have multiple positive stations. The low pN2 rate on resection in our environment confirms EBUS/EUS is effective at selecting lung cancer patients for surgery. The assessment of pathologic categorizations can provide insights in thoracic surgery and tumour biology.

OFP-02-014

The Paris System for reporting urinary cytology: 5 years of institutional experience in a tertiary hospital

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Background & objectives: The Paris System for Reporting Urinary Cytology (TPS) standardizes the triage criteria for high-grade urothelial carcinoma (HGUC) in urine specimens. Our aim was to assess the TPS accuracy through cytohistological correlation, stratified by both cytological category and histological grade.
Methods: The reports of urinary tract histological diagnoses and pertaining retrospective cytological specimens, examined in 2016-2021, were retrieved from our Department software database; non-satisfactory/non-diagnostic samples were unaccounted for. The TPS categories were divided into negative and positive tiers (suspicious and HGUC combined); the risk of malignancy (ROM) and performance parameters were then calculated, following histological correlation.
Results: A total of 1261 cytological and 638 histological samples were assessed. Each biopsy/surgical diagnosis correlated with an average of 2 urinary (voided/instrumented) specimens (ranging from 1 to 12), sampled either simultaneously or up to 52 months beforehand. The ROM ranged from 17.4% in negative samples to 71.5% in positive categories; the performance analysis revealed a sensitivity of 46.7%, a specificity of 91.8%, a positive predictive value of 78.4% and a negative predictive value of 72.7%. Atypical urothelial cells were independently analysed and revealed mixed results.
Conclusion: We present a heterogeneous series, encompassing the learning curve following TPS implementation and clustering both "de novo" diagnoses and urothelial neoplasm follow-ups. The large volume of these samples impacts its diagnostic yield and hence a low sensitivity was expected, contrasting with a high specificity that translates the atypia of even scarce shed tumour cells. On the other hand, although pathologists are not blinded to clinical information and previous diagnosis, histological false negatives due to undersampling must not be overlooked.

OFP-02-015

Fine needle aspiration biopsy of orbital masses: a review of 36 cases

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Background & objectives: Fine needle aspiration biopsy (FNA) is a useful tool to triage orbital lesions in cases where a diagnosis cannot be made by clinical and imaging findings alone. FNAB can provide crucial information before a surgical and oncologic procedure is undertaken.
Methods: Over a period of 5 years, 2017-2021, 36 patients underwent FNAB of orbital masses. Twenty-nine lesions were sampled by FNAB using a transcutaneous or transconjunctival approach and 7 patients underwent CT guided FNAB with the assistance of a cytopathologist. Thirteen patients had a prior history of malignancies. Flow cytometry was performed in 16 cases and immunocytochemical examination in one.
Results: Diagnostic material was obtained in 28 lesions. Malignant haematolymphoid lesions represented most of the malignancies: 6 primary and 4 recurrences of non-Hodgkins lymphomas and acute myeloid leukaemia. There were 8 metastatic malignancies: 3 breast, 1 lung, 1 adrenal and 2 neuroendocrine carcinomas, and 1 metastasis of glioblastoma.

One patient with history of pleomorphic adenoma in the orbit was diagnosed with carcinoma ex pleomorphic adenoma. In 2 patients FNAB disclosed primary salivary duct carcinoma and recurrence of basal cell carcinoma respectively. The remaining cases included 3 cases of lymphoid hyperplasia, 3 cases of inflammatory pseudotumour and 1 haemangioma. With exception for minor hematomas in some patients, no severe complications were observed.
Conclusion: FNAB may be considered a useful technique in the diagnostic approach to orbital masses according to strictly defined indications. This technique allows a confident diagnosis with a low risk of complications and is particularly useful in the evaluation of malignant, unresectable and retrobulbar orbital lesions.

OFP-03 | Oral Free Paper Session Digestive Diseases Pathology - Liver/Pancreas

OFP-03-001
Histopathological tumour response scoring in resected pancreatic cancer following neoadjuvant therapy (ISGPP-1): an international interobserver study

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Background & objectives: This study investigated whether gastrointestinal/pancreatic pathologists can reliably identify neoadjuvant treatment effects in pancreatic tumours based on histomorphology. Moreover, it aimed to determine the interobserver agreement for current (internationally used) tumour response scoring (TRS) systems.
Methods: Overall, 23 gastrointestinal/pancreatic pathologists reviewed whole H&E-slides of neoadjuvantly treated or treatment-naive resection specimens of pancreatic cancer. The accuracy in identifying treatment effect was investigated in 60 patients (30 treatment-naïve, 30 after NAT). Interobserver agreement for the College of American Pathologists (CAP) and MD Anderson Cancer Center (MDACC) TRS systems was assessed in 50 patients using intraclass correlation coefficients (ICC).
Results: The sensitivity and specificity for identifying NAT effect were 76.2% and 49.0%, respectively. The histological features: reduced cancer cell density, mucin pools, and cell degeneration were most frequently stated to allow distinction between treated and treatment-naïve cases. In 50 patients after NAT, the ICC values for both TRS systems were 'moderate'; 0.66 CAP and 0.71 MDACC. The ICC values of <0.50, ≥ 0.50 and <0.75, ≥ 0.75 and <0.90, and >0.90 indicate poor, moderate, good, and excellent reliability, respectively. None of the cases scored as a complete response by at least one pathologist had 100% concordance.
Conclusion: Identification of the effect of NAT in resected pancreatic cancer proved unreliable. The interobserver agreement for the current TRS systems was suboptimal. These findings support the recently published ISGPP recommendations to score residual tumour burden rather than tumour regression following NAT, which will require a new TRS system.

OFP-03-002
Two step- progression of non-functioning pancreatic neuroendocrine tumours (PanNET)

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Background & objectives: PanNETs with mutations in ATRX, DAXX and MEN1 (ADM) originate from α-cells. Alpha-like PanNETs, small and indolent, progress into intermediate (ADM), larger and with high relapse risk. We dissected epigenetic changes and activation of related pathways, occurring during such progression.
Methods: We combined DNA methylation profiles of 155 and RNA sequencing of 45 PanNET samples. DNA methylation analysis was performed using the ChAMP pipeline. Consensus clustering was performed following the ConsensusClusterPlus (v1.54.0) pipeline. Spearman correlation between expression values and correspondent beta or M values of methylation was used to identify genes which changes in both DNA methylation and expression.
Results: Combining RNAseq and DNAme data, we delineated three groups of PanNET originating from alpha cells: alpha-like PanNET, intermediate-ADM and intermediate-ADM3. We compared DNA methylation and transcriptome profiles of the three groups. We found that alpha-like PanNETs develop first into intermediate-ADM and then into intermediated-ADM3 following a two steps progression. Notably, alpha-like tumours develop into intermediate-ADM upon DAXX/ATRX mutations and changes in DNA methylation mainly at heterochromatin regions increasing Chromosomal Instability. Interestingly, only genes regulating cell proliferation were found differently expressed between alpha-like and intermediate-ADM tumours. Intermediate-ADM develop into intermediated-ADM3 acquiring changes in DNA methylation at regulatory regions, resulting in an altered expression of genes involved in cell differentiation and metabolism.
Conclusion: We described pathways of progression dependent on DAXX and ATRX and subsequent epigenetic changes, characterized by increased cellular dedifferentiation and metabolic adaptation. Additionally, our study confirmed the high relevance of DNA methylation in stratifying and classifying PanNETs with different molecular and clinical characteristics.

OFP-03-003
Mutational profile of hepatocellular carcinomas with microvascular invasion and microscopic portal vein invasion. Implications for tumour progression and recurrence

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Background & objectives: The aims of the present study are to confirm the prognostic role of microscopic portal vein invasion (MPVI) in resected hepatocellular carcinoma (HCC), and to correlate MPVI with the mutational status to create risk categories based on NGS data.
Methods: Out of 400 retrospective resected HCCs we selected all cases with a diagnosis of microvascular invasion (MVI). Then we reviewed the histopathology, subclassifying each case according to the presence of MVI vs MPVI. Survival data for each patient was then obtained. We then performed NGS analysis with a custom panel on a perspective cohort of recent resected HCCs.
Results: Kaplan-Mayer survival analysis was performed on the retrospective cohort which showed a statistically significant better Overall Survival (OS) for HCCs without MPVI ($p=0.007$). NGS analysis found that TERT(65%) TP53(26%), and CTNNB1(22%) were the most frequently observed mutations. NGS results and MVI were studied using a Chi-Square test and found that TP53-mut and MPVI were positively correlated ($p=0.039$), while TERT-promoter mutation correlates with the presence of any MVI ($p=0.038$). Although MPVI and CTNNB1-mut correlation was not significant ($p=0.076$), none of the 5 CTNNB1-mut cases had MPVI. TP53-mut HCCs were characterized by a higher

histological grade (p=0.005) and a solid/macrotrabecular architecture (p=0.017).
Conclusion: Our retrospective data confirmed the literature on resected HCCs, showing a worse OS in patients exhibiting MPVI vs MVI. The perspective phase of our study is still in progress, but our preliminary data on NGS results suggest a progression from TERT-mutated HCCs, which develop MVI, to TP53 mutation, which can predict MPVI, besides a more aggressive behaviour.

OFP-03-004
Acinar cystic transformation of the pancreas: clinical and molecular analysis for unravelling its heterogeneous nature
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Background & objectives: Acinar cystic transformation (ACT) of the pancreas is a poorly understood and rare entity among pancreatic cystic lesions. This study aims at clarifying their real nature.
Methods: The study cohort includes 25 pancreatic ACT, representing the largest series of ACT in the literature. Here we provide their clinicopathological characterization along with molecular profiling by next-generation sequencing (NGS).
Results: ACT were more common in female patients, frequently in body-tail region. At follow-up, all patients were alive and free of disease. Histologically, all cysts were lined by typical acinar epithelium, sometimes intermingled with columnar or ductal-like epithelium. Cell atypia, necrosis, mitoses, and invasive carcinoma were absent. Three cases showed a patchy distribution, and two cases were associated to ductuloinsular complexes with centroacinar microcysts. Two ACT showed peculiar histologic features: one showed a distinctive microcystic pattern, and another harboured foci of low-grade dysplasia in the areas lined by ductal-like epithelium. NGS detected the presence of two pathogenic / likely-pathogenic mutations in two different cases: KRAS, c.34G>C, p.G12R, and SMO, c.1685G>A, p.R562Q.
Conclusion: Overall considered, our findings indicate that ACT is as a heterogeneous entity. It seems to encompass lesions with different possible pathogenesis, which includes the evolution from a centroacinar microcyst, and malformative, obstructive, or neoplastic origins. The potential presence of driver mutations call for a careful management of ACT patients, taking into account also surgical resection and active imaging surveillance / life-long follow-up.

OFP-03-005
Spatially resolved transcriptomic and proteomic analysis of pancreatic cancer reveals distinct profiles which correlate with site of recurrence
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Background & objectives: Pancreatic ductal adenocarcinoma (PDAC) remains a highly lethal neoplasm. The majority of patients with localized disease will eventually develop tumour recurrence after complete surgical resection. Here we investigate tumour- and immune cell determinants of PDAC recurrence.
Methods: PDACs (n=284) were classified according to recurrence site as liver (n=93/33%), lung (n=49/17%), local (n=31/11%), peritoneal recurrences (n=38/13%) and no-recurrence (n=73/26%). Four regions of interest per tumour were selected. Spatial compartments were identified with fluorescent imaging followed by transcriptomic (pancytokeratin+tumour cell compartment) and proteomic (CD45+leukocyte compartment) analysis for immune pathway associated targets by using a digital spatial profiling platform.
Results: Median overall-survival for the PDAC-groups was 16months (liver), 27months (lung), 26months (local), 12.5months (peritoneal) and 64months (no-recurrence). The tumour cell-compartment of 60% of the non-recurrent PDACs, as well as 45%, 40% and 31% of the lung, local and peritoneal recurrences respectively, showed significant upregulation of pathways involved in T cell activation, immune cell adhesion/migration, antigen presentation and cytokine signalling, as compared to only 20% of liver recurrences. CD66b (granulocyte-marker) and STING (mediator of immunosuppressive microenvironment and feature of the basal-like subtype) were strongly up-regulated in the liver leukocyte-compartment. The non-recurrent leukocyte-compartment revealed significant up-regulation of CD3, CD4, CD8, CD20, GZMB, HLA-DR, checkpoint molecules and beta-2-microglobulin compared to all recurrent tumours.
Conclusion: We found distinct spatial and microenvironmental profiles on gene and protein level in each recurrence group, which differed from each other as well as from the no-recurrence group, underlining the heterogeneity of PDAC. Tumours with liver recurrence display poor prognosis associated with unfavourable immune signalling and features of the basal-like molecular subtype.

OFP-03-006
A comparative analysis of CPA1, BCL10 and chymotrypsin for the distinction of pancreatic acinar cell carcinomas
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Background & objectives: Pancreatic acinar cell carcinoma (PACC) is a rare tumour of the pancreas with an intermediate prognosis as compared to pancreatic neuroendocrine tumours (PNE) and pancreatic ductal adenocarcinoma (PDAC) from which it may be difficult to distinguish by morphology alone.
Methods: To study was the efficiency of immunohistochemical markers, 18 PACCs, 531 PDACs, 64 PNEs, 117 extrapancreatic neuroendocrine neoplasms (EPNN), 826 colorectal carcinomas (CRC) and 252 gastric carcinomas (GC) were analysed with antibodies for CPA1 (MSVA-601M), bcl10 (Santa Cruz sc5273), and chymotrypsin (Biorad 2100-0657) in a tissue microarray format.
Results: CPA1 was positive in 18 of 18 (100%) of PACCs, 0 of 49 (0%) of PNEs, 0 of 88 (0%) of EPNNs, 10 of 404 (2.5%) of CRCs, and 0 of 178 (0%) of GCs. Chymotrypsin was positive in 16 (87,5%) PACCs, 1 (2%) PNEs, 2 (2.3%) EPNNs, 10 (2.5%) CRCs, and 1 (0.6%) GCs. Bcl10 was positive in 18 (100%) PACCs, 2 (4.1%) PNEs, 5 (1%) EPNNs, 109 (27%) CRCs, and 18 (10%) GCs. These data resulted in a sensitivity and specificity of 100%/99.2% for CPA1, 100%/88.4% for bcl10, and 94.4%/98.6% for chymotrypsin.
Conclusion: CPA1 and chymotrypsin are both highly specific and sensitive for ACC while bcl10 is sensitive but has markedly lower specificity. Because all “false positive” cases identified by CPA1 were CRCs that only showed a positive staining in goblet cells and an identical staining pattern was observed in all these cases for chymotrypsin and bcl10, a pancreatic origin of the mucus in these goblet cells is concluded.

OFP-03-007

Targeted next-generation sequencing of endoscopic ultrasound-guided through-the-needle-biopsies from pancreatic cystic lesions

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Background & objectives: Endoscopic sampling of pancreatic cystic lesions (PCLs) with through-the-needle-biopsies (TTNBs) has been introduced in clinical management. The aim of this study was to evaluate the feasibility and diagnostic accuracy of additional next-generation sequencing (NGS) of TTNBs as a diagnostic tool.
Methods: We prospectively included patients with PCLs > 15 mm in cross-section for endoscopic ultrasound and TTNB-sampling. The TTNBs were microscopically evaluated and classified according to the WHO classification, using up to 12 slides from each TTNB with a 3 µm thickness. Secondly, additional 10 slides of each TTNB were analysed by NGS using a 51 gene customized hotspot panel.
Results: We included 101 patients of which 95 had sufficient tissue for microscopic evaluation. The TTNBs were evaluated according to the WHO classification for pancreatic neoplasms including appropriate immunohistochemical staining. Subsequently, 91 patients had available tissue for NGS. We identified genetic aberrations in 49 patients, mostly alterations in KRAS and GNAS, diagnostic for intraductal papillary mucinous neoplasm (IPMN). Sensitivity and specificity of the NGS analysis were calculated with TTNB histology as the gold standard. A sensitivity and specificity of 83.7 % (70.3-92.7 %) and 81.8 % (48.2-97.7 %), respectively, were demonstrated for a mucinous cyst diagnosis, and 87.2 % (74.2-95.2 %) and 84.6 % (54.5-98.1 %), respectively, for an IPMN diagnosis.
Conclusion: We have demonstrated that TTNBs can be used for both microscopic evaluation, immunohistochemical classification, and additional targeted NGS in the majority of patients in a large prospective cohort. TTNBs offer the possibility of assessment of an intact piece of the cyst wall with correlation to genetic aberrations. NGS has high sensitivity and specificity for the diagnosis of mucinous cysts including IPMNs. We propose TTNBs as a potential alternative to cyst fluid cytology in the diagnostic management of patients with PCLs.
Funding: The study received funding from Rigshospitalets Research Foundation, The Novo Nordisk Foundation, The Danish Cancer Society, The Danish Cancer Research Foundation, Neye Fonden, Holms Mindelegat, Harboefonden, Agnete Løvgreens legat, Carl & Ellen Hertz legat, Direktør Jakob Madsen og Hustru Olga Madsens fond, Frimodt Heineke fonden, Torben & Alice Frimodts fond, Else og Mogens Wedell – Wedellsborgs fond, Fabrikant Ejnar Willumsens Mindelegat, Aase & Ejnar Danielsens fond, AP Møllers fond, and Anita & Tage Therkelsens Fond.

OFP-03-008

EUS FNA vs. EUS FNB of pancreatic lesions: a comparative study

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Background & objectives: Endoscopic ultrasound (EUS)-guided fine-needle biopsy (FNB) is replacing EUSFNA in the diagnosis and management of pancreatic lesions in Malaysia. The aim is to document and compare the diagnostic precision, accuracy and IHC studies of EUS-FNB and EUSFNA of pancreatic lesions.
Methods: This is a cross sectional, comparative study of EUS FNA and EUS FNB samples of pancreas received in Gribbles Pathology in the year 2021, with clinical, CT scan and endoscopy correlation. A total number of 341 EUS FNA and 68 EUS FNB samples of pancreatic lesions were documented for cytological and histological evaluation, respectively, along with IHC analysis.
Results: A wide range of pancreatic lesions, mostly primary adenocarcinomas, along with a small number of neuroendocrine tumours were documented. Spindle cell tumours, mucinous cystic neoplasms, serous papillary lesions, lymphomas, and cases of chronic pancreatitis were also seen. Metastatic lesions from the lung and kidney were also noted. Correlation with clinical picture, tumour markers and CT scan findings were undertaken in all cases. EUS FNA cytology had shown fruitful results in majority of the cases and cell block with good yield helped in IHC outcome. However, EUS FNB was found to be easier, advantageous, precise, and had an additional advantage of more material for IHC and further molecular studies.
Conclusion: EUSFNB is emerging as the most safe, precise and reliable diagnostic procedure replacing the conventional EUS-FNA and cell block of pancreatic lesions in Malaysia. The precision of the procedure and accuracy of the results of EUSFNB samples have considerably increased in the year 2021. This initial, first-time comparative study carried out in Gribbles Pathology, Malaysia is to document the increasing and accurate diagnostic precision of EUSFNB in the management of pancreatic lesions.

OFP-03-009

Expression and prognostic significance of HMGA2 in pancreatic ductal adenocarcinoma and ampullary adenocarcinoma

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Background & objectives: High mobility group protein 2 (HMGA2) is a structural transcriptional protein involved in tumourigenesis, and epithelial-mesenchymal transition (EMT). We evaluated the expression and clinical prognostic value of HMGA2 in pancreatic ductal adenocarcinoma (PDAC), and ampullary adenocarcinoma (AAC).
Methods: HMGA2 expression was immunohistochemically assessed in normal pancreatic tissue (n=57), chronic pancreatitis (n=86), low-grade PanIN (n=80), high-grade PanIN (n=30), PDAC (n=57) and AAC (n=30). Immunochemical staining of EMT markers (E-cadherin and vimentin) were applied in PDAC and AAC. The relationship between HMGA2 expression and clinicopathological characteristics in the PDAC, AAC, and the neoplasia cohort (n=87) including these groups was evaluated.
Results: HMGA2 expression was not observed in normal pancreatic tissue, chronic pancreatitis, and low-grade PanIN. High expression was detected in high-grade PanIN and PDAC ($P<0.001$). Between HMGA2 expression and age, gender, tumour location, size, differentiation, lymphovascular invasion, perineural invasion, pT, and pN status in the PDAC, AAC, and the neoplasia cohort significant relationship was not found ($P>0.05$). A significant correlation was observed between loss of E-cadherin expression and vimentin positivity and HMGA2 expression ($P<0.05$). HMGA2 expression increased the risk of disease-related death and decreased overall survival in AAC and the neoplasia cohort ($P=0.002$, $P=0.016$, respectively). HMGA2 was not related to overall survival and risk of death in PDAC ($P>0.05$).
Conclusion: Our results suggest that HMGA2 is an effective immunohistochemical marker in detecting benign and malignant lesions in the pancreas, as well as a potential new prognostic marker and therapeutic target in periampullary tumours, especially

AAC. The statistically significant correlation between HMGA2 protein expression, loss of E-cadherin expression, and vimentin positivity support the role of HMGA2 in EMT.
Funding: This study was supported by Eskişehir Osmangazi University Scientific Research Projects Coordination Unit Commission within the scope of project numbered 202111D02.

OFP-03-010
Detection of perineural invasion in pancreatic adenocarcinoma using artificial intelligence
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Background & objectives: Perineural invasion (PNI) refers to invasion of cancerous cells around/in nerve. PNI is associated with a worse prognosis in pancreatic ductal adenocarcinoma (PDAC) with therapeutic target potential. We aimed to build an algorithm to identify PNI in PDAC more reliably/efficiently.
Methods: Training the algorithm involved manual segmentation of nerve and tumour using 260 slide images from 6 scanned PDAC cases. Analytical validation used 168 additional images. Clinical validation had the algorithm applied to 59 cases of previously diagnosed PDAC, presenting images of areas tumour and nerve were in closest proximity. A pathologist then determined presence or absence of PNI per case.
Results: In the analytical validation, the algorithm showed sensitivity of 86%, 55% and specificity of 78% and 83% for the detection of nerve and tumour, respectively. After incorporation of the tumour-nerve distance into the algorithm, PNI was identified in an additional 18 previously misclassified cases increasing the rate of detection from 52.5 to 81.4%. Interestingly, this required an average of only 24 seconds per case.
Conclusion: This algorithm was shown to be a very useful and time efficient tool to assist pathologists to more accurately and reliably identify PNI in PDAC. Of interest, training the algorithm to imitate pathologist thought processes (measuring the distance between tumour and nerve) allows development of a robust algorithm even based on a small cohort.

OFP-03-011
Pre-invasive lesions of pancreatobiliary cancer: immunohistochemical signatures defining biological behaviour
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Background & objectives: We investigated the immunohistochemical expression profile of pre-invasive lesions of pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA) to detect staining patterns predicting risk of tumour-progression at early stages.
Methods: We analysed 33 PanIN, 28 gastric (gIPMN) and 20 intestinal (iIPMN) IPMN, 18 BilIN and their associated invasive cancers, when present (PDAC, n=23; CCA, n=6). We investigated the expression of markers associated with subtyping (MUC1, MUC2, MUC5AC, MUC6, CDX2), tumour biology (p16, p53, GATA6, Smad4, ki67), along with recently identified markers (TFF3, MUCL3).
Results: PanINs, gIPMNs and BilINs displayed similar phenotypes with MUC stains; however, MUCL3 was increased in gIPMNs($p=0.03$) and BilINs($p=0.01$) compared to PanINs. TFF3 was increased in BilINs, compared to PanINs($p=0.03$). BilINs revealed focal MUC2(17%) and CDX2(38%) expressions. iIPMNs showed higher expression of MUC2,CDX2,TFF3, and higher Ki67-index than PanINs and gIPMNs($p<0.001$). MUC1 was overexpressed in high-grade PanIN($p=0.02$) and PDAC($p<0.001$) compared to low-grade PanIN and in CCA compared to BilIN($p=0.001$). MUC5AC was decreased in IPMNs and BilINs with associated invasive tumours compared to cases without invasive tumours($p=0.03$ and $p=0.03$, respectively). MUC6 was decreased in PDAC compared to PanIN and gIPMN($p<0.001$). Altered expression of GATA6,p53,p16 and SMAD4 was observed in high-grade lesions and/or cancers.
Conclusion: iIPMNs display peculiar marker expression and higher proliferation rates compared to gIPMNs and PanINs, which are very similar to each other apart from the expression of MUCL3. BilINs and PanINs also show overall similar immunophenotypes. However, BilINs often present aberrant marker expression, different TFF3 and MUCL3 expression and higher proliferation rate. Altered expression of differentiation markers, such as MUC1, MUC5AC, MUC6 and GATA6 and of tumour-suppressors is associated with high-grade precursors and invasive cancers.
Funding: Deutsche Forschungsgemeinschaft, project number ES 285/8-1

OFP-04 | Joint Oral Free Paper Session Soft Tissue and Bone Pathology / Infectious Diseases Pathology

OFP-04-001
Whole-exome sequencing of chordoma with special emphasis on chromatin regulatory genes and recurrences
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Background & objectives: More insight into molecular genetics of chordoma is desired for defining new therapeutic strategies. We investigated 9 primary chordomas including one case with four recurrences. Special emphasis was put on chromatin regulatory genes and differences between recurrences and primary tumours.
Methods: DNA was extracted from formalin- fixed, paraffin-embedded tissue samples of sacrococcygeal chordomas from patients between 39 and 78 years of age. After thorough quality checking, the DNA was analysed by whole- exome sequencing with a NextSeq Illumina sequencer. In addition to histopathological tumour examination the expression of brachyury p53, Ki-67,SMARCB and H3K36me3 was investigated by immunohistochemical techniques.
Results: Consistent with our immunohistochemical findings and current literature our study revealed a pattern of typical molecular alterations including brachyury, p53, APC, BRCA, CDKN, and PI3K-signaling, in both recurrences and primary tumours. Interestingly our study found an increase in quantity of mutations over time in the recurrences, most of all in chromatin regulatory genes but also in rarer Genes like LYST and HYDIN. In all cases histone modifiers (KMT, KDM) and CRC-family members especially coding for the SWI/SNF- and ISWI-complexes (SMARC, ARID, PBRM) had a high number and variety of mutations.
The number of SNVs and InDels did not show significant differences between the primary and recurrent tumours.
Conclusion: The increasing number of alterations in chromatin-regulatory genes in recurrences compared to primary tumours could point to a possible importance of these alterations in recurrence development and be the basis for new targeted therapy strategies of chordoma. The progress in tumour mutation burden as well as copy number variations in recurrences were more limited compared to the genetic evolution of carcinomas with long time

recurrences. Further studies focusing on chromatin regulators could elucidate the molecular pathogenesis of chordoma.

OFP-04-002

Extraskeletal myxoid chondrosarcoma: a morphological, immunohistochemical and molecular analysis of 31 cases

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Background & objectives: Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant tumour. Their spectrum is wide but a diagnosis based on histology can be difficult. NR4A3 gene rearrangement is the hallmark in these tumours but still lack specific immunohistochemical profile for this neoplasm.
Methods: We collected 31 cases diagnosed as EMC between 1999 and 2018 from two institutions. Corresponding clinical data were recorded. We performed a histopathological and molecular study with a wide immunohistochemical panel.
Results: The mean age of our patients was 50 years with a range between 22 and 86 years. We found a slight predominance for males. The majority of EMCs showed a typical architectural pattern. EMCs expressed (focal or positive) the following markers: FLI-1 (100%), CDK4 (100%), TRK-A (96.8%), STAT-6 (90.3%), CD99 (90.3%), CD117 (83.9%), HNK-1 (80.6%), SATB2 (67.7%) and S-100 (58.1%). Neuroendocrine markers chromogranin, synaptophysin and INSM1 showed intense and focal expression in 22.6%, 22.6% and 38.7% of cases respectively. The EWSR1-NR4A3 rearrangement was found in 19 cases and 7 patients presented the TAF-15-NR4A3 fusion. The TAF15-NRA43 rearrangement correlated with a non-typical histology (more cellular with solid pattern).
Conclusion: EMCs express some immunohistochemical markers which are used in diagnosis for other neoplasms that can also be positive for EMC and can cause extra difficulty for differential diagnosis in EMCs with non-typical histology and where molecular rearrangement is not informative. Some immunohistochemical markers such as CD99, CDK4, FLI-1, SATB2 and STAT6 may be considered positive in EMCs suggesting the possibility of incorporating these markers in the differential diagnosis with other entities.
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OFP-04-003

A single-institution experience with 11 cases of extraskeletal myxoid chondrosarcoma: rare fusions, unusual morphology and the utility of INSM1 immunohistochemistry

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Background & objectives: Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft tissue sarcoma of uncertain differentiation, most commonly driven by fusion of *EWSR1* and *NR4A3* genes. A recent report identified INSM1 as a useful immunohistochemical marker, being positive in 90% of EMC cases.
Methods: 11 cases of EMC from our institutional files where molecular genetic results were available were included in the study. Immunohistochemistry for INSM1 was performed in 10 cases. Targeted RNA sequencing (RNA-seq) using customized Archer FusionPlex Kits or FISH with *EWSR1* and *NR4A3* break-apart probes were carried out in 5 and 6 cases, respectively.
Results: 8/10 cases were positive for INSM1. However, only 4 cases showed strong expression in more than 50% of tumour cells. Using FISH or targeted RNA-seq, the classic *EWSR1::NR4A3* fusion was detected in 7/11 cases. Less common *TAF15::NR4A3* and distinctly rare *TCF12::NR4A3* fusions were detected in 1 case each. In 1 case, FISH was positive for *NR4A3* but negative for *EWSR1* rearrangement. 10 cases displayed typical morphology i.e., anastomosing cords of round/oval tumour cells situated in abundant myxoid stroma, while the case with the *TCF12::NR4A3* fusion showed a highly unusual morphology consisting of a solid cellular proliferation of bland monomorphic ovoid/spindled cells with only small foci of myxoid stroma.
Conclusion: Our analysis confirms that most cases of EMC are positive for INSM1. However, the diagnostic utility of this marker is limited by the fact that only 50% of cases show a strong INSM1 expression in most tumour cells. Furthermore, our study highlights that EMC with alternative gene partners may present with unusual morphology. As illustrated by the case with the *TCF12::NR4A3* fusion, some of these cases can be confidently diagnosed only with the use of high throughput sequencing methods.
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OFP-04-004

Differential Cyclin-E1 expression in CIC-rearranged sarcoma and Ewing sarcoma

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Background & objectives: CIC-rearranged sarcomas(CRS) - one of EWSR1-negative undifferentiated round cell sarcoma(URS)-show more aggressive behaviour than Ewing Sarcoma(ES). As CCNE1 expression is associated with tumour growth in CIC::DUX4-rearranged CRS, we aimed to demonstrate the value of CyclinE1 expression in CRS.
Methods: CyclinE1 immunohistochemistry (Abcam, 1/50, EDTA) and break-apart FISH for EWSR1 and CIC gene rearrangements (ZytoLight, Zytovision) were performed on 3-mm tissue microarrays composed of 40 small round cell tumours. CyclinE1 expression was evaluated as low and high similar to the previous study by Wei et al (J Orthop Res. 2020;38(9):1952-1964).
Results: By morphology and FISH, 5 cases were CRS, and 22 cases were ES, while 13 cases were regarded as URS. Among all three diagnostic groups, Cyclin E1 expression was higher in CRS (4/5,80%) and URS (8/13,62%) groups compared to ES (1/22,5%; $p<0.001$). Higher mean age at diagnosis, presence of atypical histological findings (such as nuclear aberrations and myxoid stroma), lack of CD99 expression, and presence of metastasis at diagnosis were significantly associated with high CyclinE1 expression. The sensitivity and specificity of the high expression of CyclinE1 in detecting EWSR1(-) cases were 66.7% and 95.5%, respectively. However, the correlation between CyclinE1 expression level and survival was not statistically significant.
Conclusion: CyclinE1 expression is significantly lower in ES compared to CRS and URS suggesting that it can be used as an adjunct in the diagnostic immune panel of small round cell sarcomas.

OFP-04-005

PDL1 expression correlates with the density of tumour-infiltrating lymphocytes (TILs) in high-grade osteosarcoma and is an independent marker irrespective of disease progression and metastasis - an ambispective cross sectional study

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Background & objectives: Osteosarcoma is the most common primary malignant bone tumour in children and young adults. Not much work has been done to explore immunotherapy targeting PD1-PDL1 axis in osteosarcoma. This study shows correlation between PDL1 expression and TILs in high-grade osteosarcoma.
Methods: PDL1 expression by immunohistochemistry and TILs were evaluated in 40 resection specimens of high-grade osteosarcoma. A score of 0-3 was given for PDL1 expression. TILs were calculated under 400X (in 10 fields) and a score of 0-3 was given based on intensity. Clinical data was collected from record section.
Results: The mean age of presentation was 16 years with male to female ratio 1.6:1. The most common bone involved was femur followed by tibia. The most common site of metastasis was lung. PDL1 was positive in 82.5% cases (33/40). 17.5% (7/40) did not show PDL1 expression. 15% (6/40) showed a score of +1, 27.5% a score of +2 and 40% (16/40) a score of +3. It was observed that PDL1 expression correlated with TILs scoring (p=0.029). However, PDL1 expression and TILs did not correlate with any parameter like age; sex; histologic type; tumour size, site and necrosis; metastasis; progression and relapse; duration of chemotherapy; radiotherapy; follow up and survival data.
Conclusion: Our research shows that PDL1 is an independent marker in high-grade osteosarcoma and cannot be taken as a basis for judging progression of the disease. However, since in our study it correlated directly with the TILs density, it can be regarded as a potential therapeutic target for tumour immunotherapy.

OFP-04-006
Osteoblastoma-like osteosarcoma: a case series and literature review
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Background & objectives: Osteosarcoma (OS) is the most common primary bone tumour in young adults and children. Osteoblastoma-like osteosarcoma (OBLOS) is a rare subtype that accounts approximately 1% of all OSs. In this study, we present three cases of OBLOS with clinicopathological correlation.
Methods: Gross materials were fixed with 10% buffered formalin. After decalcification process, hematoxylin and eosin (H&E) sections of 4-5 microns were obtained. The cases (n=3) were analysed according to their histopathological, radiological and clinical features. In one case (talus localized lesion), beta-catenin was performed immunohistochemically.
Results: Two of the three cases were male and one female, and the mean age was 43.33 years. The tumours were located in the iliac bone, 4th finger of the hand, and talus. The cross-sectional surface of the tumours was solid and heterogeneous, and haemorrhagic areas were also observed. The tumours had infiltrative borders and were composed of oval-spindle shaped cells with vesicular nuclei and eosinophilic cytoplasm. Osteoclastic giant cells and mitoses were observed. Nuclear beta-catenin staining was not observed in the talus localized lesion. Two patients had a history of neoadjuvant therapy and, the other patient died due to lung metastasis.
Conclusion: Two histological features are helpful in differential diagnosis of osteoblastoma, OBLOS. Permeation around host bone and loss of peripheral maturation of the lesion favours OBLOS, whereas osteoblastoma is well-defined and there is peripheral maturation. These lesions may be radiolucent/radiodense, and OBLOS can contain features of osteoblastoma and OS. Some studies revealed that COX2, FOS, beta-catenin immunoprofile differs between osteoblastoma-OBLOS. We consider that excisional biopsy is important to support this distinction, especially if radiological findings cannot rule out or support malignancy.

OFP-04-007
Prognostic value of vessels encapsulating tumour clusters (VETC) in sarcoma
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Background & objectives: How sarcoma metastasize is unknown. VETC has been described as an epithelial-to-mesenchymal-transition independent process of metastasis: endothelium covers neoplastic clusters allowing tumour dissemination. Our aims are to assess the presence of VETC in sarcoma, and to model its prognostic role.
Methods: The study was retrospective. We selected 54 cases of sarcomas (6_DDLPS, 10_GIST, 6_LMS, 9_MLPS, 8_MPNST, 10_SFT, 5_UPS); of them 31 were metastatic (M1 group), 23 were not (M0 group, defined as least 5 years of negative follow-up). VETC was assessed with CD31 immunohistochemistry and defined as a continuous endothelial lining around tumour clusters. We used probabilistic modelling for the analysis.
Results: Within each histology, the two groups (M0 & M1) were substantially homogeneous: most (89%CI) of posterior probability(PP) difference –i.e. the contrast CPP– included 0 for sex, age, size, and grade. VETC in SFT was basically only expressed in M1, with almost all the CPP mass above the 0. Also, in UPS and GIST, VETC was more probable to be in metastatic diseases with 79% and 78% respectively of the CPP mass above 0. VETC was prognostic of metastasis free survival in SFT and UPS with a coefficient of 2.42(CI_0.73–4.65) and 1.94(CI_0.16–3.67); only UPS reached median survival of 65 months(mo)(standard deviation, SD:74_mo) for VETC- Vs 11 mo (SD:14_mo) for VETC+.
Conclusion: VETC was present in all the investigated histotypes but two (MLPS, MPNST). VETC was prognostic of disease free survival in UPS and SFT. These findings warrants confirmations on a larger series. Moreover, in some carcinomas VETC has been shown to be predictive of tyrosine-kinase-inhibitors (TKI) response; our results prompt us to to verify if this is also true for SFT, where TKI are often used in clinical practice.

OFP-04-008
Immunohistochemical expression of H3.3G34W in 67 giant cell tumours of bone and its diagnostic mimics: a single institutional study at a tertiary cancer referral centre in India
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Background & objectives: Despite its classic histopathological features, sometimes there is a challenge in differentiating giant cell tumour of bone(GCTB) from its various mimics. Lately, Histone 3.3G34W has been identified as a useful immunohistochemical marker.
To evaluate H3.3G34W immunohistochemical staining in 67 GCTBs.
Methods: Immunohistochemical staining for H3.3G34W (monoclonal, RM263, 1:100 dilution) was graded in terms of staining intensity(1+to 3+) and the percentage of tumour cells showing crisp nuclear staining. Seventy-one(65.7 %) GCTBs

occurred in patients 15-66 years old (average=32, median=9), in femur (26,36.6%), proximal tibia (11,15.5%), distal radius (9,12.6%), pelvis, including sacrum (8,11.2%) and other bones (17,23.9%), including a single multicentric case.
Results: Out of 67 GCTBs, wherein H3F3G34W immunostaining worked, 55(82.1%) cases showed positive staining in the mononuclear cells, including tumours with fibrous histiocytoma-like areas, sparing the osteoclast-like giant cells. The average percentage of tumour cells showing positive immunostaining was 69%, with 3+ staining intensity in 42/55(76.4%) cases and 2+ in 13(23.6%) GCTBs. All 4/4(100%) malignant GCTBs showed positive staining, including the mononuclear and pleomorphic/sarcomatous cells. Three(4.3%) cases developed metastasis(axillary nodes, mediastinum and lung). All 3/3(100%) metastatic GCTBs showed positive immunostaining in the metastatic lesions. Out of seven post-denosumab treated GCTBs, four showed no residual giant cells and lacked H3.3G34W immunostaining. None of the other 37 "giant cell-rich" lesions displayed H3.3G34W immunostaining.
Conclusion: The diagnostic sensitivity of H3.3G34W for GCTB was 82.1% and specificity was 100%. The present study, constituting one of the first reports from our country, further validates the value of H3.3G34W in differentiating GCTB, including metastatic and malignant type from its diagnostic mimics. Its utility in identifying residual tumour cells in post-denosumab treated GCTBs is worth exploring.
Funding: Intramural grant, Tata memorial Hospital, Parel, Mumbai

OFP-04-009
COVID-19 placentitis in pregnant women may be complicated by foetal death
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Background & objectives: Dominant clinical manifestations of the SARS-CoV-2 infection are in the lungs, however, pathological consequences of COVID-19 in different organs have been documented in multiple studies. Only limited data are available about the outcome of this infection in pregnant women.
Methods: Two cases of intrauterine death of the foetus in mothers after overcoming COVID-19 with mild symptoms were studied in detail. Placentas hebd. 38 and 35, respectively, were nodular, hard-elastic, with whitish to dark pink areas affecting 70 – 80%. Autopsy of the babies was performed. No pathological abnormalities were grossly identified in either case.
Results: Microscopic evaluation of the placental tissue revealed broad intervillous and perivillous deposits of fibrin with marked histiocytic infiltration, scant lymphocytes and focally with neutrophils, especially in areas of forming infarctions. Inflammation of villi was not prominent. Immunohistochemistry and in-situ hybridization proved the ongoing presence of syncytiotrophoblast infection by the SARS-CoV-2 virus. This finding was also confirmed by the +PCR test from placental tissue samples. Histological evaluation of tissues of the foetuses showed only mild interstitial lymphocytic infiltration in lungs and sporadic immunohistochemical and in-situ hybridization positivity of SARS-CoV-2 in individual cells in lungs and kidneys, which was also confirmed by the +PCR test in lung tissue samples.
Conclusion: The two presented cases documented the development of placentitis caused by SARS-CoV-2 infection after uncomplicated COVID-19. This process is associated with massive deposition of intervillous fibrin and placental infarctions with consequent ischemia and death of the foetus. Although the vertical transfer of the infection was documented, the SARS-CoV-2 virus infection did not contribute to the foetal demise in the presented cases. This rare complication of pregnancy appears to be independent of the seriousness of COVID-19 clinical course in the mother.
Funding: Supported by APVV grant PP-COVID-20-051.

OFP-04-010
Histological and molecular features of placental and foetal tissues in pregnancies with SARS-CoV-2- positive mothers during second and third trimester: the Bergamo experience in vertical transmission
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Background & objectives: Intrauterine transplacental transmission of SARS-CoV-2 to the foetus is rare but possible in infected pregnant women. According to WHO 2021 classification criteria, both stillborn and liveborn neonates appear to have the possibility to acquire transplacental COVID-19 infection prior to delivery.
Methods: During the first pandemic wave, two Covid-19 positive women delivered two positive babies at third trimester. In September 2021 a case of second trimester twin stillbirth have found positives to SarS-Cov-2 from an asymptomatic infected mother. All specimens collected were analysed by real time PCR, immunohistochemistry and in situ hybridization RNA in order to detect and to localize SARS-CoV-2.
Results: All placentas showed unusual pathology abnormalities that include chronic histiocytic intervillositis with presence of CD68+ macrophages, syncytiotrophoblast necrosis and positivity of the syncytiotrophoblast for SARS-CoV-2 antigen or RNA. Notably, Hofbauer cells do not resulted infected by viral particles as outlined by double staining for CD163+(marker for Hofbauer cells) and ISH for SARS-CoV-2 (spike protein) RNA. Foetal autopsies didn't show any malformations. The lung of the first foetus only showed interstitial pneumonia features with vascular congestion and neutrophilic infiltrate. Viral genome sequencing identified the lineage B.1.1 in two women who delivered in March 2020, while in the third positive woman, who aborted during the third pandemic wave, was detected B.1.36 lineage.
Conclusion: We gave evidence that SARS-CoV-2 vertical transmission mother-foetus is possible also in second trimester of pregnancy and in asymptomatic pregnant women and can lead to severe morbidity. We found a specific histologic pattern in all infected placentas and our studies ruled out the pathogenic involvement of Hofbauer cells. Furthermore, as far as we know, it does not appear that different genetic variants of the virus affect its possible transplacental vertical transmission.

OFP-04-011
Diagnostic value of ITS sequencing in mucormycosis – a retrospective single-centre study
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Background & objectives: Mucormycosis is a fast-progressing disease with a high mortality rate. Rapid and accurate diagnosis is of utmost importance, but microbiological culture may lack sensitivity. Molecular techniques are therefore increasingly recommended; however, real-world data about their value are still sparse.
Methods: Between 2015 and 2022, we performed internal transcribed spacer (ITS) sequencing in 491 tissue and body

fluid samples from 432 patients. Clinical, pathological, and microbiological data were extracted from medical records and correlated with sequencing results.
Results: Taxa from the order Mucorales could be detected in 11/432 patients. 7 of these 11 patients were male, and the median age was 54 years (range 5-74 years). All 11 patients had severe comorbidities (9 with hematological cancers and 2 with other cancers; 1 had additionally COVID-19). Specimen sites included lung (6x), upper respiratory tract (2x), myocardium (2x), and soft tissue (1x). The most commonly detected Mucor species was Rhizopus microsporus (5x), followed by Lichtheimia corymbifera (2x), Rhizopus oryzae (1x), Actinomucor elegans (1x), Rhizomucor pusillus (1x), and Rhizomucor miehei (1x). Microbiological culture was performed in 7 cases, always yielding negative results.
Conclusion: The rising incidence of mucormycosis in patients with COVID-19 has raised awareness of this rare but lethal fungal infection. Due to the fast-progressing clinical course of mucormycosis, early diagnosis is key. Our study demonstrates that ITS sequencing is a reliable tool in diagnosing this devastating disease with a much higher sensitivity than microbiological culture. Thus, especially when combined with histopathology, ITS sequencing enables a rapid and accurate diagnosis of mucormycosis, with important implications for clinical practice.

OFP-04-012
Comprehensive analysis of bronchoalveolar lavage in severe COVID-19 patients
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Background & objectives: A few and inconclusive data are reported about the broad analysis of bronchoalveolar lavage (BAL), a demonstrated safe procedure in COVID-19 patients. We aim to report the comprehensive cytological, microbiological, and molecular analysis of BAL from critically ill COVID-19 patients.
Methods: BAL fluid was obtained from 12 COVID-19 patients admitted in the intensive care unit in the second wave (February 2021 - May 2021). BAL from lung transplant recipients (n=12), and lung donors (n=12), represented the 'fragile' and 'healthy' control groups, respectively. Cytological analysis, microbiological investigation (culture and molecular determination), and wide cytokine expression analysis using Real-Time PCR were performed.
Results: SARS-CoV-2 (mainly A variant) was positive only in severe COVID-19 patients. Microbiological analysis showed bacterial coinfections with K. pneumoniae, P. aeruginosa, and S. aureus in COVID-19 and transplant patients. Fungal coinfections were found only in COVID-19 patients (C. albicans and A. fumigatus). Molecular analysis identified the viral coexistence of Epstein Barr virus, Cytomegalovirus, and Herpes simplex virus type-1 in both COVID-19 and lung transplant groups; lung donors were negative for all microorganisms. The molecular cytokine profile in the COVID-19 group was remarkable for a low expression of interferon-gamma (IFN-γ), and significantly overexpression of interleukins (IL) IL-1β, and IL-9.
Conclusion: The full comprehensive analysis of BAL is crucial to specifically detect frequent coinfections in patients with severe COVID19 pneumonia. IL-1β, and IL-9 overexpression could represent a possible therapeutic target. Although confirmation is required on larger case series, the obtained results underline a complex and overall different inflammatory profile in COVID-19 BAL in comparison to blood or upper airways as reported in the literature.

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OFP-05-001
Outcomes according to consensus molecular subtypes of urothelial carcinoma after neoadjuvant chemotherapy in the GETUG-AFU V05 VESPER trial
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Background & objectives: The molecular subtypes of urothelial carcinoma may impact the outcomes after neoadjuvant chemotherapy in muscle invasive bladder cancer. Our aim was to assess the 3-year progression free survival according to the consensus molecular subtypes within the prospective Vesper clinical trial.
Methods: 493 patients received dd-MVAC or GC after randomization in the VESPER trial (NCT01812369). This ancillary study was restricted to neoadjuvant treated patients. To take into account intra-tumoural heterogeneity, we performed 3' mRNA sequencing of distinct tumour areas when morphology and/or multiplexed GATA3 Cytokeratin 5/6 TUBB2a immunostaining highlighted distinct pattern. Consensus molecular subtype was determined for each area from transcriptomic profile.
Results: Out of 296 cases, 97 with heterogeneous immunostaining were selected for multiple sampling. For 251 cases, one single subtype was detected per tumour (i.e. pure): 37 luminal papillary, 60 luminal unstable, 17 luminal non specified, 53 stroma-rich, 81 basal/squamous and 3 neuroendocrine-like. 45 cases were mixed with 2 or more subtypes (27 with basal/squamous component). Pathological response was not different between pure subtypes but was decreased for mixed cases (OR adjusted for randomization arm: 0.43, 95% CI 0.19-0.96, p=0.040). Compared with luminal and stroma rich, the 3yr PFS was decreased for basal/squamous, either pure or admixed with another subtype (HR adjusted for randomization arm: 2.16, 95% CI 1.46-3.20, p<1e-3).
Conclusion: In the VESPER trial, the basal/squamous molecular subtype (pure or mixed) is associated with a decreased 3 yr PFS after neoadjuvant chemotherapy. Further studies will investigate the molecular basis associated with this adverse feature and explore new systemic treatments for the basal/squamous subtype.
Funding: French governmental grant (Institut National du Cancer)

OFP-05-002
Clinicopathologic and molecular spectrum of testicular sex-cord stromal tumours not amenable to specific histopathologic subclassification
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Background & objectives: Testicular neoplasms of sex-cord or stromal derivation that cannot be definitively classified into a specific tumour subtype are designated "unclassified sex-cord stromal tumours" (USCSTs). Given the rarity of USCSTs, their clinicopathologic and molecular features remain largely unexplored.
Methods: This study evaluated a multi-institutional series of testicular USCSTs to better define the spectrum of tumours comprised in this diagnostic category. Twenty-six USCSTs from 25 patients

diagnosed between 1996 and 2021 were evaluated by review of histology slides, review of clinicopathologic data and massively parallel DNA sequencing. Further evaluation by comparative methylation profiling was conducted on a subset of tumours.
Results: Cytomorphologic patterns included monophasic spindled (5/26), monophasic epithelioid (10/26), and biphasic or mixed (11/23). Histopathologic features suggestive of malignancy (size >5 cm, invasive growth, necrosis or prominent mitotic activity) were seen in 11 cases. DNA sequencing was successful in 19 tumours. Two molecular patterns emerged, including recurrent whole-chromosome gains of 3, 6, 7, 8, 9, 12, 14, 15, 17 and 20. (5/23), and pathogenic mutations in the WNT signalling pathway (8/19). A subset of WNT-altered tumours showed methylation profiles consistent with Sertoli cell tumours, NOS. Follow-up for fifteen cases included 9 patients alive without disease (median 9 mo), 4 alive with disease (median 7 mo), and 2 dead of disease.
Conclusion: The results of this study demonstrate that USCSTs comprise tumours with variable clinicopathologic features and molecular alterations. Two major trends emerged in the cytologic and molecular analysis that facilitated re-classification of ~40% tumours into distinct sex cord stromal tumour entities, including a significant proportion driven by mutations of WNT pathway genes (CTNNB1, APC), some of which could be reclassified as Sertoli Cell tumours, NOS. The remaining unclassified tumours were enriched for aggressive pathological features and malignant clinical behaviour.

OFP-05-003
Defining lineage plasticity in androgen indifferent prostate cancer
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Background & objectives: Combined alterations in TP53 with RB1 and/or PTEN characterize aggressive variant prostate cancers (AVPC) and are associated with androgen indifference and lineage plasticity. A measurable definition of lineage plasticity is needed to enable the development of 'plasticity-inhibiting' therapies.
Methods: MDA PCa-177-B (AR-negative, basal expression profile) and MDA PCa-189-1 (AR-positive, luminal expression profile) are AVPC PDX models derived from one patient's prostate tumour, before and after chemotherapy respectively. They share a p.Y163N Tp53 mutation, suggesting a common clonal origin. We performed scRNAseq, DNA methylation profiling and H3K27me3, H3K27ac and H3K4me3 ChIPseq to identify a shared candidate signature of lineage plasticity.
Results: scRNAseq analysis revealed clusters with a "high-plasticity cell state" (HPCS), in each PDX, characterized by a diversity of lineage identities, similar to that associated with aggressive features and progression in lung cancer mouse models (Marjanovic et al., 2020). ChIPseq of histone markers (H3K27ac, H3K27me3, H3K4me3) and DNA methylation profiling showed shared chromatin profiles at enhancer and super-enhancer regions linked to lineage plasticity events. Taken together, these results suggest that lineage plasticity events drive the evolution of lethal PCa and identified a cell plasticity signature for AVPC.
Conclusion: We identified shared HPCS clusters and chromatin profiles in phenotypically distinct PDX, which may serve as candidate signatures of lineage plasticity. Ongoing analyses are determining the association between the chromatin profiles and the HPCS clusters to arrive at clinically applicable markers. Future studies will determine the effect of drugs presumed to target plasticity on these candidate signatures. These markers will be tested as prognostic indicators and may help identify tumours destined to follow the aggressive variant pathway of PCa progression.
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OFP-05-004
RNA-seq profiling of upper tract urothelial carcinoma: relevance of the bladder cancer consensus molecular classification, molecular heterogeneity, and differential immune signatures
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Background & objectives: Extensive analyses of transcriptomic data in large datasets of muscle-invasive bladder cancer (MIBC) have resulted in a consensus molecular classification. Our objective was to determine the relevance of the consensus classification in ≥pT1 upper tract urothelial carcinoma (UTUC).
Methods: We constituted a novel cohort of ≥pT1 UTUC patients with clinico-pathological data. We evaluated GATA3-CK5/6-TUBB2B in multiplex, CK20, p16, MMR proteins and PD-L1 expression by immunohistochemistry (IHC). Heterogeneity was assessed morphologically and/or with subtype marker IHC expression. FGFR3 mutational status was determined using pyrosequencing. Gene expression was profiled using 3' RNA-seq for each tumour, including multiple samples in heterogeneous cases.
Results: In our cohort of 66 patients with ≥pT1 UTUC, the majority were men (77.3%) with pT1 (35.4%) or pT3 (46.2%) stage disease. FGFR3 mutations and MSI-H status were identified in 41.5% and 4.7% of patients, respectively. The consensus classifier was robustly applicable to UTUC samples and reflected intrinsic subtypes, determined by unsupervised clustering. The proportion of LumP samples (68.4% in ≥pT1, 57.2% in ≥pT2 UTUC) was significantly higher than in MIBC. Ten patients (15.2%) harboured areas of distinct consensus classes. Consensus classes were associated with FGFR3 mutational status, pT stage, morphology and subtype IHC. The majority of LumP tumours were characterized by low immune infiltration and low PD-L1 IHC expression.
Conclusion: We characterized a novel cohort of 66 patients with ≥pT1 UTUC based on morphology, immunohistochemistry, FGFR3 mutation status and transcriptomics. The consensus classification of MIBC efficiently classified UTUC samples, and highlighted intratumoural molecular heterogeneity. In contrast to MIBCs, the majority of ≥pT1 UTUC patients harboured a LumP tumour, a class mostly characterized by low immune infiltration, low PD-L1 expression and a high proportion of FGFR3 mutations. These findings may suggest differential response to novel therapies between UTUC and MIBC patients.

OFP-05-005
Spatial interplay between TIM3+, PD-L1+, PD-1+ and CLTA-4+ immune/ tumour cells using 18+1 BLEACH&STAIN mfIHC in more than 5 000 tissue samples
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Background & objectives: A combination of different immune-checkpoint-inhibitors (ICIs) have shown remarkable success in several tumour entities. However, the likelihood of positive response to ICIs is poor in most tumour entities. Little is known about the spatial orchestration between immune checkpoint+ cells.
Methods: To study the spatial interplay between TIM3, PD-L1, PD-1, and CTLA-4 expression on lymphocyte-, macrophage subsets, dendritic cells, in relation to panCK+ malignant cells, and other structural tumour compartments, a 18 marker BLEACH&STAIN multiplex fluorescence immunohistochemistry approach was used to analyse >5000 carcinoma samples from 40 different carcinoma entities. A deep learning-based framework for image analysis was used.
Results: TIM3, PD-1, PD-L1, and CTLA-4 expression was successfully quantified on tumour cells (panCK+), cytotoxic T-cells (CD3+CD8+), T-helper cells (CD3+CD4+), regulatory T-cells (CD3+CD4+FOXP3+), M1 and M2 macrophages (CD68+CD163+/ CD68+ CD163-) and dendritic cells (CD11c+). TIM3 as well as CTLA-4 expression on CD3+CD8+ cytotoxic T-cells and CD3+CD4+FOXP3+ regulatory T-cells showed a spatially more diverse expression pattern – particularly in bladder cancer – compared to PD-1 expression on all analysed T-cells subsets that was consistently accompanied by PD-L1 expression on immune and tumour cells ($p<0.001$). A high density of immune checkpoint positive T-cells, macrophages and dendritic cells was linked to low pT stage ($p\leq0.014$ each).
Conclusion: BLEACH&STAIN facilitates deep profiling of 18 biomarkers in more than 40 different carcinoma entities and revealed complex changes in the spatial orchestration of a wide range of immune cell subsets that were driven by the expression profile and composition of TIM3, PD-L1, PD-1 and CTLA-4.

OFP-05-006
Successful deployment of an AI solution for prostate biopsies diagnosis in clinical practice
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Background & objectives: This study aimed to prospectively evaluate the performance and clinical utility of the AI-based Galen Second Read Prostate workflow solution on detection of prostate adenocarcinoma in real world clinical routine use.
Methods: A prospective, single-centre observational diagnostic study including digitized histopathology slides of all consecutive prostate core needle biopsies (CNBs), TRUS and MRI-targeted, was performed. Slides were blindly processed by the AI solution, while, in parallel, pathologists reviewed the cases. Alerts were triggered in case of discrepancies between the AI results and initial pathologist's diagnosis, prompting a second review by the pathologist.
Results: Five senior pathologists participated in the study and reported on 109 prostate CNBs comprising 2,684 H&E slides, 60% of which were MRI-targeted biopsies that had up to 66 H&E slides/case. Analysis was performed at block level, 109 cases comprised 986 blocks, 190 (19.3%) were reported as adenocarcinoma, 2 (0.2%) as ASAP and 794 (80.5%) were benign. The AI solution demonstrated extremely high performance for detection of cancer with AUC = 0.994 (95% CI: 0.991-0.997), sensitivity of 96.9%, specificity of 94.96% and NPV of 99.21%. Moreover, following the second review by the pathologists, five alerted cases were revised from benign to cancer, leading to 4.6% decrease in diagnostic error rate.
Conclusion: This prospective study reports the successful deployment of the Galen Prostate diagnostic support solution, in routine clinical practice. The AI solution enabled 100% Quality Control on prostate biopsies and increased diagnostic accuracy and patient safety, decreasing diagnostic errors by 4.6% and preventing missed cancers. Thus, AI solutions could be used as significant aiding tools for pathologists in clinical decision-making in routine pathology practice.

OFP-05-007
The new entities LOT and EVT among oncocytic tumours of the kidney: a retrospective mono-institutional experience with re-analysis of 16 cases
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Background & objectives: Low-grade oncocytic and eosinophilic vacuolated tumours (LOT and EVT) have been proposed as distinct entities with low malignant potential in the spectrum of renal oncocytic neoplasms. We report 16 further cases of these rare and controversial categories with clinico-pathological description.
Methods: Oncocytomas (RO), Hybrid Tumours (HT), and Chromophobe carcinomas (ChRCC) diagnosed in our Institution from 2015 to 2021 were retrospectively reviewed. On all selected cases, we performed immunohistochemical analysis for CD117 and CK7 to identify LOTs and EVTs. Histological features, phenotype, molecular profile, and clinical data were recorded.
Results: From 431 tumours, 7 LOTs and 9 EVTs were identified. Male/female ratio was 1:1,3 and 2:1, with median age of 67 and 58 yrs, and median size of 2,7 and 4,2 cm, respectively. LOTs overlapped RO/ChRCC with eosinophilic cytoplasm and perinuclear halos; EVTs showed intracytoplasmic vacuoles and atypical nuclei. LOTs were positive for CK7, CKpan, CD63, AMACR, CD15 (but CD117 negative overlapping ChRCC). EVT were positive for CD117, AMACR, CKpan, and CD10 (but CK7 negative/focally+, opposed to LOT/ChRCC). Interestingly, EVTs CKpan immunoreactivity often reflected a biphasic cellularity (6/9 cases). Rearranged genes in mTOR pathway were occasionally found in both tumours. Both LOTs and EVTs behaved indolently (follow-up 9-72 months).
Conclusion: Here, we described a further group of LOTs and EVTs from a retrospective cohort analysis. Our data confirm LOT and EVT as emerging entities with peculiar histological features, a specific immune-profile, and indolent behaviour, which should be identified among "pink" tumours of the kidney. In the future, these tumours deserve further clinico-pathological studies for promoting the awareness and improving classification of these new categories that will be described in the 2022 Genitourinary WHO classification.

OFP-05-008
A novel pT1 substaging system for high-grade urothelial bladder carcinoma: a prospective mono-institutional confirmatory progression risk analysis
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Background & objectives: The Rete Oncologica Lombarda (ROL) system for substaging pT1 high-grade (HG) urothelial carcinoma (UC) showed high predictive value for progression after

transurethral resections (TUR) in retrospective studies. We aimed to validate ROL system on a prospective large mono-institutional series.
Methods: From 2013 to 2020, we adopted ROL for all patients with pT1HGUC on TUR and collected clinico-pathological data. We employed a cut-off of 1 mm (or diameter of an objective 20x high-power field) to stratify tumours in ROL1 and ROL2, corresponding to one invasive focus or multiple foci extending together for <1 mm and for >1 mm, respectively.
Results: A total of 229 confirmed pT1HGUC were analysed. Mean age was 73yrs, with male predominance (74.7%); 70 tumours showed multifocality (30.57%), 33 divergent differentiation (14.4%). Associated CIS and vascular invasion occurred in 14% and 9% of cases. ROL was feasible in all but one case (99.6%): 94 cases were ROL1 (41%) and 134 ROL2 (59%). At a median follow up of 23 months (IQR 12.33-38.5), 59 patients had recurrence (25.76%) and 37 progression (16%). ROL predicted progression in univariate (OR= 3.58, 95% CI 1.50-8.56; p=0.004) and multivariate (OR= 2.95, 95% CI 1.11-7.87; p=0.03) Cox regression analysis. At Kaplan-Meier estimates, ROL showed correlation with progression (p<0.01), but not with recurrence (p>0.05).
Conclusion: Our results confirmed the strong predictive role of ROL system for progression in pT1HGUC on a large prospective series. The management of pT1HGUC patients is still a challenging issue in urological practice, and depth and amount of lamina propria tumour invasion is a key prognostic variable. We foster the application of ROL system for substaging T1HGUC, a simple and feasible method alternative to pT1a/b that might identify high-risk patients and drive urological decision-making.

OFP-05-009
Computational analysis of nuclear features as a grading tool for urothelial carcinoma
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Background & objectives: Tumour grade determines prognosis in urothelial carcinoma. The two-tiered classification of low and high grade is based on nuclear morphological features. The purpose of this study is to assess the value of computer-based image analysis tool for urothelial carcinoma grading.
Methods: 400 images of urothelial tumours were graded by five pathologists and one uropathologist using a scale of 1 (lowest grade) to 5 (highest grade). A computer algorithm was used to segment the nuclei and to provide 40 morphometric parameters for each nucleus, which were used to establish the grading algorithm. Grading algorithm was compared to pathologists' agreement.
Results: In the training cohort 10 different nuclear parameters showed >85% agreement with the uropathologist's score. All 10 parameters showed >85% agreement with the uropathologist's score in the independent validation cohort. Three parameters showed 94.5% agreement in the validation cohort. The agreement of the pathologists with the uropathologist ranged from 88.5% to 97.5%. Unexpectedly, the parameter that was most associated with grade was the 10th percentile of the nuclear circumference, and high grade was surprisingly associated with lower 10th percentile nuclei, caused by the presence of more inflammatory cells in the high-grade tumours.
Conclusion: Quantitative nuclear features could be applied to quantitate urothelial carcinoma grade. AI assisted grading systems could explore new nuclear parameters with better correlation to grade than those currently used.

OFP-05-010
Tumour microenvironment immune markers associated with pathologic response to neoadjuvant pembrolizumab in muscle-invasive bladder cancer (Pure-01 trial: an open label, single arm, Phase II study)
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Background & objectives: PURE 01 trial enrolled 143 patients who received 3 cycles of pembrolizumab (IO) every 3 weeks before radical cystectomy. We compared tumour-microenvironment immune markers expression in pre-IO TURB specimens in complete/major and non-responders to identify features associated with pathologic response.
Methods: Immunohistochemistry expression of CD3, CD8, CD68-KP1, CD163, CD20, PD1, PD-L1, MHC-I, HLA-DR and Beta2-microglobulin on tumour cells and tumour-microenvironment was evaluated in 18 complete responders (CR: ypT0), 6 major responders (MR: ypTa/ypT1) and 19 non-responders (NR: ypT2/ypT3, N0 or N+) with a semiquantitative count of the positive cells percentage (0, 0%; 1, <25%; 2 , 25-50%; 3, 51-74%; 4, 75-100%).
Results: Seven markers (CD8, stromal or tumour PD-L1, HLA-DR on tumour cells and B2M on tumour cells) were significantly more expressed (p value range: 0.001 to 0.048) on TURB lesions from responders (CR + MR) compared to non responders (N0 or N+). In addition to such markers, patients achieving a CR, compared to non responders, showed significantly higher expression of CD68 and CD163, of PD-1 on lymphocytes, as well as of tumour MHC-I molecules. Comparison of lesions from patients with CR vs MR revealed significant differences for CD3, CD163, PD-1 and MHC-I, all these markers being more frequently expressed on the former group compared to the latter.
Conclusion: The tumour immune microenvironment of pre-therapy TURB lesions of patients achieving a complete or major pathologic response after neoadjuvant pembrolizumab shows significant enrichment for T cells and myeloid cells, for stromal or tumour PD-L1 as well as increased MHC-I expression on tumour cells compared to lesions from non responders.
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OFP-05-011
CD163+ M2 macrophage tissue infiltration and urinary soluble CD163 in IgA nephropathy
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Background & objectives: Macrophages play an important role in renal inflammation and fibrosis. We evaluated M2 macrophage (CD163+) infiltration in IgAN and correlated it with other parameters of monocyte activation including monocyte-derived circulating microparticles (MMPs), urinary soluble CD163 (sCD163), KIM-1 and MCP-1.
Methods: Twenty-one IgAN, classified with Oxford MEST-C score, two age and sex-matched healthy and four Lupus Nephritis (LN) disease controls were included. Plasma MMPs (AnnexinV+/CD14+), quantified by flow cytometry were estimated as % of total MPs. CD163 immunohistochemistry (clone-EP324) was performed on renal biopsies and quantified in glomeruli and the tubulo-interstitium. Urinary sCD163, KIM-1 and MCP-1 levels were estimated by ELISA.

Results: The mean age in IgAN was 34±10 years; fourteen were males; mean s. creatinine 3.1±1.8mg/dl and 24-hour proteinuria 2.5±0.8gm/day. Mean circulating MPs levels in IgAN, LN and healthy were 8.1x105/µl, 6.7x103/µl and 2.4x105/µl, respectively. MMPs in IgAN constituted 54% of total MPs. Mean urinary sCD163, KIM-1 and MCP-1 in IgAN, LN and healthy controls were 11.4ng/ml, 27ng/ml and 0.18ng/ml; 2.5ng/ml, 1.84ng/ml and 0.37ng/ml; 2.3ng/ml, 7.05ng/ml and 0.13ng/ml respectively. CD163+ macrophages in IgAN were 4.8±5.1/glomeruli and correlated significantly with presence of endocapillary hypercellularity (E1) and crescents (C2). The mean number of CD163+ cells in tubulo-interstitium were 69±35/hpf. Urinary sCD163 levels correlated significantly with number of CD163+ cells in glomeruli.
Conclusion: We found monocyte activation and M2 (CD163+) macrophage tissue infiltration in IgAN. M2 macrophage tissue infiltration and urinary sCD163 levels correlate with proliferative glomerular changes suggesting its role in the early active stage of renal disease. Urinary sCD163 may act as non-invasive biomarker in assessing active proliferative lesions in IgAN.
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OFP-05-012
Podocyte injury – aristolochic acid nephropathy in mice
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Background & objectives: Aristolochic acid nephropathy is a chronic tubulointerstitial renal disease in which important symptoms can be proteinuria and albuminuria. In this study, we examined glomerular morphometric features and protein excretions in NMRI mice treated with aristolochic acid I.
Methods: Experimental animals were treated intraperitoneally with 10 mg/kg aristolochic acid I for seven consecutive days, vehicle control received 2.5% polyethylene glycol 400, and the control received saline only. The experiment lasted 60 days, with several different euthanasia time points for light and transmission electron microscopy glomerular injury assessment. Nestin and WT1 were used as immunohistochemical markers for identifying podocytes.
Results: For every euthanasia time point, mean mesangial score in glomeruli between aristolochic acid treated mice and control groups showed no significant difference. Furthermore, glomeruli of aristolochic acid treated mice had a decreased number of WT1 positive podocytes, lower cytoplasmic nestin expression and area fraction than mice that received 2.5% polyethylene glycol 400 and saline. In addition, ultrastructural changes of podocytes in the aristolochic acid treated group, observed under a transmission electron microscope, indicate foot process effacement, karyopyknosis, and thickening of the glomerular basement membrane with electron-dense deposits. Significant albuminuria occurred in experimental animals from later experiment phases compared with control groups.
Conclusion: Our findings suggest that exposure to aristolochic acid I induce glomerular damage by reducing the number of podocytes and affecting the normal functioning of the glomerular filtration barrier, thus serving as valuable data in further research related to the treatment of aristolochic acid nephropathy.

OFP-05-013
Deep learning-based histopathologic segmentation of peritubular capillaries in kidney transplant biopsies
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Background & objectives: Peritubular capillaritis scoring is an important feature for diagnosing antibody-mediated rejection (ABMR). This task suffers from interobserver variability and might benefit from automation. As a first step towards automatic peritubular capillaritis quantification, we developed a peritubular capillary (PTC) segmentation algorithm.
Methods: Kidney transplant biopsies (n=54) were 1) stained with periodic-acid Schiff (PAS), 2) scanned into whole-slide images (PAS WSI), 3) re-stained using CD34-antibody, and 4) scanned again (CD34 WSI). Guided by the CD34 WSI, a pathologist manually annotated approximately 19.000 PTCs on the PAS WSI. The dataset was used to train (n=40) and test (n=14) a deep learning (DL)-based network.
Results: We developed a U-net DL network architecture, with an Efficientnetb2 backbone and a pre-trained encoder using ImageNet. The network was trained using 12,000 patches (512 x 512 pixels) per epoch. Various techniques were applied to prevent overfitting and to improve the model's generalization. Training the network on a resolution of 0.5 µm/pixel using a non-PTC/PTC ratio of 3:1 yielded an F1 score of 0.74, with a precision and recall of 0.78 and 0.70, respectively. We observed reduced performance on cases with prominent interstitial alterations, as PTCs become less recognizable, while certain pathologies mimic PTCs (e.g. atrophic tubules, matrix deposition).
Conclusion: This study presents a DL-based algorithm for the segmentation of PTCs in PAS-stained kidney transplant biopsies. This is a first step towards a more accurate, reproducible scoring of peritubular capillaritis using DL. The results highlight the applicability of DL for clinical use to guide pathologist in routine diagnostics. Next steps will include incorporation of this algorithm in the development of a fully automated Banff classification algorithm, as part of our DIAGGRAFT project, funded by the Dutch Kidney Foundation.

OFP-05-014
Training a deep learning model for quantification of fibrosis in non-neoplastic kidney biopsies - a feasibility study
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Background & objectives: Interstitial fibrosis is a key prognostic marker of kidney disease. Accurate quantification is therefore important. The study aim is to develop a deep learning algorithm for quantification of interstitial fibrosis that can be used on haematoxylin-eosin (HE) stained kidney sections.
Methods: To create annotated training data, tissue sections were first stained with HE and then - after destaining - with sirius red. Masks of the sirius-red stained fibrosis areas were created using conventional image analysis. A deep learning algorithm was trained with these masks to measure fibrosis in the identical HE stained slide. The model performance was validated with the F-statistics.
Results: The advantage of this approach is that time and resource consuming manual annotations of the fibrosis areas are avoided but supervised learning still can be performed. A deep neural network based on U-Net was used for image segmentation. HE and the mask images were divided into tiles (512 x 512 pixels). Feasibility of the method was tested in a pilot study with 10 representative renal biopsies with varying degrees of interstitial fibrosis. The deep

learning model was able to learn from the masks and found the fibrotic areas in the HE stained digital sections with an associated F-score of 0.76 in the validation data set.
Conclusion: The proposed method is feasible and can provide a rapid and reproducible quantitative result for interstitial fibrosis in HE stained kidney biopsies. We will train and fine-tune the deep learning model with more data and expect to see even better performance. The model will then be tested for robustness in an independent cohort.
Funding: Western Norway Regional Health Authority

OFP-05-015
Relationship between immunosuppressive treatment, morphology, and gene expression in T-cell-mediated rejection of the transplanted kidney
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Background & objectives: Belatacept preserves renal function better than calcineurin inhibitor (CNI)-based immunosuppression. However, higher frequency of first-year T-cell-mediated rejection (TCMR) in belatacept-treated patients hampered the adoption of costimulation blockade. We set out to study the patomechanism of TCMR in this patient group.
Methods: Formalin-fixed paraffin-embedded renal biopsy samples were analysed from 92 patients stratified by histopathologic diagnosis (TCMR, borderline changes, or normal) and immunosuppression regimen (belatacept, CNI). We applied gene expression analysis and whole slide inflammatory cell quantification to assess the impact of belatacept on intragraft immune signature.
Results: Ninety-one percent of genes overexpressed in TCMR showed significant correlation with whole-section inflammatory load. There were 27 genes that had a positive association with belatacept treatment. These were mostly related to myeloid cells and innate immunity. Genes negatively associated with costimulation blockade (n=14) could be linked to B-cell differentiation and proliferation.
Conclusion: We concluded that expression levels of genes characteristic of TCMR are strongly interconnected with quantitative changes of the biopsy inflammatory load. Our results might suggest differential involvement of the innate immune system, and an altered B-cell engagement during TCMR in belatacept-treated patients relative to CNI-treated referents.

OFP-06 | Joint Oral Free Paper Session Pulmonary Pathology / Thymic and Mediastinal Pathology

OFP-06-001
Multi-case learning model for predicting EGFR and KRAS gene mutation in non-small cell lung cancer
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Background & objectives: To develop an artificial intelligence learning model for predicting EGFR and KRAS gene mutation in non-small cell lung cancer (NSCLC) by integrating the information of pathological images.
Methods: 934 NSCLC biopsy whole slice images (WSIs) were collected. EGFR and KRAS gene mutation were detected by next-generation sequencing (NGS). The WSIs were divided into training set, validation set and test set, and a transformer-based multi-instance learning (T-MIL) model was developed to predict EGFR and KRAS gene mutation. Moreover, T-MIL model was compared with the other models.
Results: The area under the cure (AUC) was 0.711 by using T-MIL model to predict EGFR gene mutation, and the sensitivity, specificity, the positive predictive value (PPV), and the negative predictive value (NPV) were 81.6%, 55.6%, 61.7%, 77.5%, respectively. For predicting KRAS gene mutation, T-MIL model AUC value was 0.601, and the sensitivity, specificity, PPV, and NPV were 56.2%, 65.1%, 13.2%, 94.0%, respectively. Compared with other learning models, including attention-based multiple instance learning (A-MIL) and RNN architecture for bag representation generation in MIL (RNN-MIL), T-MIL model demonstrated better performance. For EGFR gene mutation, the AUC value were 0.485, 0.6767, 0.711 respectively, and 0.5753, 0.5593, 0.601 respectively for KRAS gene mutation.
Conclusion: We developed a T-MIL learning model for predicting NSCLC gene mutation, and demonstrated well performance. Its performance in predicting EGFR mutation was better than KRAS(AUC 0.711 vs 0.601). Our research proved that the performance of T-MIL learning model through pathological images was better than A-MIL and RNN-MIL model in predicting key driver gene mutation.

OFP-06-002
Three cancer associated fibroblasts subtypes are associated with histological features, immune environment and prognosis in resected non-small cell lung cancer (NSCLC)
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Background & objectives: Three cancer-associated fibroblasts (CAFs) subtypes have been recently identified in breast cancer, characterized by the differential expression of FAP and ANTXR1. We aimed to assess, in NSCLC, the association of these CAF subtypes with histological features, immune environment and prognosis.
Methods: Expression of FAP and ANTXR1 was assessed by immunohistochemistry (H-score) on tissue micro-array built from a retrospective series of 186 NSCLC surgical samples. Three CAF subtypes were defined by the differential expression of FAP and ANTXR1 (FAPLow; FAPHigh/ANTXR1Low; FAPHigh/ANTXR1High) and correlated with histological features, immune environment (assessed by CD8, CD4, and FOXP3 expression) and prognosis.
Results: 82 adenocarcinomas (ADC) and 104 squamous cell carcinomas (SCC) were included. We found a predominance of FAPHigh/ANTXR1High CAFs in SCC and FAPLow CAFs in ADC ($p<0.001$). In SCC, FAPhigh/ANTXR1low CAFs were associated with a higher CD8/CD4+CD8 ratio ($p=0.02$), but there was no correlation of CAFs subtypes and the immune environment in ADC. In ADC, a higher proportion of FAPHigh/ANTXR1High CAFs was detected in poorly differentiated tumours ($p<0.001$). Finally, in ADC, tumours with FAPHigh/ANTXR1High CAFs were associated with a poorer disease-free survival in patients that did not have adjuvant chemotherapy ($p<0.05$). In SCC, no association of CAFs subtypes with disease free survival was found.
Conclusion: These three CAF subtypes are differentially expressed between ADC and SCC, and are associated with the immune environment in SCC and with tumour differentiation and disease free survival in ADC. These preliminary results suggest that FAP and ANTXR1 could be used as prognostic biomarkers in ADC.

OFP-06-003

Some aspects of lung fibrosis in COVID-19

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Background & objectives: Lung fibrosis is considered as one of the most significant lesions in late stages of acute COVID-19 infection and post Covid syndrome. Many questions related to its pathogenesis and sequels remain unclear.
Methods: We studied lungs in 16 lethal cases with known genotype of SARSCOVi2, nearby routine methods the slices were stained according Mallory, IHC included sera against macrophages CD68+, CD163+ and collagens of 1 and 3 types. In 14 cases the slices, stained for CD68+ cells were scanned and then counted with the help of morphometric program and related to square.
Results: We found that fibrosis was practically equally expressed in all cases nevertheless exact duration of the disease, which was difficult to evaluate in several cases. Genotype of the virus. Collagen was of both types 1 and 3, with the prevalence of the latter. The number of CD68+ macrophages varied from 27 till 93/ mm2. Notable that both, collagen 1 and 3 were detected not only typical fibres but also in cytoplasm of macrophages. In these regions accumulation of CD163+ macrophages was noted. In one case cirrhotic changes of the lung developed in previously healthy man in less than a year after first disease (finished clinical recovery) during the second episode.
Conclusion: Thus, many issues of lung fibrosis of clinical importance have to be additionally studied.

OFP-06-004

Evaluation of acquired resistance to sotorasib in patients with KRAS p.G12C-mutated non-small cell lung cancer: biomarker analysis using plasma from the CodeBreaK 100 trial

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Background & objectives: The CodeBreaK 100 trial supported approval of sotorasib, a specific, irreversible KRASG12C inhibitor, for adults with *KRAS* p.G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with systemic therapy. We consider acquired resistance to sotorasib.
Methods: In the Phase 1/2 CodeBreaK 100 trial, patients with advanced *KRAS* p.G12C-mutated NSCLC received sotorasib monotherapy 960 mg once daily. The primary endpoint was objective response rate (ORR). An exploratory endpoint examined genomic alterations, absent at baseline but present at disease progression. Plasma samples collected at baseline and progression were analysed with the 23-gene Resolution Bioscience ctDx Lung™ assay.
Results: The ORR in 174 sotorasib-treated patients was 41%. Median progression-free survival and median overall survival were 6.3 and 12.5 months, respectively (median 22.5-months follow-up). Of 67 patients with sequenced plasma samples, 19 (28%) exhibited at least one newly acquired genomic alteration; 7 (10%) had more than one mutation. Variants were detected across multiple genes and pathways. The receptor tyrosine kinase (RTK) genes were the most prevalent putative mechanism of resistance, with alterations apparent in 16 (24%) patients, including 6 (9%) with *EGFR* gene mutations. PI3K/AKT/mTOR, secondary *RAS,* and ERK/MAPK mutations were evident in 3 (4%), 2 (3%), and 1 (1%) patient, respectively. Six (9%) patients had undetectable tumour shedding.
Conclusion: Genomic alterations observed in *KRAS* p.G12C-mutated NSCLC patients treated with sotorasib suggest acquired resistance can arise via a range of mechanisms; however, new RTK alterations were frequently apparent at disease progression. This highlights a potential benefit of combining sotorasib with upstream inhibitors of RTK, such as SHP2 or EGFR inhibitors. Overall, patterns of acquired resistance suggested by DNA analysis of plasma samples at baseline and disease progression support the development of KRASG12C inhibitor combination therapies.
Funding: Amgen Inc.

OFP-06-005

PD-L1 22C3 Lab Developed Test (LDT) for the Ventana's BenchMark platform is clinically effective in NSCLC and can be used safely instead of the FDA approved DAKO platform: nation-wide experience and real-life validation (2016-2022)

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Background & objectives: PD-L1 companion diagnostic by Dako (22C3 clone), for immunotherapy patient stratification, is a common requirement. Our group described a 22C3-based LDT for the Ventana platform, and showed its reliability and reproducibility (2016). However, real-time data about the reliability is lacking.
Methods: Ventana's BenchMark immunohistochemistry (IHC) platform is widely used around the world. Between July 2016 and January 2022, 1444 non-small cell lung cancer (NSCLC) patients were evaluated at the Hadassah Medical Center for PD-L1 by immunohistochemistry. All patients were evaluated by using the clone 22C3 Ventana's BenchMark immunohistochemistry (IHC) platform as a Lab Developed Test (LDT).
Results: The overall PD-L1 tumour proportion score (TPS) of ≥50%, 49-1%, and <1% of the keynote010 trial and our cohort is 28.48%, 37.89%, 33.63%, and 28.39%, 33.85%, 37.80%, respectively. Tumours with a PD-L1 TPS of ≥50% were not associated with patient gender, ethnicity, or biopsy type.
Conclusion: Our PD-L1 22C3 Lab Develpoed Test (LDT) for the Ventana's BenchMark platform and the Keynote 010 display similar scoring distribution (strongly positive cases versus weakly or negative results) in NSCLC. Our cohort represent a nation-wide, real-time, heterogenic group, outside of clinical trial setup.
This support the notion that our PD-L1 LDT is clinically effective in NSCLC and can be used safely instead of the FDA approved DAKO platform for all of the indications based on the 22C3 clone.

OFP-06-006

Pulmonary asbestos fibre burden, fibre types and their effects on mortality in patients with malignant pleural mesothelioma

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Background & objectives: Malignant pleural mesothelioma (MPM) is associated with a dismal prognosis and is strongly related to occupational asbestos exposure. Our aim was to survey retrospectively the asbestos fibre types and concentrations and their effect on the mortality of MPM patients.
Methods: We used a national dataset of MPM patients. For this study, we included patients where an evaluation of the pulmonary asbestos fibre and type had been made using electron microscopy at the Finnish Institute of Occupational Health (FIOH).
Results: A total of 590 patients were included. The median asbestos concentration within dry lung tissue was 3.20 million fibres/gram (range: 0 - 1700). The most prevalent asbestos fibre types detected in lung issue were crocidolite and anthophyllite, respectively. In multivariable survival analyses, overall asbestos fibre concentration increased the Hazard ratio (HR) for mortality.

Interestingly if the survival time was under 7 months the HR decreased with asbestos fibre concentration. The age of these patients was high, and they were probably not involved in follow up programs for the asbestos exposed possibly resulting in a delayed diagnosis. No effect of fibre type for the HR of mortality could be established.
Conclusion: We found that the total asbestos fibre concentration increased mortality over follow up time in general except for an initial phase. The most common fibre types were anthophyllite and crocidolite, the usage of crocidolite has been relatively small. However crocidolite has been used for asbestos spraying explaining its prevalence in the lungs. Anthophyllite was recognized to be the sole fibre sizable population of patients with isolated anthophyllite exposure supporting its role in the pathogenesis of MPM.
Funding: Several grants from the Helsinki University Hospital, the Finnish Cancer Foundation, the Finnish Work Environment Fund, and the Foundation of Finnish Anti-Tuberculosis Association have funded this study.

OFP-06-008
Do different ALK positivity rates affect treatment response and prognosis in non small cell carcinoma of the lung?
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Background & objectives: Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase and therapeutic target in non-small cell lung cancer (NSCLC). We compared the therapeutic efficiency of targeted therapy between ALK-positive cases near the threshold value (≥15%) and other ALK-positive cases.
Methods: Our study included 73 patients with ALK-positive adenocarcinoma or NSCLC, 29 of whom were treated with ALK inhibitors and were followed up and treated at our centre. The percentage of ALK-positive tumour cells and the predominant signal pattern (break-apart or single red) were obtained from pathology reports, and their relationship to prognosis was statistically evaluated.
Results: The median age was 64.4±0.8(41-91). 52 were male (71.2%). The percentage of ALK rearrangements was 15-20% in 29, %15-25 in 47 cases. 51.4% of the cases died. There was no statistical significance between the percentage and signal pattern groups and prognosis. However, the single-red signal dominant group had a lower mortality rate than the break-apart dominant group (33.3%vs58.3%, p=0.056). The treatment response in the 15-20% ALK-positivity group was lower than in the ≥21% group (%14.3vs%35.7, p=0.314).<gwofw> The treatment response in the single red dominant group was higher than the break apart dominant group (62.5%vs26.3%, p=0.09). 15-25% group showed progression in 5.9 months, while the ≥26% group showed in 8.3 months.</gwofw>
Conclusion: The mortality rate was lower and the treatment response rate was higher in the single red dominant group. Treatment response was lower in the group with 15-20% compared to the ≥21%group. The time to progression was 2.4 months shorter in the group with 15-25% compared to the ≥26%group. In conclusion, "borderline ALK-positive tumours" and cases with predominant break apart signal may have a worse prognosis. Nonetheless, these findings must be validated by larger-scale research with a greater number of cases.

OFP-06-009
Pathologic assessment of resected stage III non-small cell lung cancer after neoadjuvant chemotherapy: identification of new prognostic factors
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Background & objectives: Non-small cell lung cancer (NSCLC) patients undergoing neoadjuvant chemotherapy followed by surgery represent an ideal clinical setting to discover prognostic/predictive factors. The aim of the study was to identify clinical/pathological features useful for a better patient stratification.
Methods: Fifty-four stage III NSCLC patients were included between 2013 and 2021. Main clinical/laboratory data at the time of the diagnosis were recorded. All the morphological parameters of the surgical samples were evaluated, including the tumour bed and the new WHO grading for adenocarcinomas. Computer-assisted morphometrical quantification of fibrosis and inflammation extension was performed. Survival analyses were done by Kaplan-Meier curves.
Results: Longer disease-free survival (DFS) was found in patients with higher blood lymphocytes count (p=0.005) and higher fibrosis extension (p=0.05). Overall survival (OS) was related to gender (p=0.02), histotype (p=0.03) and pleural infiltration (p=0.05). When considering only adenocarcinomas, DFS was longer in patients with numerous blood lymphocytes (p=0.0006), lower WHO grades (p=0.01), lower proliferative index (p=0.01), less necrosis (p=0.004) and higher fibrosis extension (p=0.04). OS was related only to stage (p=0.02). A combined score that included lymphocytes, vascular infiltration, proliferative index, necrosis, fibrosis and inflammation, resulted more useful in stratifying patients for DFS(p=0.008). In adenocarcinomas the combined score seems to show a better performance when also WHO grading was included (p<0.0001).
Conclusion: Different morphological aspects resulted crucial for the patient prognostic stratification, especially for DFS. The precise computer-assisted quantification of stromal components can overcome observer bias and inaccuracy, and the combination of different parameters will result in a more effective prognostic stratification of the stage III NSCLC patients.

OFP-06-010
Asbestos body number in the lung of malignant pleural mesothelioma resected by extrapleural pneumonectomy
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Background & objectives: Malignant pleural mesothelioma (MPM) is still dreadful disease, and has been recognized as related to asbestos inhalation. The aim of this study is to analyse the asbestos body number in the lung of MPM patients who underwent extrapleural pneumonectomy (EPP).
Methods: Sixty consecutive MPM patients who underwent EPP from 2006 to 2019 were reviewed. Asbestos body quantification involved the digestion of 1-4 grams of lung tissue in bleach employing a modified Smith and Naylor method (Smith MJ, Naylor B. Am J Clin Pathol 1972; 58:250-254). In addition, age, sex, affected side, MPM type, cause of asbestos exposure, and prognosis were investigated.
Results: The median age at EPP was 62 years old. 49 males and 11 females were operated. Right side was 30, and left side was 30. Epithelioid was 40, biphasic was 15, sarcomatoid was 2, and special variant was 3. 5-year survival and median survival of 30

epithelioid patients after 2011 were 36% and 58 months. Many patients had occupational asbestos exposure. 9 patients were judged as environmental asbestos exposure. The median asbestos body number in one gram of dried lung was 7,189. The asbestos body numbers in one gram of dried lung of 13 patients (22%) were less than 1,000, and those of 35 patients (58%) were more than 5,000.
Conclusion: Strong relationship between inhaled asbestos in the lung and MPM was re-confirmed. The representative occupations were construction worker, asbestos factory worker, plumber, and railroad car maker. Although the dried lung of MPM patients were investigated, the asbestos body numbers of 22% were less than 1,000/g, and those of only 58% were more than 5,000/g.

OFP-06-011
Prevalence of TTF-1 negative lung adenocarcinoma on lung core biopsy with EGFR, ALK and PD-L1 status
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Background & objectives: TTF-1 negative (TTF1neg) lung adenocarcinoma is relatively infrequent, typically CK7+ HepPar1+ and has SMARCA4 gene mutations. The objective was to retrospectively examine biomarkers/immunohistochemical characteristics of local TTF1neg lung adenocarcinomas. Locally, the TTF-1 immunostain clone in use is 8G7G3/1 (Dako).
Methods: All in-house lung core biopsies (LCBs) from Jan 2011-Dec 2020 were retrieved and analysed using a hierarchical free text string matching algorithm (HFTSMA) to establish the diagnosis, and a logical text parsing tool (LTPT) to retrieve results for immunostains, PD-L1, EGFR, and ALK status. A full review/audit was done by pathologists on cases selected by the HFTSMA and LTPT.
Results: Of 5,867 LCBs, 3,142 had immunostains (IHC) from 4,973 patients. The HFTSMA classified 5,725 (98%) LCBs. LTPT identified 85% of LCBs based on TTF-1 status. TTF-1 was done but not reported in 11%. 748 of 1,640 LCBs with adenocarcinoma were TTF-1 positive (TTF1+). 73 cases were TTF1neg, CK7+ and negative for non-lung markers. 50 of these 73 were deemed primary lung, of which 0/29 were EGFR+ and 0/28 were ALK+. PD-L1 was positive in 2/17 (11%), low positive 3/17 (18%) and negative in 12/17 (71%) cases. Only 1/28 cases was positive for Napsin A. HepPar1 was done in only four cases; three matched the SMARCA4 deficient profile TTF1neg CK7+ HepPar1+.
Conclusion: Using the HFTSMA and LTPT, additional TTF1neg lung adenocarcinomas were identified, and these were uniformly negative for EGFR and ALK. In the cohort, 6% (50/ (748+50)) are TTF1neg lung adenocarcinomas. PD-L1 appears to be frequently negative compared to TTF1+ adenocarcinomas. IHC reporting is uneven in our environment. The possible utility of HepPar1 positivity in identifying TTF1neg LCBs appears to be underutilized in our environment. Napsin A negativity appears to be a common finding in TTF1neg lung adenocarcinomas.

OFP-06-012
Histologic features, nuclear grading, BAP1 and PD-L1 expression in malignant pleural mesothelioma: analysis of a mono-institutional series
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Background & objectives: The most common primary malignant tumour of the pleura is malignant pleural mesothelioma (MPM) which has a poor outcome. This study aims to identify any relation between histological features, nuclear grading, and expression status of BAP1 and PD-L1 in MPM.
Methods: 52 tumour samples diagnosed as MPM between 2001-2022 were re-evaluated and nuclear grading was performed. Whole sections were analysed for BAP1 and PD-L1 (73-10 clone) expression by using IHC assays. Presence or absence of the nuclear expression of BAP1 was noted. Any pattern of staining was accepted in PD-L1 the 73-10 clone, and cut-offs were set as ≥1%, ≥50%, ≥80%.
Results: Male/female ratio was 27:25 and age range was 33-83 (mean:60). Forty-nine cases were epithelioid and 3 were biphasic. Among epithelioid MPMs, 37/49 were low grade(LG). BAP1 expression was lost in 69%(67% of epithelioid, 100% of biphasic) of cases. There was no statistically significant correlation between BAP1 loss and nuclear grade or overall tumour grade. PD-L1 was negative in 43%(95% epithelioid, 84% LG, 65% BAP1-lost); ≥1% positive in 40%(95% epithelioid, 74% LG, 65% BAP1-lost); ≥50% positive in 11%(75% epithelioid,33% LG, 100% BAP1 lost) and ≥80% positive in 6%(100% epithelioid, 67% LG, 67% BAP1-lost) of the cases. Rhabdoid features were seen in 5/49 cases all of which were BAP1-lost, and PD-L1 positive.
Conclusion: MPM is an aggressive tumour. BAP1 is the most common somatic mutation, and its loss of expression remains to be common regardless of tumour grade or PD-L1 status. In epithelioid MPMs, expression of PD-L1 seems to be associated with certain histologic features such as rhabdoid morphology, but not with tumour grade or BAP1 expression. Immune checkpoint inhibitors were shown to be effective for some aggressive tumour types, and it may be promising for a subset of MPM patients as well.

OFP-06-013
Evaluation of predictive markers for the patterns of metastatic disease in patients with pulmonary adenocarcinoma
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Background & objectives: The majority of patients diagnosed with pulmonary adenocarcinoma present at an advanced stage of the disease or will develop metastases during follow-up. Finding predictive biomarkers for the development of metastatic disease during diagnostic workup is important to guide therapeutic strategies.
Methods: Histologic growth pattern and a diagnostic genetic panel customized for lung cancer alterations, were evaluated in biopsy and resection specimens of 319 patients presenting with metastases from pulmonary adenocarcinoma. A subset of patients with early-stage lung adenocarcinoma who developed metastasis during follow up was compared to a group who did not develop metastatic disease.
Results: Primary lung tumours presenting with a dominant solid growth pattern and absence of driver mutations correlate with brain metastasis and are found predominantly in early brain metastasis. EGFR mutations are found in early metastasis of brain and non-brain origin irrespectively of the growth pattern. MET mutations were seen in early non-brain metastasis. We observed a major change of the dominant growth pattern between the primary lung tumour and the corresponding metastasis. Both, early and late brain metastasis show more often a papillary dominant growth pattern whereas the acinar dominant pattern is found in early brain and non-brain metastasis.
Conclusion: Routine histopathology and genetic biomarkers of primary pulmonary adenocarcinoma specimens predict to some extent the development of metastasis. These parameters are by themselves

insufficiently specific to reliably predict metastatic behaviour. This is, however, a first step towards the development of a predictive algorithm on which therapeutic strategies can be based. We are currently investigating additional parameters such as tumour microenvironment as well as additional histological and clinical parameters to improve the specificity of our predictive model.

OFP-06-014

Expression of phagocytosis markers and phagocytosis inhibitors in Usual Interstitial Pneumonia (UIP)

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Background & objectives: Fibrosis in UIP is facilitated by senescence cells, which secrete inflammatory cytokines. Phagocytosis counteracts the inflammation by removing cellular debris. We want to identify cells expressing phagocytosis-associated molecules and cells protecting themselves by expressing CD47 within the peripheral lung.
Methods: We performed immunohistochemistry on 44 cases of UIP with different aetiology using antibodies against LAMP1, Rab7, TRAP (all phagocytosis-associated), and CD47 (phagocytosis-protecting).
Results: Phagocytosis-associated molecules were expressed in all macrophages, but also by a considerable proportion of regenerating cells within the remodelled areas. Myofibroblasts, endothelia, and bronchial/bronchiolar epithelial cells were all negative. Expression of LAMP1 and Rab7 were sometimes focally seen in type II pneumocytes within normally structured lung. CD47 was expressed by macrophages, but also by few regenerating epithelial cells within the remodelled peripheral lung, much less compared to the expression of phagocytosis markers. As we suspected these to be senescent cells, we performed double immunohistochemical staining for p16 (senescence marker) and CD47.
Conclusion: Our results indicate that senescence cells have probably activated a mechanism, protecting them from being attacked and phagocytosed by leukocytes. Thus, they maintain inflammation and proliferation of myofibroblasts.

OFP-06-015

Large-scale human tissue analysis identifies Uroplakin 3B as a useful diagnostic marker for mesothelioma and normal mesothelial cells

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Background & objectives: Uroplakin 3B (Upk3b) stabilizes the urothelial cell layer lining the bladder. Based on RNA expression studies Upk3b is expressed in a only limited number of normal tissues and tumour entities. This study assessed the diagnostic utility of Upk3b immunohistochemistry.
Methods: A set of tissue microarrays containing 8071 samples from 125 different tumour types and subtypes and 608 samples of 76 different normal tissue types was analysed by immunohistochemistry.
Results: Normal cell expression of Upk3b was largely limited to mesothelial cells, umbrella cells of the urothelium, and amnion cells. Upk3b was detectable in 13 (10,4%) of 125 tumour entities. The rate of Upk3b positivity was highest in malignant epitheloid mesotheliomas (81,5%), followed by various categories of urothelial tumours (14,6-45,7%) including Brenner tumours of the ovary (10,8%), four further subtypes of ovarian cancers (1,1-10,4%) and adenocarcinoma of the ampulla of Vater (2,7%). Within urothelial tumours, Upk3b positivity decreased from 45,7% in pTaG2 (low grade) to 34,2% in pTaG3 (high grade), and 14,6% in pT2-4 cancers ($p<0,0001$). Within pT2-4 cancers, Upk3b staining was unrelated to pT, pN, and patient prognosis.
Conclusion: Upk3b immunohistochemistry is a useful diagnostic tool for the distinction of mesotheliomas from other thoracic tumours and the visualization of normal mesothelial and umbrella cells.

OFP-06-016

The relationship of VSIR(VISTA) and PD-L1 expressions with histologicalsubtypes in mesothelioma

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Background & objectives: Mesothelioma is a tumour with low response to treatment and poor prognosis. This has led to the search for new treatment methods such as antibodies that block immunocontrol points. We evaluated the immune checkpoint markers PD-L1 and VISTA in mesotheliomas.
Methods: VISTA and PD-L1 expression analysed in 45 epithelioid,10 sarcomatoid, 9 biphasic mesotheliomas 3 well-differentiated mesothelial tumours (WDPMT) and 2 atypical mesothelial proliferation cases (AMP). Positive staining for VISTA in tumour cells was defined as the presence of any cytoplasmic and/or membranous staining, and for PD-L1, the presence of any membranous staining.
Results: Positive VISTA staining was seen %91 of cases, more frequently in epithelioid (%98) and biphasic (89%) compared to sarcomatoid (60%) mesotheliomas. Benign mesothelium, WDPMT, AMP, testicular and peritoneal mesotheliomas were all positive with VISTA. PD-L1 was expressed more frequently in sarcomatoid (80%) mesotheliomas compared to epithelioid (29%) and biphasic (33%) mesotheliomas. All PD-L1 positive cases were pleural mesothelioma except 2 epithelioid peritoneal mesothelioma. While 1/23 low-grade and 10/17 high-grade pleural epithelioid mesotheliomas were positive with PD-L1. A significant correlation was found between VISTA($p=0.00$) expression with epithelioid mesotheliomas, while PD-L1 expression with sarcomatoid ($p=0.01$) and high-grade epithelioid mesotheliomas ($p=0.00$). An inverse negative relationship between VISTA and PD-L1 scores was observed.
Conclusion: VISTA expression was observed more frequently in sarcomatoid mesotheliomas compared to epithelioid mesotheliomas, while PD-L1 expression was mostly observed in sarcomatoid mesothelioma. It is known in the literature that PD-L1 expression is associated with a bad prognosis and VISTA expression is associated with a good prognosis. We also observed higher PD-L1 expression in high-grade epithelioid mesothelioma than in low-grade. We wanted to emphasize the importance of the expression of immuc check point inhibitors in mesothelioma subtypes in target-directed drug selection.

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OFP-07-001

Mutations detected by next generation sequencing in primary and metastatic melanoma samples and correlation with clinico-histopathological parameters

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Background & objectives: Melanoma accounts for the vast majority of death related to skin cancer. Its incidence increased during the last few decades. The underlying pathogenetic mechanisms have to be further elucidated, but several oncogenic mutation have been reported to be involved.
Methods: This is a retrospective study on 220 melanoma samples (primary or metastatic) from equal patient number. A NGS-DNA Oncomine Focus Assay was performed in all cases. The results are correlated with different clinico-pathological parameters, among which metastatic status and response to therapy. We present the preliminary results on 114 patients; the study is ongoing. The final results follow upon presentation.
Results: The median age at the time of diagnosis was 62,3 years. Less than half of the patients underwent a sentinel node (SN) procedure and 60,87% of the SNs showed metastatic deposits. Distant metastasis was seen in 46,5% of the cases. The metastatic locations ranged from one up to six. Among the mutations, BRAF and NRAS comprised the majority. Patients with a BRAF but no TERTp mutation had more metastatic locations than those with both a BRAF and TERTp mutation (p=0.044). However, the latter had higher rates of brain metastasis than those with BRAF but no TERTp(p=0.037). Patients with NRAS and TERTp mutations displayed a higher Breslow thickness than NRAS alone(p=0.045).
Conclusion: We present the preliminary results of our retrospective study on 114 melanoma samples. We correlated their molecular status with different clinico-pathological parameters. BRAF mutated melanomas seem to can give rise to multifocal metastatic disease, even in the absence of TERTp mutation. However, TERTp mutations are responsible for the more aggressive, brain metastasis. TERTp in combination with NRAS mutation correlates with higher Breslow thickness of the primary tumours. The study is ongoing and final results are about to be completed.

OFP-07-002
The utility of PRAME in the diagnostic approach of cutaneous melanocytic lesions
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Background & objectives: The PReferentially expressed Antigen in Melanoma(PRAME) has been extensively researched for its expression in cutaneous melanomas. Yet, little is known about its expression in non-malignant melanocytic lesions. Here we investigate PRAME expression in a large series of cutaneous melanocytic lesions.
Methods: We performed a retrospective study on the immunohistochemical expression of PRAME in 296 melanocytic lesions. These were classified according to a modified MAPTH-Dx classification in group 1:benign, group 2:moderate atypical, group 3:severe atypical and group 4:malignant. PRAME expression was analysed based on the percentage of cells with expression (< 1%, 1-25%, 26-50%, 51-75%, 76-100%) and on intensity (none/light, moderate, intense).
Results: PRAME percentage of 76-100% was seen in 2%, 4%, 11 % and 52% for groups 1 to 4 respectively (p<0.05). Strong intensity was seen in 10%, 9%, 27% and 62% for groups 1 to 4 respectively (p<0.05). The AUC for percentage of PRAME expression in discriminating between groups 1 and 4 was 85.09%, between groups 2 and 4 84.90% and between groups 3 and 4 74.61%. The AUC was 64.07% for discrimination between groups 2 and 3, 51.02% between groups 1 and 2 and 63.57% between groups 1 and 3. Comparison of the AUC for percentage, intensity and their combination had no significant difference (p>0.05 in all cases).
Conclusion: These results suggest that immunohistochemical analysis for PRAME expression is a useful adjunct for distinguish melanoma from non-malignant cutaneous melanocytic lesions. In the non-malignant category it may play a role in discriminating moderate from severe atypia. The significance of these findings need to be further determined in a larger cohort including the follow up clinical data.

OFP-07-003
PRAME immunoexpression in 275 cutaneous melanocytic lesions: a single institutional experience
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Background & objectives: In recent years PReferentially expressed Antigen in MElanoma (PRAME) has been used in the histopathological diagnosis of melanocytic lesions. We performed a single-centre study to evaluate the data on the usefulness of PRAME could also be confirmed by our group.
Methods: From 1 December 2021 to 29/03/2022 we collected 275 cases of melanocytic lesions that were immunostained with PRAME. We categorized PRAME tumour cells percentage positivity and intensity of immunostaining in a cumulative score obtained by adding the quartile of positive tumour cells (0,1 +, 2 +, 3 +, 4 +) to PRAME expression intensity in tumour cells.
Results: Of these 275 lesions, 136 were benign, 12 were of uncertain potential for malignancy, and 127 were malignant. The immunoexpression of PRAME was totally negative in 125/136 benign lesions with only a few positive melanocytes, with intensity 1+ in the remaining 11 cases (8.1%). Of the 127 cases of melanoma, PRAME was strongly positive in 104/127 cases with intensity 4+ and 3+. In 17 cases PRAME was positive in percentage 2+ and with intensity ranging from 2+ to 3+. In 6 cases of desmoplastic melanoma, PRAME was 1+ positive or completely negative. Of the 12 cases of spitzoid lesions, PRAME was much more heterogeneous and irregularly distributed throughout the lesion.
Conclusion: These data are perfectly in agreement with the current literature, they demonstrate that the reliability of PRAME is quite high, but its use cannot disregard the morphological information and the execution of other ancillary immunohistochemical stains such as Melan-A, HMB-45, MiTF and SOX-10.

OFP-07-004
Cutaneous histopathological findings in systemic amyloidosis
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Background & objectives: Amyloidosis comprehends a group of diseases characterized by the deposition of amyloid fibres within tissues and organs. Skin biopsy is a simple and safe procedure with a high yield and might be used to support the diagnosis of systemic amyloidosis.
Methods: We analysed 59 skin biopsies from 47 patients with systemic amyloidosis (SA) (26 males, 21 females), including 18 amyloid light chain (AL); 19 serum amyloid A (AA), and 10 non-AL/non-AA amyloid types. We evaluated the distribution of amyloid deposits within the tissue.
Results: For each group of systemic amyloidosis, AL, AA, and non-AL/non-AA type, secondary cutaneous amyloidosis was confirmed in 15 (83,3%), 6 (31,5%), and 6 (60%) cases respectively.

Amyloid deposits within the skin biopsies in AL type were in the papillary dermis, interstitial infiltration, and hair follicle shaft involvement. In AA-type skin biopsies showed amyloid infiltration at the sweat glands and hair follicle shaft involvement. In non-AL/Non-AA type the amyloid deposits described an interstitial infiltration and deep small blood vessel wall deposition. In a subgroup of biopsies(N=13), C4d staining was evaluated for identifying amyloid deposition being positive in 84,6%(n=11) of cases.
Conclusion: The diagnosis of SA sampling abdominal fat tissue has variable rates of sensitivity. Skin biopsy is a simple procedure providing valuable findings for amyloidosis. Descriptions of skin involvement and histopathological findings in SA are scant noticing skin compromise in 40% of cases. We detected amyloid deposits at different layers and components of the skin, increasing the probability of detection of SA, supporting this procedure as a diagnostic tool, especially for AL-type amyloidosis where positive findings are frequently detected allowing an early diagnosis for this condition.

OFP-07-005
Rare histopathological findings in erythema migrans: a 5 year retrospective study from Freiburg Dermatopathology Unit and review of the literature
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Background & objectives: Erythema migrans represents the skin lesion of early manifestation of Lyme disease typically as an erythematous, circular, annular plaque with central clearing, generally greater than 5cm. Some cases can be defiant, leading to a histopathological evaluation, occasionally with uncommon findings.
Methods: We describe 88 cases with PCR test positivity for Borrelia burgdorferi and diagnosis of erythema migrans with rare histopathological findings diagnosed from 2016 to 2021. Our series had a female predilection, representing 71% of total patients and an age distribution between 21 and 82 years old. There was correlation with the clinical information in 59% of the cases.
Results: Erythema migrans is characteristically described as a superficial and deep perivascular inflammatory infiltrate, predominantly composed by lymphocytes with occasional plasma cells and eosinophils. Besides these features, our study presents cases with rare findings. There were interface changes like vacuolar and lichenoid infiltrate in 29% of the cases. Granulomatous features were present in 50,6% of this casuistic, with granuloma formation and a predominantly interstitial histiocytic infiltrate. There was also observed a pseudolymphomatous pattern with superficial, deep and severe lymphocytic infiltrate in 17% of the cases. And 3,4% of these patients presented with histopathological findings similar to mycosis fungoides with epidermotropism and papillary dermal fibroplasia.
Conclusion: The diagnosis of erythema migrans is usually clinical and serologic testing is not recommended due to low sensitivity; but some difficult clinical cases benefit from a biopsy evaluation. However, the findings can be too subtle and unusual, suggesting other entities like granuloma annulare, lupus erythematosus, drug eruptions, and mycosis fungoides, all of which require a distinct therapeutic approach. Although those differential diagnosis can often be excluded with additional histopathologic findings, close clinicopathologic correlation is necessary for a definite diagnosis.

OFP-07-006
Cutaneous lupus erythematosus: a 5-year casuistic study from a Portuguese dermatopathology department
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Background & objectives: Cutaneous lupus erythematosus (LE) occurs in the context of systemic LE or restricted to the skin, and it can be subclassified into acute, subacute or chronic. While there are differences between them, some histopathological hallmarks are present in most subtypes.
Methods: Retrospective study of 54 patients with histopathological diagnosis of cutaneous lupus erythematosus from 2016 to 2021. There was a female predilection representing 70,4% and our study had a broad age distribution, the youngest case with 8 years-old and the oldest one with 88 years-old, with almost 6% of cases being diagnosed at the paediatric age.
Results: Cutaneous lupus erythematosus diagnosed in the setting of systemic lupus erythematosus represents 13% of the patients while the cases limited to the skin represent 87%. Subacute cutaneous lupus erythematosus accounts for 23,4% and chronic cutaneous LE 76,6%. No cases of acute lupus erythematosus were described. In our study, discoid LE (DLE) is the most common subtype of chronic cutaneous LE (69,4%), followed by tumid LE (19,4%). Bullous LE represents 5,6%, while hypertrophic / verrucous LE and lupus panniculitis account for 2,8% each.
Four cases (8,4%) were diagnosed in the context of scarring lymphocytic alopecia.
Conclusion: The diagnosis of cutaneous LE requires clinical and histopathological correlation. However, the overlap with other connective tissue diseases warrants integration of serologic findings, as a systemic autoimmune disorder may be considered in the differential diagnosis.
Our study also reveals that the majority of cases were responsive to treatment, presenting only hyperpigmented residual lesions. Nevertheless, 11% had persistent lesions, especially patients with other associated autoimmune diseases like Sjogren syndrome, psoriasis and alopecia, or in the context of HIV infection.

OFP-07-007
Correlation between line-field confocal optical coherence tomography and histopathology. Preliminary results
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Background & objectives: Line-field confocal optical coherence tomography (LC-OCT) is a new, non-invasive technique that provides in-vivo, high-resolution images in both vertical and horizontal sections. Our study evaluated LC-OCT imaging in some inflammatory disorders and to correlate the resulting features with histopathology.
Methods: The retrospective study included patients with histopathological confirmed diagnosis of plaque psoriasis, atopic eczema and lichen planus, who were imaged with LC-OCT before the biopsy. LC-OCT was performed with the commercially available LC-OCT device.
Results: A total of 15 adult patients with histopathologically proven plaque psoriasis (N: 5), atopic eczema (N: 5), and lichen planus (N: 5) were included. In all cases, LC-OCT allowed the in-vivo recognition of the main microscopic features of the examined inflammatory skin disease, with a strong correlation with histopathology.

Conclusion: Although future studies on larger series of patients are necessary, LC-OCT, based on these preliminary findings, may represent a promising tool in inflammatory skin disorders with potential applications including enhanced diagnosis, biopsy guidance, follow-up and treatment monitoring.

OFP-07-008

The challenging differential diagnosis of ALK-positive cutaneous lesions, a case series

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Background & objectives: ALK-positive cutaneous lesions comprise epithelioid fibrous histiocytoma (eFH), ALK-positive non-Langerhans cell histiocytosis (non-LCH) and Spitz lesions. These are rare entities, sometimes with overlapping histologic features, hence their differential diagnosis can be challenging.
Methods: We collected a series of 14 patients with ALK-positivity on immunohistochemistry (IHC). Two case were diagnosed as non-LCH, 4 as eFH and 8 as Spitz lesions. IHC with the same ALK clone (5A4) was implemented in all cases. A NGS-RNA Oncomine Focus Assay was performed in the 6 non-Spitz lesions. We compared the morphological, immunohistochemical and molecular findings.
Results: The median age for the non-LCH was 16,5 years(all females), for the eFH 40 years(females=males) and for the Spitz lesions 20 years(75% females).
The entities shared common morphologic features: circumscribed or ill-defined lesion, spindle or epithelioid cell morphology, fascicular, storiform or nodular growth pattern.
On IHC, all tumours demonstrated diffuse and strong ALK expression. The histiocytic tumours were at least partially positive for CD68. S100 was focally expressed in some eFH, whereas SOX 10 and/or melan-A were confined to the Spitz lesions. No other IHC stainings aided in the differential diagnosis.
Molecular analysis in the non-Spitz lesions showed a SQSTM-ALK fusion in 2 eFHs and a KIF5B-ALK in a non-LCH.
Conclusion: We present a series of ALK-positive non-LCH, eFH and Spitz lesions. These three entities show overlapping morphological features. However, Spitz lesions are characterized by SOX10 and/or Melan-A positivity, which is not seen in eFHs and non-LCH. Still, for the histiocytic entities, IHC is not able to narrow down the differential diagnosis. Additional molecular testing may help, since specific ALK fusion partners have been demonstrated in certain entities.

OFP-07-009

Melanoma in situ with regression

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Background & objectives: Regression in melanoma in situ (MIS) has been reported but not well studied. Defining the clinical and histopathological features of cases with regression can help work-up of patients and be a step to determine the value of regression in prognosis.
Methods: Ffifty-six cases with a diagnosis of MIS in 2014-2022 were retrieved from the archives and retrospectively examined for the type of MIS, presence of melanophages, fibrosis, vascular proliferation and/or vertically arranged vessels, presence and degree of inflammation, elastosis, presence of folliculotropism, immunohistochemical stainings and surgical margins. Demographic features, clinical history and follow-up findings were recorded.
Results: There were 40 patients with regression, 19 males and 21 females with an average age of 61.8 and 51.3 respectively. Head and neck were the most frequent localization (45%). The mostly seen MIS type was lentigo maligna (62.5%), MIS developing on dysplastic nevus being the second (20%). Melanophages together with inflammation were present in 71.4% of cases. Folliculotropism was seen in 55%, vascular proliferation in 42.5%, and fibrosis in 25% of cases. Immunohistochemistry with melan A and/or HMB45 was studied for the detection of dermal invasion in 40%. Sentinel lymph node sampling was done in 2 patients with negative results. Invasive melanoma was detected in 22.5% of patients.
Conclusion: Evaluation of regression in different types of MIS is valuable in the sense that upstaging can be conceivable in some clinical settings since it can be a sign of invasive melanoma. Step sectioning and immunohistochemical studies are important tools to detect invasion. Folliculotropism and vascular proliferation along with inflammation and melanophagocytosis are frequently seen in cases with regression. Regression in a dysplastic nevus is a known phenomenon and the severity of structural and cytologic atypia derive the diagnosis of MIS.

OFP-07-010

Progressive disease in sentinel-negative melanoma patients: biological differences and importance of sentinel lymph node biopsy

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Background & objectives: Among the most important prognostic factors in melanoma is the sentinel lymph node (SLN) status.
Methods: Using our electronic database we identified 109 of 890 SLN-negative patients with progressive disease (PD). These patients were characterized for melanoma type, molecular type, sequence and extent of metastatic spread.
Results: A total of 61 of 109 SLN-negative patients had PD in the SLN-basin indicating false-negative SLN (group-1). 48 of 109 patients had PD at distant sites and were therefore impossible to be identified using SLN biopsy (group-2). Despite distant spread these patients had significantly more single organ metastasis ($p<0.001$) and significantly longer disease-free-survival ($p=0.001$) compared to group-1. Additionally, to significant differences on a molecular basis between the two groups ($p=0.01$), all lentigo maligna and spindle-cell-melanomas belonged to group-2 and all, except one lentigo maligna melanoma, had single visceral metastasis.
Conclusion: Two different biological groups among SLN-negative patients with PD were demonstrated. Extravascular-migratory-metastasis, rather than hematogenous spread, might be responsible for the observed PD with single organ involvement.

OFP-07-011

PRAME expression in dysplastic nevi

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Background & objectives: PRAME is a melanoma-associated antigen whose expression is well documented in cutaneous and ocular melanoma. Our study aimed to investigate the expression of PRAME in a series of low- and high-grade dysplastic nevi in which little is still known.
Methods: Immunohistochemistry for PRAME was carried out on formalin-fixed paraffin-embedded samples applying the specific

antibody (clone EPR20330, Rabbit Monoclonal, Abcam) on automated system (Ventana Benchmark Ultra), according to the manufacturer's instructions. Samples were scored blindly according to both the percentage of positive cells and the intensity of expression (H-score). The study was approved by the local Ethical Committee.
Results: The study included a total of 250 melanocytic tumours of which: 50 high grade and 50 low grade dysplastic nevi; 50 nevi with architectural disorder and minimal cytological atypia; 50 melanomas and 50 common nevi as controls. The histopathological diagnosis was reviewed collegially by four expert dermatopathologists according to the 2018 WHO classification of skin tumours. Written consent was obtained from each participant. Statistical analysis was performed using ANOVA analysis and Kruskal-Wallis test. As expected, PRAME immunoreactivity was markedly different between melanomas (diffuse and strong staining) and common nevi (weak and focal). Instead, among dysplastic nevi PRAME protein displayed different staining patterns in the epidermal and dermal portions.
Conclusion: This work represents the first large study on PRAME expression in dysplastic nevi in a real-world setting. Our results suggest that immunohistochemical analysis for PRAME expression may aid in the differential diagnosis between low grade and high grade dysplastic nevi as well as between high grade dysplastic nevus and melanoma, in addition to and as a complement to the WHO morphological criteria used in routine practice.

OFP-07-012
Somatostatin receptor type 2a (SSTR2a) immunohistochemical expression pattern in Merkel cell carcinoma- a pilot study
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Background & objectives: Merkel Cell Carcinoma (MCC) is an aggressive, high-grade cutaneous neuroendocrine carcinoma. Recent data suggest that MCC patients may benefit from therapies targeting somatostatin receptors. Our aim was to evaluate the expression pattern of somatostatin receptor type 2a (SSTR2a) in MCC.
Methods: SSTR2a immunohistochemistry was performed in ten MCC specimens (five primary and five metastatic to lymph nodes). SSTR2a expression was evaluated by using a scoring system proposed from Volante and colleagues. Specifically, score 0 describes no staining and score 1+ cytoplasmic staining whereas membrane expression corresponds to score 2+ (staining in <50% of tumour cells) or score 3+ (>50% of cells).
Results: All primary MCC were SSTR2a positive with membrane staining in 4/5 cases and focal cytoplasmic staining (score 1+) in one case. Membrane SSTR2a staining was scored as 2+ in two cases and 3+ in the other two. Score 2+ cases displayed heterogeneous-focal membrane staining of moderate intensity with partial or circumferential pattern whereas score 3+ cases were characterized by a circumferential, strong and diffuse membrane expression of SSTR2a. In contrast with primary MCC, 3/5 metastatic MCC were SSTR2a negative (score 0) with endothelial and follicular dendritic cells serving as internal positive controls. The other two metastatic MCC displayed focal cytoplasmic SSTR2a staining (score 1+) of weak to moderate intensity.
Conclusion: SSTR2a is expressed in 6/10 MCC cases, with membrane staining that is considered as clinically important in 4/10. Although preliminary, our data are in agreement with the few imaging and immunohistochemical studies that previously assessed the SSTR2a expression in MCC. Given that SSTR2a is typically expressed in well-differentiated neuroendocrine tumours (NETs), the positive SSTR2a staining in MCC is a surprising finding. SSTR2a may represent a potential target for imaging and therapies with somatostatin analogues, in a similar fashion with NETs.

OFP-08 | Joint Oral Free Paper Session Paediatric and Perinatal Pathology / Autopsy Pathology

OFP-08-001
Digital pathology approach for prognostisation of neuroblastoma
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Background & objectives: Neuroblastoma (NB) diagnosis needs precise percentages of differentiating/proliferating cells and mitosis-karyorrhexis index (MKI), which are hard to assess manually and objectively. Our aim was to test the benefit of using digital pathological evaluation to harbour these features, especially for prognostisation.
Methods: Our retrospective study was performed on 41 NB-cases from Semmelweis University, Budapest, Hungary. Hematoxylin-Eosin and Ki-67 immunostained slides were digitalized by Pannoramic 1000 Scanner (3DHistech, Budapest, Hungary). MKI, tumour differentiation, Ki-67 proliferation index were digitally calculated with Quant Center algorithms of the same vendor. Statistical correlations, ROC analysis, t-tests and graphic visualisation were performed with Microsoft Excel and XLSTAT programs.
Results: Our pilot study incorporated 5 undifferentiated, 28 poorly differentiated and 7 differentiating NBs. Average age at diagnosis was 25,54±38,39 months, with slightly more males (23:18). 5-year overall survival was 80%, disease-free survival was 65%. Manual and digital MKI values correlated well ($r=0,78$, $p<0,05$) and delivered prognostic value. Manual and digital Ki-67 values correlated well ($r1=0,63$, $r2=0,56$, $r3=0,91$, $p1,2,3<0,05$), and proved to be prognostic in different aspects. Tumour cells' biometric data visualisation by violin-plots showed differences among differentiation classes, offering promising ways for digital classification. Combining the various digitally assessed features into the Neuroblastoma Digital Pathology Index we reached a classification accuracy of 94% in non-high-risk and 88% in high-risk NB-patients.
Conclusion: Our epidemiological findings were similar to literature data. Digital MKI counting is accessible and delivers prognostic data. Ki-67 proliferation index's own prognostic value falls behind some classic prognostic factors such as MKI, though it adds valuable tools for NB prognostisation through complex formulas, especially by automatic digital evaluation on hot-spots or whole slides. Our Neuroblastoma Digital Pathology Index's classification accuracy is promising, just like the visual representation of tumour cells with violin-plots which might show differentiation related distribution patterns.

OFP-08-002
Wilms' tumour 1 expression in eutopic and ectopic decidua: a correlation with the pregnancy status
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Background & objectives: Wilms' tumour 1 gene (WT1) is reported to be overexpressed in decidual cells during pregnancy, however, case series are lacking. Our aim is to evaluate WT1 expression in eutopic and ectopic decidua and correlate it with pregnancy status.

Methods: We evaluated 99 cases (94 tissue microarrays) of decidual tissue (72 eutopic; 27 ectopic). WT1 nuclear immunoexpression was independently evaluated by four pathologists. Percentage and intensity of positive cells were estimated using a semi-automated open-source software. A staining score was obtained by multiplying the percentage and intensity of positive cells. Clinical data was reviewed and the results were statistically analysed.
Results: We evaluated 99 cases of decidual tissue in total, 36,4% associated with pregnancy (23 eutopic; 13 ectopic) and 63,6% non-pregnancy associated (49 eutopic; 14 ectopic). Nuclear expression of WT1 was observed in 93,9% cases (97,2% in pregnant women; 92,1% in non-pregnant women), with no statistical differences (p=0,550). The percentage and nuclear intensity of cells were higher in non-pregnancy related decidua, mainly in eutopic location (p<0,001 and p=0,003, respectively). Accordingly, the WT1 score was also higher in non-pregnancy related eutopic decidua [moderate (14,3%); strong (77,6%); p=0.034]. The WT1 percentage of positive decidual cells was associated, independently of the pregnancy status, with the eutopic location (p=0,024).
Conclusion: In our study of a case series we did not verify a higher imunoexpression of WT1 associated with pregnancy status. We verify a higher percentage of WT1-positive decidual cells in eutopic tissues, especially in non-pregnancy related cases.

OFP-08-003
Chronic histiocytic intervillositis and related clinical findings: a multicentric, retrospective analyses of 34 cases in a 17 year period
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Background & objectives: Chronic histiocytic intervillositis (CHI) of unknown aetiology is a rare placental disorder defined by the presence of an histiocytic infiltrate in the intervillous compartment. According to literature, it is related to poor foetal outcome, maternal autoimmune diseases (AD) and recurrence.
Methods: A retrospective review was conducted in all placentas and products of conception (over 21000 specimens) received in three major hospitals in Lisbon metropolitan area, between June 2003 and February 2022, to detect cases with CHI as a major finding; cases with other major placental findings were excluded. Medical records were analysed regarding the associated clinical and obstetric data.
Results: A total of 34 cases were selected, which corresponded to 32 women with mean age of 37 years (+/- 5 years). Half (17 cases) of pregnancies resulted in viable births, 9% (3 cases) in intrauterine deaths and 41% (14 cases) in spontaneous abortions. In 41% of cases there was intrauterine growth restriction, 3 cases (9%) had a single umbilical artery and 5 (15%) were associated with foetal malformations.
Only 25 women had an available medical record, AD were present in 3 (1 a previous diagnosis, 2 revealed after placental evaluation). Recorded recurrency was seen in 2 women and 3 other had a history of repeated aborditions without known histologic assessment.
Conclusion: Our incidence of CHI is similar to the literature; regarding the prevalence of maternal AD, our study reveals a lower incidence than usually observed. The question remains if an undiagnosed AD is present at the time of gestation or if CHI can precede the full setting of an AD and, if so, how long it takes between both events. We propose follow-up of these patients in a 5 years period, with special focus on CHI recurrency and AD incidence/prevalence.

OFP-08-004
Left ventricular non-compaction in foetal autopsy: a report of 6 cases
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Background & objectives: Left ventricular non-compaction (LVNC) results from arrest of normal process of ventricular compaction, resulting in a ratio between non-compacted and compacted myocardial layers >1. It is a rare condition of uncertain aetiology although likely genetic with dominant pattern of inheritance.
Methods: Cases with LVNC were retrieved from pathology files. Ultrasonographic and genetic data when available were retrieved from clinical charts. Histology when available was reviewed.
Results: LVNC was identified in 6 cases (three termination of pregnancies and three intrauterine foetal deaths) out of 3000 foetal autopsies. Gestational ages ranged from 13 to 25 weeks. Four out of five cases had ultrasound abnormalities with two foetal hydrops and one additional subcutaneous oedema. Cardiac abnormalities were identified in two cases. Three out of four cases with available genetic analysis had genetic alterations: X monosomy, 8q23 deletion and heterozygous compound LDB3 mutations. Healthy carriers of LDB3 mutations were identified among the relatives of this case. Two of three sibs that shared the heterozygous compound LDB3 mutations had LVNC, one being a live-born girl.
Conclusion: LVNC incidence was higher in this foetal autopsy series than it is reported in the paediatric population. Noncompacted cardiomyopathy must be considered in the differential diagnosis in cases of foetal hydrops and dilated cardiomyopathy. It must also be ruled out when other structural cardiac defects are found. The inheritance pattern found in LDB3 mutations, consistent with a recessive pattern, was not previously described.

OFP-08-005
Umbilical cord compromise versus other clinical conditions predisposing to placental foetal vascular malperfusion
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Background & objectives: Foetal vascular malperfusion (FVM) can be due to cord compromise, hypercoagulability, foetal cardiac dysfunction, or hypoxia. Although the cord compromise is most common, the relative importance of other factors is unclear which is the aim or this retrospective analysis.
Methods: 580 placentas were examined: Group 1: 52 placentas with clinical cord compromise/anatomical abnormalities, Group 2: 204 placentas with maternal/ foetal conditions predisposing to FVM; Group 3: 286 placentas with coexisting at least one variable of Group 1 and one variable of Group 2 predisposing to FVM, Group 4: 38 placentas with no clinical conditions or cord factors predisposing to FVM.
Results: Average gestational age was the shortest in Group 4, followed by Groups 1, 2 and 3. Groups 1 and 4 featured more cases with poor prenatal care, less frequent cesarean sections, more frequent macerated stillbirths, less frequent neonatal stay in intensive care unit, atherosis of spiral arterioles, retroplacental hematomas, and luminal vascular abnormalities of chorionic villi. Clusters of sclerotic/stromal vascular karyorrhectic/mineralized chorionic villi, large vessel foetal vascular malperfusion, and low grade distal foetal vascular malperfusion were statistically significantly more common in Groups 1 and 3. There were no statistically significant differences in inflammatory and hypoxic lesions or patterns (acute or chronic) or lesions of shallow placental implantation among the groups.

Conclusion: Cases with isolated clinical umbilical cord compromise were associated with the most unfavourable clinical outcome as umbilical cord complications and pathology strike unexpectedly and are notorious for unpredictability, causing stillbirths not associated with other maternal or foetal diseases. This finding paralleled the histological segmental FVM most common in Groups 1 and 3, both with the umbilical cord aetiology. The clinical risks alone for FVM alone, without the umbilical cord factors (Group 2), were not associated with increased rate of FVM.

OFP-08-006

Placental recent/on-going foetal vascular malperfusion with endothelial fragmentation is diagnostically equivalent to established distal villous lesions of foetal vascular malperfusion

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Background & objectives: CD34 immunostaining increases sensitivity of placental diagnosis of foetal vascular malperfusion (FVM). This comparative retrospective study was performed to find out whether recent distal FVM lesions diagnosed with CD34 immunostaining are diagnostically equivalent to remote FVM lesions diagnosed with hematoxylin-eosin
Methods: Clinical and placental phenotypes of 562 placentas from ≥20weeks high-risk pregnancies were analysed: Group 1 - 158 placentas with remote distal villous FVM (by H&E only), Group 2 - 142 placentas showing clustered endothelial fragmentation by CD34 immunostaining, 98 of them also with H&E distal FVM lesions (on-going, temporal heterogeneity), Group 3 - 262 placentas without distal villous FVM.
Results: Foetal congenital malformations were seen in most cases of each group (58.5% of all cases). Using Bonferroni correction, there were no statistically significant differences in clinical or placental phenotypes between Group 1 and Group 2, or among the 3 groups ($p>0.002$). However, in Group 1, gestational age was the shortest, postnatal mortality most frequent, placental weight the smallest, intra villous haemorrhage, erythroblasts in foetal blood, hypertrophic decidual arteriopathy, and foetal vascular thrombi most common, and in Group 2, placental infarction, post-uterine pattern of chronic placental injury and excessive extra villous trophoblasts of chorionic disc were most common ($p<0.05$).
Conclusion: In this cohort of foetuses/neonates dominated by congenital malformations, distal villous FVM was the most common pattern of placental injury. The absence of statistically significant differences in clinical or placental phenotypes among all 3 groups indicates that distal villous FVM diagnosed by CD34 and that diagnosed by H&E are diagnostically/prognostically equivalent. CD34 immunostaining is therefore a powerful tool in diagnosis of distal villous FVM.

OFP-08-007

Cardiac arrest with successful cardiopulmonary resuscitation induces histologic changes that correlate with survival time and lead to misdiagnosis in sudden arrhythmic death syndrome

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Background & objectives: Sudden arrhythmic death syndrome (SADS) is defined as sudden cardiac death (SCD) with a morphologically normal heart. Cardiac arrest with cardiopulmonary resuscitation (CPR) may induce cardiac histologic changes. We aimed to assess whether such changes could confound SADS diagnosis.
Methods: Retrospective observational study analysing all consecutive cases of sudden death prospectively referred to a UK national cardiac pathology centre between January 2017 and November 2021. Cases showing hypoperfusion features due to cardiac arrest followed by CPR were identified after review of clinical information and examination by two expert cardiac pathologists. Data is presented as percentage or median.
Results: Out of 2,568 SCD cases, 126 (4.9%) were identified with hypoperfusion changes. Macroscopically, the commonest finding was left ventricular focal or diffuse subendocardial haemorrhage (13.5%). Microscopically, haemorrhage and contraction band necrosis (n=50, 37.7%), subendocardial acute infarction (n=44, 34.1%), interstitial mixed inflammatory cell infiltrates (n=31, 24.9%), granulation tissue (n=9, 7.1%) and subendocardial fibrosis (n=1, 0.7%) were observed. These changes correlated to duration of survival following resuscitation, with subendocardial infarction and granulation tissue being observed later at 2 and 9.5 days, respectively ($p<0.001$). In a subcohort of 41 cases, autopsy pathologists misinterpreted such changes as ischaemic myocardial infarction (n=7; 17%), myocarditis (n=5; 12.1%), or other pathologies (n=2; 4.8%) in 14 SADS cases.
Conclusion: We provide a comprehensive characterisation of hypoperfusion-related changes in the heart following successful CPR with survival, which are time related. These features can lead to diagnostic confusion among pathologists but knowledge of history of resuscitation with survival should help with general and expert pathology assessment and improve SADS diagnostic yield, prompting genetic screening of decedents' relatives.
Funding: Cardiac Risk in the Young Grant numbers: 12840-14

OFP-08-008

Post-mortem pulmonary findings in a large series of COVID-19 cases at the University of Texas Medical Branch (2020-2022): insights from an ancient and still relevant procedure

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Background & objectives: COVID-19 is an infection due to SARS-CoV-2 and was declared by WHO a pandemic on March 11, 2020. This project addresses the spectrum of pulmonary pathology in 294 autopsy cases performed at a single tertiary care institution.
Methods: A total of 294 autopsies were performed in our service between April 2020-2022. All cases were diagnosed by nucleic acid amplification (real-time RT-PCR) using post-mortem nasal swabs. Demographics, clinical history, gross and histologic findings were collected prospectively. Histologic sections were routinely stained with H&E, Masson's Trichrome and MOVAT pentachrome. Other special stains were performed as needed (PAS-D, MSB, etc).
Results: The average age was 60 years (range: 28-94). Clinical spectrum ranged from asymptomatic infections (cause of death unrelated to COVID-19) to lethal outcome. Clinical course was 2-120 days with an average of 19. The main risk factors included systemic hypertension, morbid obesity, diabetes mellitus, coronary artery disease, congestive heart failure, emphysema, cirrhosis and chronic renal disease. The main complications were hepatic encephalopathy, thrombotic microangiopathy, acute kidney injury (AKI) and bacterial bronchopneumonia. Virtually all lungs showed markedly increase weight and consolidation. Histologic findings included interstitial pneumonitis, oedema, hyaline membranes, acute fibrinous organizing pneumonia, type 2 pneumocyte hyperplasia, reactive/atypical type 2 pneumocytes, fibroblastic foci in alveolar spaces, fibrosis, squamous and bronchiolar metaplasia.
Conclusion: Virtually all patients had at least one risk factor, the most common being systemic hypertension. Numerous patients had two or more risk factors. The spectrum of histologic findings in the

lung is broad with overlapping features, and spatial and temporal heterogeneity as opposed to conventional diffuse alveolar damage. The most common complication is hepatic encephalopathy due to the presence of liver cirrhosis in this population, followed by thrombotic microangiopathy and AKI. Other complications were related to hypercoagulability or bleeding diathesis.
Funding: George Dock Professorship. University of Texas Medical Branch

OFP-08-009
Patterns of infectious disease identified in clinical autopsy. The role of autopsy as an ancillary study in determining the cause of death
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Background & objectives: Infectious diseases are one of the most prevalent diseases in clinical autopsies. Despite its value, the use of autopsies has decreased and infectious diseases are often undiagnosed or misdiagnosed due to the lack of pathological understanding.
Methods: This was an 8 year retrospective study of autopsy cases with final diagnosis of infectious diseases.
Results: The study consisted of 52 autopsies which comprised of 32 female (61.53%) and 20 males (38.46%) with mean age of 28 years. HIV/AIDS was the commonest comorbidity (17/52; 32.69%). Bacterial pneumonia (80.76%) was one of the most common infectious diseases, followed by septic shock (19.23%), candidiasis (14%), bacterial meningitis (9.61%), tuberculosis (7,69%), cryptococcosis (7.69%), cytomegalovirus infection (5.26%) and herpes simplex virus infection and mucormycosis each 1.92%. Antemortem diagnosis was incorrect in 63.46% (33/52) of the cases.
Conclusion: The use of autopsy for years has been the gold standard for establishing the causes of death and have played a valuable role in the diagnosis and understanding of diseases. Autopsies have also informed public health strategies in the fight against these communicable diseases.

OFP-08-010
The impact of the COVID-19 pandemic on autopsy practice
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Background & objectives: Tallaght University Hospital autopsies from the two years before and after the onset of the COVID-19 pandemic were analysed. We hypothesised that the pandemic would cause fewer autopsies, increased use of ancillary testing and prolonged time from death to autopsy.
Methods: All autopsies conducted between mid-March 2018 and mid-March 2022 were analysed for basic demographic information, location of death (community, emergency department or hospital inpatient) and the use of ancillary studies such as toxicology, histology, microbiology and subspecialty examination. The data from the two years prior to the pandemic (Study Period 1) and following two years (Study Period 2) were compared.
Results: Fewer post-mortem examinations were conducted in Study Period 2 (n = 238) compared to Study Period 1 (n = 418). An institutional change in autopsy practice accounts for much of this decrease, however the data for emergency department deaths only also showed a significantly fewer autopsies between Study Period 1 and 2 (n = 90 v n = 52). Average time from death to autopsy significantly increased (2.3 days v 3.8 days, p-value <0.01). The use of toxicology, histology, neuropathology and non-SARS-CoV-2 microbiology did not change significantly. The use of post-mortem microbiology has increased primarily due to screening for SARS-CoV-2 with 95.4% of decedents undergoing nasopharyngeal swabbing since mid-March 2020.
Conclusion: Since the beginning of the pandemic our institution has found a reduction in autopsy examinations, an increased interval between death and autopsy and an increased use of microbiological ancillary testing. The demographic characteristics of our autopsy cases, and rates of use of non-microbiology ancillary testing have not changed significantly.

OFP-08-011
Analysis of the causes of death in cases of COVID-19 based on maternal mortality cases during the pandemic
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Background & objectives: Officially COVID-19 led to a sharp increase in maternal mortality in the Republic of Kazakhstan. There were 156 cases of maternal death in 2020 and 200 cases in 2021.
Methods: We conducted a retrospective analysis of 78 cases of maternal death for the period of 2020-2021 with a clinical diagnosis of COVID-19 to determine a cause of death. All women (32-39 weeks of pregnancy) were admitted to the hospital with positive PCR results for COVID-19. The death of women occurred within 3 to 45 days after hospitalization.
Results: In 67 cases out of 78 morphological signs of COVID-19 were identified. However, the morphological spectrum of lung damage was quite diverse, including acute tracheobronchitis, pulmonary oedema, and massive hyaline membranes (in 8 cases). In 31 cases, there were signs of bacterial and fungal infection with COVID-19. In 28 cases, the cause of maternal death was obstetric pathology, but squamous metaplasia of the epithelium of the trachea and large bronchi and signs of exudate organization in the alveoli were detected.
Conclusion: Based on our analysis of COVID-19, massive hyaline membranes were the cause of death, but in a small number of cases. The death of patients with COVID-19 in most cases was associated with a bacterial or fungal infection. Squamous metaplasia of the epithelium of the trachea and large bronchi and giant cell transformation of alveolar macrophages indicate a viral infection.

OFP-09 | Joint Oral Free Paper Session Endocrine Pathology / Head & Neck Pathology

OFP-09-001
Cadherin-16 (CDH16) immunohistochemistry: a novel diagnostic tool for renal cell carcinoma and papillary carcinomas of the thyroid
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Background & objectives: Cadherin-16 (CDH16), also termed kidney specific cadherin (ksp-cadherin), is a membrane-associated glycoprotein with a role in the embryonal development of tubuli in kidney and thyroid. Downregulation of CDH16 RNA was found in papillary carcinomas of the thyroid.
Methods: A set of tissue microarrays containing 14,978 samples from 149 different tumour types and subtypes as well as

608 samples of 76 different normal tissue types was analysed by immunohistochemistry to determine the expression of CDH16 in cancer and to assess the diagnostic utility of immunohistochemical CDH16 analysis.
Results: Among normal tissues, a membranous CDH16 immunostaining predominated in thyroid, kidney, cauda epididymis, and in mesonephric remnants. In the thyroid, CDH16 staining was seen in all normal samples, 83% of follicular adenomas, 58% of follicular carcinomas, but in only 9% of papillary carcinomas ($p<0.0001$). CDH16 positivity was particularly frequent in nephrogenic adenomas (100%), oncocytomas (98%), chromophobe (97%), clear cell (85%), and papillary (76%) renal cell carcinomas (RCCs), clear cell (56%), mucinous (36%), and endometroid (16%) carcinomas as well as carcinosarcomas (18%) of the ovary, adenocarcinomas of the cervix uteri (40%), serous (33%), clear cell (33%), and endometroid carcinomas (18%) of the endometrium and in various subtypes of neuroendocrine neoplasms (4-26%).
Conclusion: Given the massive loss of CDH16 expression in >90% of papillary carcinomas of the thyroid, CDH16 is a highly useful diagnostic marker for these tumours. CDH16 immunohistochemistry is also useful for the identification of nephrogenic adenomas and the distinction of renal cell carcinomas from other neoplasms.

OFP-09-002

Pediatric thyroid nodules: a multi-institutional study from India based on the applicability of the Bethesda System with analysis of the risk of malignancy (ROM) and comparison with adult thyroid nodules

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Background & objectives: This study analyses the paediatric thyroid nodules based on the Bethesda system and compares the risk of malignancy (ROM) with adults (>18 yrs) across various Bethesda categories. It also compares young adults (19-21 yrs) with the other two age groups.
Methods: This is a retrospective multi-institutional, where archival thyroid cytology and histology data were retrieved. The cases were segregated into paediatric (<18 years), young adult (19-21 years), and adults (>18 years) age groups. The Bethesda distribution across the different age groups and diagnosis on follow-up resection were collated. The ROM in the various categories was compared across the different age groups.
Results: A total of 5,958 FNA for thyroid swelling were performed over a period of 5 years. The paediatric patients constituted 3.3% (n=199) of all the cases. Follow-up histology was available in 2276 patients. The malignancy was significantly higher in patients <18b yrs as compared to adults (18 % vs. 12.7% p-value 0.02). Interestingly, surgical resection rates were also higher in paediatric groups in almost all the categories except benign. Similar to the paediatric age group, the young adult patients also underwent a significantly higher number of resections as compared to adults. The risk of malignancy was comparable between paediatric and young adults age groups.
Conclusion: There was no significant difference in the distribution of Bethesda categories between the adult and paediatric age groups. When resected, paediatric patients are more likely to harbour malignancies than adults with thyroid nodules as the overall risk of malignancy is higher in children as compared to adults. Importantly, the young adult group (19-21 yrs) may behave in a similar manner to paediatric suggesting a reconsideration of the upper age limit, however, more studies are required to further validate this finding.

OFP-09-003

Diagnostic utility of menin immunohistochemistry in multiple endocrine neoplasia type 1 syndrome patients

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Background & objectives: The diagnosis of multiple endocrine neoplasia type 1 (MEN1) syndrome is confirmed with a germline mutation in the *MEN1* gene. As 5-25% of patients suspected of MEN1 remain without definitive genetic diagnosis we investigate the added value of menin immunohistochemistry.
Methods: From 16 MEN1 syndrome patients 31 parathyroid adenomas were collected. As control group, 61 parathyroid adenomas were collected from 32 non MEN1 syndrome patients, these included sporadic (n=30), multiple endocrine neoplasia type 2A (n=1) and hyperparathyroidism-jaw tumour (n=1) patients. Menin immunohistochemistry was performed and its use for identification of MEN1 syndrome related tumours was assessed.
Results: 14 out of 16 MEN1 syndrome patients and 3 out of 32 non MEN1 patients showed nuclear menin loss on immunohistochemistry. On average 1,9 tumours were resected per patient. Using a cut-off of at least one tumour showing menin loss on immunohistochemistry per patient, the sensitivity and specificity in diagnosing MEN1 syndrome was 87,5% and 90,1% respectively. Using a cut off of 2 tumours showing menin loss on immunohistochemistry, the specificity raised to 100%. Menin immunostaining on two cases with a germline variance of unknown significance in the MEN1 gene illustrates the additional value of menin immunohistochemistry in MEN1 diagnosis.
Conclusion: Menin immunohistochemistry is useful in the recognition of MEN1 syndrome and in the genetic analysis of patients with inconclusive MEN1 germline testing.

OFP-09-004

BRAF mutation and AXL (hyper)expression as markers of high risk for persistent/recurrent papillary thyroid cancer (PTC)

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Background & objectives: Thyroidectomy followed with 131-radioiodine therapy (RIT) is the main treatment for differentiated thyroid cancer (DTC) patients with an excellent response rate. The understanding of the PTC molecular mechanisms may be useful to identify patients with higher risk of persistent disease.
Methods: We analysed 42 low (n=32) or intermediate (n=10) risk PTC patients subjected to total-thyroidectomy and RIT with ablative or adjuvant purpose. The response to treatments were evaluated 6-12 months after RIT. The mutational status of BRAF, RAS, TERT, PIK3 and RET, the expression of PD-L1 (as CPS score) and AXL gene and CD4/CD8 ratio were analysed on surgical pathology specimens.
Results: Thirty patients had an excellent response (ER), 6 an indeterminate/incomplete bio-chemical response (BIndR/ BIR) and 6 a structural incomplete response (SIR). A significant correlation was found between BRAF mutation and high expression of AXL gene ($p= 0.001$) and between these parameters and persistent/recurrent disease, respectively ($p=0.02$ and $p=0.03$). BRAF mutation and high expression of AXL gene were also correlated to PD-L1 expression ($p=0.004$ and $p=0.002$). Moreover, PTC patients with persistent disease showed significantly higher PD-L1 and AXL expression and lower level of CD4/CD8 ratio ($p=0.021$, $p=0.032$

and p= 0.015, respectively). No significant association was found about RAS, TERT, PIK3 and RET alterations and persistent/recurrent disease, PD-L1 and AXL expression.
Conclusion: This data suggests that BRAF mutation and AXL (hyper)expression are correlated with increased expression of PD-L1 and CD8 in PTC patients with persistent disease with respect to those without persistent/recurrent disease after initial treatments. Accordingly, they should be considered as potential biomarkers of aggressive behaviour of PTC also suggesting other possible therapeutical targets.

OFP-09-005
Medullary thyroid carcinoma: conventional and emerging prognostic factors
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Background & objectives: Prognosis of patients with medullary thyroid carcinoma (MTC) remains difficult to establish. The objective of our study was to evaluate the prognostic value of the pathomolecular characteristics in MTC.
Methods: Tumour tissues from primary MTC patients diagnosed at Gustave Roussy between 2003 and 2020 were reviewed to assess conventional prognostic factors and immunophenotype. Mutational status of RET was determined using New Generation Sequencing. Outcomes included overall survival (OS), biological (B-DFS) and morphological disease free survival (M-DFS). Univariate and multivariate statistical studies were conducted.
Results: 207 patients were included: 56% were females and the median age was 54 years. In the univariate study for OS: age (>50 years), size (>4cm), extrathyroidal extension, positive surgical margins, absence of encapsulation (AE), necrosis, high mitotic index (MI) (≥5 mitosis/2mm2), lymphovascular invasion, atypical mitosis were significantly associated with poor outcome. In the multivariate study, only AE(p=0.034), necrosis(p=0.001) and MI(p<0.001) remained statistically significant. Using the IMTCGS grading system, high grade tumours (MI≥5 and/or Ki67≥5 and/or necrosis) were associated to a decreased OS, B-DFS and M-DFS. Somatic RET_M918T mutation was found in 31/127(37%). There were no prognostic significant difference between high grade (15/50) and low grade (16/77) RET mutated MTC.
Conclusion: In patients with MTC, AE, necrosis and high MI were associated with poor OS, thus validating the prognostic value of IMTCGS in an independent cohort. Ten of the high grade and seven of the low grade RET_M918T mutated cases experienced relapse, suggesting that this biological trait may represent an independent biological prognostic factor from IMTCGS. Analysis of a larger panel is necessary to confirm these data.

OFP-09-006
Differential expression profiles of immunoregulatory genes in poorly differentiated and anaplastic thyroid carcinomas progressive from papillary carcinoma
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Background & objectives: Few data are available on the immunoregulatory mechanisms of thyroid cancer, with special reference to aggressive forms. We aimed at identifying profiles of expression of immune-related genes in anaplastic (AC) and poorly-differentiated (PDC) carcinomas with associated papillary carcinoma (PC) components.
Methods: Expression levels of over 700 genes involved in immune to tumour response mechanisms were investigated by using the nCounter® PanCancer Immune Profiling Panel in 9 PDC and 12 AC, all having a PC associated component. Moreover, in the 12 AC cases the matched PC component was analysed in parallel.
Results: Over 200 genes were differentially expressed in PDC as compared to AC samples, affecting all main pathways covered by the panel. All pathways were down-regulated in PDC. Pairwise analysis of AC and matched PC components showed a stable pattern of expression for most genes, with a few showing a high statistically significant differential expression (p<0.001 in t test analysis). Among those, 5 (MAP3K1, PRKCD, CYFIP2, BLNK and EPCAM) were down- and 6 (RIPK2, ITGB1, CCL3L1, ITGA5, PLAUR and TICAM2) were up-regulated in AC. Interestingly, for 9 of these 11 genes the pattern of deregulation between PC and AC components was consistent in all samples.
Conclusion: PDC and AC possess specific and different expression profiles of immunoregulatory genes even in the presence of a similar histological pattern of progression. Unexpectedly, progression of PC to AC is not associated with a wide deregulation of immunoregulatory mechanisms. However, a subset of genes is consistently impaired during AC progression, whose role as biomarkers and functional mechanisms need to be assessed and validated in future studies.
Funding: This work was supported by the Associazione Italiana per la Ricerca sul Cancro (Milan, Grant IG 20110 to M.P.).

OFP-09-008
High-grade medullary thyroid carcinoma, morphological features and prognostic value of the international grading system
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Background & objectives: Medullary thyroid carcinoma (MTC) is a rare malignant tumour without a widely accepted grading scheme. In 2021, a multicentric study developed the International Medullary Thyroid Carcinoma Grading System. We seek to employ this system and analyse its prognostic value.
Methods: We reviewed slides from a single-centre cohort of 28 MTC since 2002. Tumours were assigned high-grade based on the presence of at least one of three parameters: mitotic index ≥5 mitosis/2mm2, Ki67 proliferative index ≥5%, and tumour necrosis. We compiled additional pathological features and clinical information to perform a survival analysis.
Results: We identified 7 high-grade carcinomas (25%) and 21 low-grade carcinomas (75%). Two high-grade carcinomas showed all three parameters, whereas one presented both Ki67 proliferative index and tumour necrosis. Two expressed only Ki67 proliferative index ≥5% and the remaining two had tumour necrosis. High-grade carcinomas frequently showed an infiltrative pattern, spindle cell morphology, lymphovascular invasion, lymph node metastasis at diagnosis, AJCC stage III or IV, extrathyroidal extension, and affected surgical margins. Statistical analysis demonstrated decreased overall survival (median 41.57 months vs 64.80 months; LR= 17.412; p<0.001) and decreased disease-free survival (median 6.57 months vs 46.87 months; LR= 10.276; p=0.001) in high-grade carcinomas.
Conclusion: We confirm the prognostic value of the International Medullary Thyroid Carcinoma Grading System in an independent cohort. High-grade carcinomas associated significant decreased

overall survival and disease-free survival, in addition to other pathological parameters of worse prognosis. Therefore, we advocate for a widespread use of this system to help clinicians on patient risk assessment.
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OFP-09-009

Apocrine differentiation in salivary duct carcinoma: immunohistochemical evaluation for GATA3, p62 (Sequestosome1) and FABP7 in 106 cases

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Background & objectives: The up-regulation of p62(sequestosome1) and brain fatty acid binding protein(FABP7) was reported in apocrine carcinoma of the breast(ACB). Salivary duct carcinoma(SDC) is frequently seen as carcinomatous component of carcinoma ex pleomorphic adenoma(CXPA). We aim to elucidate their expressions in SDC.
Methods: We selected SDC cases from a pathology file of 11 institutions during 2000-2020, immunostained them for p62, FABP7 and GATA3, adding to androgen receptor(AR), and gross cystic disease fluid protein(GCDFP)-15. In the assessment for p62, nuclear signals were estimated as N type, whereas cytoplasmic signals were estimated as CY type. We examined with statistical analysis using R version 3.6.2 software.
Results: One hundred six cases were selected as SDC, including 59 cases of CXPA (20 cases of intracapsular type, 8 cases of minimally invasive type and 31 cases of widely invasive type). Eighty one percent of SDC was positive for p62 (N type, 59%; CY type, 10%; N+CY type, 23%). Twenty-nine percent and 90% of SDC were positive for GATA3 and FABP7, respectively. Fifty-two percent and 45% of SDC were positive for AR and GCDFP-15, respectively. The expression status of p62 CY type or (-) was related to worse outcome, whereas the GATA3(+) cases were related to better outcome. Atypical pleomorphic adenoma expressed p62(N type only) in the atypical luminal cells.
Conclusion: SDC should be called "apocrine carcinoma of the salivary glands", due to the positivity for p62, FABP7 and GATA3, like ACB. Adding to GCDFP-15 and AR, the combinations of p62, FABP7 and GATA3 were considered to be new diagnostic markers for SDC. On the other hands, in the cases of CXPA, the luminal cells of PA may acquire the apocrine differentiation during the malignant transformation to SDC.

OFP-09-010

The prognostic role of cortactin overexpression in oral squamous cell carcinoma of tongue: large cohort study

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Background & objectives: Among oral cancer patients, those with squamous cell carcinoma of the oral (anterior 2/3rd) tongue are more likely to have higher mortality rates. Cortactin protein has been linked with progression and nodal involvement in the head and neck carcinoma.
Methods: One hundred twenty-five HPV negative, formalin fixed paraffin embedded specimens were used to show cortacin expression by constructing tissue microarrays using tissue cores of 2 mm diameter from both tumours invading front and the corresponding superficial/central areas. Followed by an analysis of tumour cell invasion in 3D-organotypic co-culture models after siRNA mediated silencing of CTTN gene.
Results: Cortactin expression was higher at the invading core than at the corresponding central cores. High overall cortactin expression was positively associated with tumour size and distant metastases. High overall cortactin expression was associated with reduced 5-year overall survival. siRNA-mediated knockdown of cortactin resulted in reduced proliferative and invasive abilities of cell lines in 3D-organotypic co-culture models.
Conclusion: We showed that the expression of cortactin was significantly higher at the invading cores than at the corresponding central cores. The results of current study also demonstrated that the overexpression of cortactin was associated with a significantly reduced overall survival. Increased expression of cortactin was similarly associated with tumour size and distant metastasis. These findings were further confirmed by analysing the invasive and proliferative abilities of cells in 3D-organotypics. Our findings suggest a prognostic value for cortactin in oral cancer.
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OFP-09-011

Diagnostic utility of NR4A3 and NR4A2 immunohistochemistry in salivary gland pathology: a single-institution experience with 108 cases of acinic cell carcinoma

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Background & objectives: Acinic cell carcinoma (AciCC) is a common salivary gland malignancy, typically composed of neoplastic acinic cells with zymogen granules. The vast majority of cases are driven by a t(4;9)(q13;q31) leading to enhancer hijacking and upregulation of the *NR4A3* gene.
Methods: Seventy-one cases of classic low-grade AciCC, as well as 37 cases with high-grade transformation (HGT), were retrieved from institutional files and included in the analysis (n=108). Immunohistochemistry for DOG1, SOX10 and NR4A3 was performed in all cases; all NR4A3-negative and 10 NR4A3-positive cases were subsequently stained for NR4A2. FISH analysis of *NR4A3* gene rearrangement was carried out in 1 case.
Results: The patients' age ranged from 17 to 86 years (mean=56). Patients with HGT were almost two decades older than patients with low-grade AciCC (mean=67 vs. mean=50). 67% of patients were female. One hundred cases were primary tumours, most commonly occurring in the parotid gland, 6 cases represented recurrences, and 2 lung/pleural metastases were sampled. Immunohistochemical staining for DOG1 and SOX10 was positive in 94% and 97% cases, respectively. NR4A3 was at least focally positive in 104/108 (96%) cases. NR4A3 rearrangement was confirmed by FISH in 1 analysed case. Out of the 4 NR4A3-negative cases, 2 displayed strong nuclear immunopositivity with the NR4A2 antibody, while all 10 NR4A3-positive cases were negative.
Conclusion: Our analysis confirms that majority of AciCC, including cases with HGT, are immunopositive for NR4A3, and suggests that NR4A3 immunohistochemistry is a powerful tool in the differential diagnosis of salivary gland tumours. However, its utility is limited in older and/or sub-optimally fixed samples which often display weaker and focal positivity. Our study also indicates that in minority of cases, AciCC might be negative for NR4A3 immunostaining because the pathogenic genetic event in these cases is rather the overexpression of *NR4A2*.
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OFP-09-012

Molecular-genetic profile of sinonasal tumours: molecularly heterogeneous but histologically distinctive low-grade and high-grade tumours

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Background & objectives: Sinonasal adenocarcinomas (SNAC) are classified as salivary and non-salivary adenocarcinomas. Non-salivary adenocarcinomas encompass a spectrum of high-grade intestinal-type adenocarcinomas (ITAC) and low-grade lesions potentially originating from seromucinous structures non-intestinal type adenocarcinomas (non-ITAC). The molecular genetic background is pleomorphic and inconsistent.
Methods: Retrospectively, 12 cases of sinonasal lesions with a detected gene mutation or gene fusion were selected from the registry of tumours. The cohort included seven cases of low-grade lesions or benign tumours and 5 cases of high-grade carcinomas. These tumours were compared morphologically and immunohistochemically.
Results: Low-grade lesions represented classic forms of seromucinous hamartoma / respiratory epithelial adenomatoid hamartoma or non-ITAC. High-grade tumours were basaloid, keratin positive, solid to papillary. The architecture was mostly monotonous.
In the low-grade malignant/benign subgroup there were detected 6 gene mutations (2x *BRAF* 2x *RET*, 1x *KRAS*, and 1x *PDGFRA* – this case showed an *MYB::NFIB* gene fusion).
In a group of high-grade carcinomas, *ETV6::NTRK3* and *EWSR1::COLCA1/2* were found in 2 cases. One case of epithelial-myoepithelial sinonasal carcinoma harboured an HRAS mutation. One case of sinonasal undifferentiated carcinoma developed two gene mutations in *IDH2* and *ASXL1* genes. One case of high-grade carcinoma showed dual *CREBBP* and *BRIP1* gene mutation.
Conclusion: The sinonasal tract encompasses a wide spectrum of high-grade or low-grade lesions with pleomorphic molecular-genetic backgrounds and only a few of them are truly defined by gene fusion/mutation. There is a need to perform a further investigation to state the correlation between morphology and molecular genetics to better understand pathogenesis.
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OFP-09-013

Update to seromucinous hamartomas and respiratory epithelial adenomatoid hamartomas with dysplastic features and malignant transformation

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Background & objectives: Sinonasal hamartomas (SH) and respiratory epithelial adenomatoid hamartoma (REAH) are rare and underestimated lesions. The term hamartoma is used for an indolent lesion without neoplastic potential, however, SH/REAH does not always behave accordingly.
Methods: We have investigated twenty cases of "dysplastic" polypoid lesions diagnosed either as REAH and SH, adenoid cystic carcinoma (AdCC) arising in SH or REAH, and low-grade non-intestinal-type tubulopapillary adenocarcinoma (LG non-ITAC) arising in SH, low-grade adenocarcinoma ex REAH, and solitary fibrous tumour with SH. All cases were evaluated morphologically and immunohistochemically and 17 cases were tested by molecular-genetic methods.
Results: Dysplastic features of SH/REAH contained irregular cystic glands with atypical epithelial lining with occasional loss of stratification and often intraluminal snouts. The cells had nuclear membrane irregularities and coarse chromatin. The stroma was densely fibrotic almost of desmoplastic character. Immunohistochemical expression of p63 was patchy or negative in SH but preserved in AdCC. Interestingly, expressions of both S100 and SOX10 markers were observed in the seromucinous component but were lost in the AdCC component. We have detected 4 cases with gene fusions (*MYB::NFIB and MYBL1::NFIB*) and 5 cases with developed gene mutation (*BRAF, RET*, and *PDGFRA*).
Conclusion: Our findings not only strongly support that SH/REAH are genuine tumours, but also suggest that may represent a precursor lesion for the development of malignancies. SH/REAH may develop dysplastic features with the potential for risky behaviour. To the best of our knowledge, this is the largest molecular-genetic study of REAH/SH with the occurrence of glandular atypia in them and with a subset of cases with a direct transition into AdCC or LG non-ITAC.
Funding: This study was supported by study grant SVV 22639 from the Ministry of Education, the Czech Republic.

OFP-09-014

Multiparametric, in situ study of the microenvironment (MTE) of head and neck squamous cell carcinomas (HNSCC): impact of human papillomavirus (HPV). Macrophagic Infiltration Study

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Background & objectives: Our study aims to explore the composition of HPV-driven Head & Neck Squamous cell carcinoma (HNSCC) tumour microenvironment (TME), in particular the macrophagic infiltration.
Methods: A multiplex immunofluorescence macrophage signature was applied to 127 patients with HPV-driven HNSCC, using the OPAL® technique developed by AKOYA BioSciences®.
This technique allowed us to apply a macrophage labelling of 7 markers in a sequential manner. Macrophage polarization (CD68, CD163), expression of immune checkpoint inhibitors (PD-L1, PD-L2), tumour cells (CK) and negative regulation pathway of phagocytosis (SIRPa, CD47).
Results: A mapping of the distribution of macrophages between stroma and tumour could be established: unconventional macrophages called "M2" would be more abundant in the stroma, conventional macrophages called "M1" appear to be evenly distributed between tissues and stroma.
The expression of PD-L1 by M1 and M2 macrophages does not seem to be associated with the level of expression of HPV E6 and E7 mRNA in CISH. However, there is a statistical trend in favour of a correlation between the population of intratumoural M1 macrophages expressing SIRPa and the level of E6 and E7 expression.
Conclusion: Thus, E6 and E7 oncoproteins appear to influence SIRPa expression on macrophages M1 in HPV-driven OPSCC. There is a need to confirm the prognostic value of SIRPa expression and to further identify interactions with different lymphocyte populations.

OFP-09-015

Differential expansion of innate lymphoid cells and their role in oral squamous cell carcinoma

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Background & objectives: Oral cancers are the commonest reported cancers in Pakistani males and 2nd commonest in females. We investigated infiltration and potential role(s) of innate lymphoid cells (ILCs) in an accelerated murine model of oral carcinogenesis and in well-defined human cancers.
Methods: We established an accelerated murine model of oral carcinogenesis and characterized tissue infiltration of ILCs in harvested cancer tissues using flowcytometry. We also investigated ILCs infiltration in well-defined human oral cancer tissues. Moreover, we inhibited ILCs using α-Th1 antibody to investigate potential role of ILCs in progression of oral cancers.
Results: 84% of the mice treated with 9,10-dimethyl-1,2-benzanthracene (DMBA) carcinogenic regime developed moderately differentiated squamous cell carcinoma and showed differential expansion of ILCs in various cancers. Moreover, well defined human oral squamous cell carcinoma samples also exhibited increased infiltration of ILCs (along with increased expression of selected/relevant cytokines). Tumour progression did not significantly differ upon inhibition of ILCs using α-Th1 antibody. However, ILCs expansion was different amongst the antibody treated and untreated groups.
Conclusion: We present novel data on differential expansion of ILCs in oral cancers which demands further exploration to exploit these newly discovered cells to devise novel diagnostic, therapeutic and prognostic strategies to prevent/treat oral cancers.

OFP-09-016

High-grade transformation in salivary gland tumours: a rare and under-recognized phenomenon

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Background & objectives: High-grade transformation (HGT) in salivary gland tumours (SGT) is an extremely rare phenomenon associated with aggressive clinical course. Herein, we aimed to study the clinicopathological spectrum of SGT with HGT diagnosed at our institute.
Methods: Clinical data and pathologic material of all cases (2014-2022) was reviewed and diagnosis confirmed as per the WHO 2017. HGT was defined by presence of unequivocal areas of high-grade carcinoma coexisting with conventional low-grade salivary gland carcinoma. Clinical and treatment details were recorded from the electronic medical records. Pathologic features of HGT and conventional areas were recorded and compared.
Results: 18 cases were identified. The median age was 53 years; male-to-female ratio was 2:3. The sites included:submandibular (n=5), parotid (n=4), palate (n=4), tongue (n=2), and 1 case each in nasopharynx, nasal cavity, floor of mouth, buccal mucosa, and maxilla. The histologic types included: adenoid cystic carcinoma (ACC, n=12), epithelial-myoepithelial carcinoma (n=4), polymorphous adenocarcinoma (n=1), acinic cell carcinoma (n=1). HGT areas displayed high-grade cytology, necrosis, brisk mitoses, and higher Ki-67 in comparison to their low-grade counterparts. Poorly differentiated adenocarcinoma was the most common HGT histology. Extra-parenchymal spread, margin involvement, lymphovascular and perineural invasion were identified in 50%, 25%, 30%, and 50%, respectively.
Conclusion: HGT of salivary neoplasms is a rare and frequently under-recognized occurrence that portends a poor prognosis. ACC is the most frequent underlying histology. Accurate diagnosis is essential as aggressive treatment is warranted.

OFP-10 | Oral Free Paper Session Breast Pathology

OFP-10-001

Mucoepidermoid carcinoma of the breast: multidimensional profiling reveals novel biomarkers and genetic drivers

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Background & objectives: Breast mucoepidermoid carcinomas (MEC) are rare salivary gland-type triple-negative breast cancers (TNBC), often considered low-risk malignancies. Their biology is poorly understood, so they pose diagnostic and clinical challenges. We sought to characterize the molecular landscape of breast MECs.
Methods: Thirteen breast MEC were histologically confirmed and subjected to tumour-infiltrating lymphocytes (TILs) profiling and PD-L1 (combined positive score, CPS), EGFR, and amphiregulin (AREG) immunohistochemistry. The MAML2 and EWSR1 rearrangements (recurrent in salivary MECs) were investigated by fluorescent in situ hybridization. Eight cases with enough tissue material were subjected to next-generation sequencing (NGS) of 161 cancer-related genes.
Results: Most cases were of low histological grade with Ki67<30% (n=10/13, 77%). TILs were found in 2 (17%) cases, while PD-L1 CPS ranged from 0 to 20 (median 12.5). All cases with available material showed EGFR overexpression and were AREG-positive (n=9/9, 100%). No MAML2 and/or EWSR1 rearrangements were detected. Pathogenic mutations in PIK3CA were highly recurrent (n=4/8; 50%), though only 1 (12.5%) case harboured a TP53 mutation. Additional somatic mutations affecting cancer-related genes found in MECs included CDK2, NF1/2, AKT1, SMARCB1, MYC, KRAS, CDK4, NOTCH1, and FGFR3/4. Taken together, complex patterns of genetic alterations were observed in PI3K/AKT/mTOR and cell cycle regulation pathways.
Conclusion: Here, we present the broadest collection of breast MECs comprehensively profiled for their molecular alterations. We demonstrate that these tumours lack the hallmark TP53 mutations often found in high-grade TNBC as well as MAML2 or EWSR1 rearrangements. The low TILs and PD-L1 levels suggest an immunoediting deficiency and that MECs may unlikely respond to immunotherapy combination strategies. Finally, the EGFR-AREG axis activation, and genomic alterations in PI3K/AKT/mTOR and cell cycle regulation pathways warrant caution in considering MECs as low-grade TNBCs.

OFP-10-002

Association of metastatic pattern in breast cancer with tumour type and patient specific factors: a nationwide autopsy study using artificial intelligence

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Background & objectives: Heterogeneity of metastatic pattern of breast cancer hampers treatment decisions. Large scale studies into underlying biological and patient specific factors are necessary to progress for future treatment of metastatic diseases.
Methods: Pathological records of 4831 patients diagnosed with breast cancer who underwent autopsy between 1974 and 2010 were retrieved from Dutch nationwide pathology databank (PALGA). Natural language processing (NLP) methods were applied to extract data from autopsy reports. Named entity recognition was based on SNOMED codes that are utilized in PALGA.
Results: The accuracy of data retrieval with NLP was above 0.9 and recall was 0.94 for majority of cases. Our model outperformed manual extraction of value of interest. We identified 2622 (54.2%) of patients with metastatic disease. Invasive ductal carcinoma, and mucinous carcinoma more frequently metastasized to lung and liver, whereas for invasive lobular carcinoma and mixed type this was to bone and liver respectively. There was no statistically significant association between lateralization and metastatic patterns, except for kidney (right= 5.0%, left= 8.9%, bilateral= 13.3%, p= 0.007). In a subgroup of patients, we found that (ER+/HER2+) patients, were more likely to metastasize to liver and bone, compared to (ER-/HER2+) patients.
Conclusion: This is the first large-scale study that demonstrates artificial intelligence methods are efficient for extracting information from Dutch pathology reports. We show differences in frequencies and combinations of metastatic sites between histological subtypes. The patterns and frequencies identified in this autopsy study may reflect the underlying biology of metastatic breast cancer and potentially influence the future follow-ups and patient-tailored treatment strategies depending on other clinical correlations.

OFP-10-003
Automated prognosis marker assessment in 2,004 breast cancers using an artificial intelligence-based framework for BLEACH&STAIN mfIHC
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Background & objectives: Prognostic markers in routine clinical practice of breast cancer are currently assessed using multi-gene panels. However, the fluctuating tumour purity can reduce the predictive value of such tests. Immunohistochemistry holds the potential for a better risk assessment.
Methods: To enable automated prognosis marker detection (i.e. HER2, GATA3, progesterone- [PR], oestrogen- [ER], and androgen receptor [AR], TOP2A, Ki-67, TROP2), we have developed and validated a framework for automated breast cancer identification, which comprises three different artificial intelligence analysis steps and an algorithm for cell-distance analysis of 11+1 marker BLEACH&STAIN multiplex fluorescence immunohistochemistry (mfIHC) staining in 2'004 breast cancers.
Results: The optimal distance between Myosin+ basal cells and benign panCK+ cells was identified as 25 µm and used to exclude benign glands from the analysis combined with several deep learning-based algorithms. Our framework discriminated normal glands from malignant glands with an AUC of 0.96. The accuracy of the approach was also validated by well-characterized biological findings, such as the identification of 13% HER2+, 73% PR+/ER+, and 14 triple negative cases. Furthermore, the automated assessment of GATA3, PR, ER, TOP2A-LI, Ki-67-LI and TROP2 was significantly liked to the tumour grade ($p<0.001$each). Furthermore, a high expression level of HER2, GATA3, PR, and ER was associated with a prolonged overall survival ($p\geq0.002$ each).
Conclusion: A deep learning-based framework for automated breast cancer identification using BLEACH&STAIN multiplex fluorescence IHC facilitates automated prognosis marker quantification in breast cancer.

OFP-10-004
Upgrade rate and predictive factors for benign breast intraductal papilloma on core biopsy in Vancouver, Canada
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Background & objectives: The management of benign intraductal papillomas (IDPs) diagnosed on core biopsy is controversial. We aim to determine the upgrade rate of IDPs diagnosed on core biopsy in subsequent surgical excision specimens and to identify associated clinical, pathologic, and radiologic factors.
Methods: This is a retrospective population-based study of all breast papillary lesions diagnosed on core biopsy from 2017-2019 in Fraser Health Authority in Greater Vancouver, Canada. Patient demographics, histopathologic, and radiologic findings were analysed. Upgrade was defined as atypical ductal hyperplasia (ADH), ductal carcinoma in situ (DCIS), encapsulated papillary carcinoma (EPC), solid papillary carcinoma (SPC), and invasive carcinoma on surgical excision.
Results: A total of 129 patients with benign IDPs diagnosed on core biopsy were included. The overall upgrade rate to atypia or malignancy was 9.3% (12/129) on final excision. This included 7 with ADH, 7 with DCIS, EPC or SPC, and 1 with invasive carcinoma. Predictors of upgrade included older age (55.6 vs 66.1 years, $p < 0.0001$) and larger lesion size (11.1 vs 15.1 mm, $p = 0.001$). Older age ($\geq$ 55 years) (OR [95%CI] 5.3 [1.04-27.08]) was an independent predictor of upgrade. In our study, location (central vs peripheral) and BI-RADS radiologic category were not associated with predicting upgrade.
Conclusion: Our findings support surgical excision of IDPs diagnosed on core biopsy in women aged 55 years or older with large lesions, while a conservative approach (close clinical follow-up) may be warranted for younger women with smaller lesions.

OFP-10-005
Evaluation of dual colour-dual in-situ hybridization (D-DISH) for HER2/neu testing in breast cancer
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Background & objectives: To standardize and validate the HER2 Dual ISH DNA Probe Cocktail (D-DISH) assay by VENTANA for HER2/neu testing in breast cancer using FISH as the gold standard and to assess the interobserver variability in interpreting D-DISH.
Methods: HER2/neu IHC, FISH, and D-DISH assay by HER2 Dual ISH DNA Probe Cocktail Assay (Ventana Medical Systems, Inc., Tucson) were performed on 120 breast carcinoma cases. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated against D-DISH results for four pathologists (FISH-gold standard). The absolute agreement between FISH and D-DISH ratios, average signals was assessed.
Results: A concordance of 98.3% was observed between FISH and D-DISH assays. D-DISH showed a sensitivity of 95.92%, specificity of 100%, PPV of 100%, and NPV of 97.26%, with respect to FISH. Cohen's kappa statistic was 0.96 demonstrating perfect agreement. Intraclass correlation coefficient (ICC) values of 0.97 (HER2), 0.92 (CEP17), and 0.97 (HER2/CEP17) were observed. Interobserver variability showed an almost perfect agreement

(kappa values 0.98-1.0) and ICC values of 0.96-0.98, 0.91-0.95, and 0.96-0.98 in measuring the HER2 signals, CEP17 signals, and HER2/CEP17 ratio, by D-DISH respectively. Interobserver variability between the four pathologists showed perfect agreement for genomic heterogeneity and group categorization, and moderate agreement for polysomy by D-DISH.
Conclusion: Our study successfully validated the D-DISH test using the updated version of HER2 Dual ISH DNA Probe Cocktail Assay (Ventana Medical Systems, Inc., Tucson, AZ) as a substitute for FISH assay in accurately predicting the HER2 gene status with significant interobserver reproducibility. We conclude that this D-DISH test may be introduced in rouine diagnostic services as a reflex test for detecting HER2 gene status.

OFP-10-006
Image-based identification of HER2 status in H&E-stained breast cancer slides
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Background & objectives: Determination of HER2 status is critical for prognosis and guiding treatment decisions in breast cancer patients. Here we present a method to detect HER2 expression directly from routinely prepared diagnostic H&E slide images, using an image-based deep learning approach.
Methods: A HER2-classifier was generated using 251 H&E-stained slide images and their relevant IHC and FISH status from the pathology department at Sourasky Medical Center. Convolutional neural network (CNN) analysis was performed on on-the-fly augmented images. Multiple instance learning (MIL) algorithms and ranking training schemes were applied to create the categorical HER2-classifier (positive/negative), powered by Imagene-AI.
Results: The HER2-classifier was evaluated on a validation set including H&E images only of 104 retrospective cases. The model performance values were 87.5% sensitivity, 85.9% specificity, 86.14% accuracy and 0.89 AUC. To further evaluate the AI-solution additional 245 cases were analysed. In this set, a high proportion (n=9/20; 45%) of false callings was observed in samples with HER2 IHC=3. The IHC slides of samples with score 3 in the set were re-evaluated by two pathologists. While three of the 9 false-negative cases (33%) status was changed to 2, by at least one pathologist, there were no changes in the true-positive group (n=9).
Conclusion: Implementation of Image-based solution to routine pathology workflow can support fast, cost-effective and standardized method for biomarker detection. We evaluated the use of an AI-model to analyse HER2 status compared to conventional IHC and FISH methods. Analysis of 349 cases resulted in 85.3% accuracy. IHC, manually analysed by pathologists, is a subjective method with both intra- and inter-observer discordance's reported. An AI-solution can support the routine workflow flagging cases where re-evaluation can support the pathologist analysis of difficult cases.

OFP-10-008
Application of molecular imaging as potential prognostic biomarker for triple-negative breast cancer (TNBC)
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Background & objectives: The administration of the antihypertensive syrosingopine in combination with metformin provided a synergistic effect against different tumours, including breast cancer. We aimed to investigate the response to metformin and/or syrosingopine, evaluating the [18F]FDG and [18F]FLT as potential early prognostic biomarkers.
Methods: Balb/c female mice were inoculated subcutaneously with murine TNBC cells (4T1) and divided into six treatment groups: vehicle, cisplatinum, metformin, syrosingopine or cisplatinum plus metformin and metformin plus syrosingopine. The response to treatment was monitored by caliper measuring, for tumour volume and PET studies. Molecular biomarkers of glucose metabolism and tumour invasiveness were analysed by means of immunohistochemistry and q-RT-PCR.
Results: A significant tumour growth inhibition (%TGI) has been observed only after metformin plus syrosingopine administration, confirming a synergistic effect after ten days of treatment. PET analyses revealed a significant reduction of [18F]FLT tumour uptake in cisplatinum plus metformin ($*p<0.05$) and metformin plus syrosingopine ($*p<0.001$) treated groups, whereas [18F]FDG uptake increased in all experimental conditions. Molecular analyses performed by both immunohistochemistry and q-RT-PCR demonstrated a significant decrease of the lactate transporter MCT4 levels in mice treated with cisplatinum and metformin plus syrosingopine ($*p<0.05$) as well as low levels of the EMT biomarker Snail only in the group treated with the combination of metformin plus syrosingopine ($*p<0.05$).
Conclusion: Our data suggested that the combined administration of metformin plus syrosingopine is able to modulate the glucose metabolism and inhibit the tumour invasiveness and growth of cancer cells. Moreover, the use of [18F]FLT radiotracer may represent a potential biomarker for the early response to treatment of TNBC.

OFP-10-009
Challenges of breast NEN: NEN G3 and genetic analysis
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Background & objectives: The Breast NEN(Br-NEN)was graded according to Nottingham standard, resulting in confusion between Br-NENG3 andNETG3. It was unclear whether therapeutic targets associated with gastroenteropancreatic NENare applicable in Br-NEN. This study aims to illustrate these issues.
Methods: The 50 cases were re-diagnosed according to the 5thWHO classification criteria. The gastroenteropancreatic NEN characteristic immunohistological staining (SSTR1-5, DLL3, ISL-1, INSM-1) were performed, and DNA was isolated from the primary tumour for exome sequencing. In this study, NET G3 was set as Nottingham grade 3, excluding small cell carcinoma and large cell neuroendocrine carcinoma.
Results: 1)Compared with G3 and NEC,the MYC pathway was enriched in G3, and the TP53 pathway was more common in the latter (P=0.036).
2)The G3 had more ZNF703 and FGFR1 genetic mutations than NEC, and was more likely to exhibit the genetic characteristics of Luminal B.
3)The SSTR2 and INSM1 positive expression was more common in the G1-2, P=0.006 vs 0.012, and showed decreasing trend in NEC compared with G3. No positive expression of DLL3 was found in G3except NEC.
4)The metastasis occurred in 3 cases (6% G3,11% NEC, 4% G1-2) and the breast cancer-related deaths occurred in 4 cases(12%

G3,22% NEC). G3 showed poor prognosis than G1-2, but better than NEC.
Conclusion: 1)The poorly differentiated group has more frequent genetic alterations and poor prognosis.Br-NET G3 show genetic alterations and a better prognosis distinct from Br-NEC. Whether the Br-NET G3 concept is different from the Br-NEN G3 needs to be explored by more data.
2)The expression pattern of SSTR1-5, DLL3, ISl-1 and INSM-1 in Br-NEN was similar to that in gastroenteropancreatic NEN, so based on these biomarkers, it may be necessary to explore the potential therapeutic significance in Br-NEN.

OFP-10-010
Prediction of the efficacy of neoadjuvant therapy for breast cancer with immunologic and genome characteristics
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Background & objectives: The effect of different immune cells and genomic alterations in tumour microenvironment before neoadjuvant therapy (NAT) in breast cancer patients on efficacy is currently uncertain. This study aimed to explore its impact on efficacy of NAT in breast cancer patients.
Methods: 81 cases of breast invasive cancer diagnosed by core needle biopsy before NAT were selected. Multiple Immunohistochemical/Immunofluorescence (mIHC/IF) detected CD3, CD8, PD-L1 and PD-1. Next generation sequencing (NGS) technology analysed the genome and detect somatic cell variation. Logistic regression analysis was used to draw a nomogram to predict the pCR rate of breast cancer patients.
Results: Patients were divided into two groups by NAT efficacy: pCR and non-pCR. The mIHC/IF results showed expression level of stromaCD8+cells, parenchyma and stroma PD-L1+cells in pCR was higher, with statistically significant differences ($P < 0.05$).NGS testing results showed the highest mutation rate was TP53(81%), followed by ERBB2(49%), PIK3CA(47%), CDK12(46%) and LRP1B (8%), et al. The mutation types include missense mutation, copy number amplification, synonymous mutation, et al. Only the difference in LRP1B mutation rate between two groups was statistically significant (P=0.011).Cox regression analysis showed expression level of stromal CD8+ cells, stromal and parenchymal PD-L1+ cells and LRP1B mutation rate influenced pCR ($P < 0.05$). The calibration chart(AUC:0.78) showed that the nomogram performs well and has high pCR predictionability.
Conclusion: There is a difference in immune microenvironment and gene expression profiles between pCR and non pCR patients. And the expression levels of CD8 + cells in tumour stroma, PD-L1+ cells in tumour parenchyma and tumour stroma are high, and LRP1B gene is prone to mutationin pCR patients. The nomogram of predicting pCR rate has good consistency, which can provide a certain predictive value for breast cancer patients with neoadjuvant therapy.

OFP-10-011
Histological assessment of large fresh breast surgical specimens with ultra-fast slide-free confocal microscopy: a feasibility study
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Background & objectives: A new generation of ultra-fast confocal microscope (UFCM) with a large field of view allows ex-vivo analysis of surgical specimens. We present the standardization of UFCM protocol for breast lumpectomy and the original online training program in breast UFCM images.
Methods: Fresh lumpectomies from 55 patients with breast conservative surgery were cut in two, stained with acridine and imaged with Histolog-Scanner-field of view of 20 cm^2 (Samantree Medical). The images were colored in purple to simulate frozen sections and annotated by three pathologists expert in breast and confocal pathology. The images were used for a training program followed by two pathologists.
Results: All surgical specimens were successfully imaged. Among these 55 cases, 49 were carcinomas (31 invasive no special type, 11 invasive lobular, 7 ductal carcinoma in situ) and in 6 cases no tumour was present at definitive histological examination. The UFCM protocol was completed in 8-10mn. The global architecture of the tissue was evaluated at low magnification and the cellular details at zoom (x40). The 30µm of axial resolution resulted hypercellularity compared to final histology. Training program was composed of 135 reading sheets including tumoural and non-tumoural features. Pathologists who completed the training program performed a diagnosis on the 88 self-assessment sheets getting 100% accuracy.
Conclusion: UFCM allowed to quickly image a 20 cm^2 area of an entire section of fresh breast lumpectomy. The training of pathologists in reading UFCM images was successful, probably since the images resemble traditional frozen sections. However a training is mandatory because the magnification of the images is lower than with microscope and the optical section is 30 µm thick. The pilot study points the feasibility of UFCM for fast and extensive intraoperative margin assessment during breast surgery.
Funding: SamanTree medical, European Union's Horizon 2020 research and innovation program under grant agreement No 823284

OFP-10-012
PIK3CA mutations in endocrine-resistant breast cancer
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Background & objectives: The majority of breast cancer patients' tumours express oestrogen receptor alpha (ER) but despite endocrine therapy, one-third progress or relapse. Studies investigate the phosphoinositide-3-kinase pathway, introducing therapies targeting PIK3CA. This study aims to examine the mutational prevalence in endocrine-resistant tumours.
Methods: In a retrospectively collected cohort of verified endocrine-resistant breast tumours diagnosed in 2008-2012, primary ER+ and human epidermal growth factor receptor 2 (HER2) negative breast cancers with an ER+/HER2- relapse during ongoing endocrine therapy were included. Targeted gene panel sequencing was performed on formalin-fixed paraffin-embedded tumour tissue and paired analysis was carried out between the relapse and primary tumours.
Results: The overall preliminary analysis showed PIK3CA mutations in 48.9% of all patients (n/N=23/47), of which 65.2% (n=15) had mutations in the 11 known hotspot regions. 65.2% of the mutations were similar between the primary and relapse tumours, 73.3% of these were found in hotspots, whilst 34.8% seem to develop or disappear during ongoing endocrine therapy. In primary tumours of patients that eventually relapsed during endocrine therapy, 60.9% had mutations in hotspots and 30.4% outside of these regions. In their relapse tumours, 56.5% had hotspot mutations and 26.1% elsewhere.
Conclusion: Our study of this unique cohort suggests that endocrine-resistant breast cancers are associated with high PIK3CA

mutation frequencies, with significant proportions occurring outside of the known hotspot regions; analysis is ongoing for prognostic value combined with clinical data. Similar mutational profiles of primary and relapse tumours suggest invariability through treatment and may thus aid in utilizing diagnostic tools for therapeutic response prediction. Moreover, similar and alternating mutations of the tumours can be further investigated for incorporation of future mutation-targeted treatments.
Funding: This trial is a non-interventional study set up as a research collaboration between Karolinska Institutet and Novartis Sweden AB.

OFP-10-013
Breast carcinoma with apocrine differentiation: less indolent than expected?
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Background & objectives: Breast carcinoma with apocrine differentiation is a rare (1%) breast cancer histotype characterized by apocrine morphology in >90% of cells, that typically shows positivity for androgen receptor (AR) and it's either triple-negative or HER2-positive, non luminal.
Methods: At our Institution, 37 patients were diagnosed with breast carcinoma with apocrine differentiation between January 2010 and December 2020. Data about patient's age, and tumour histological grade, ER, PR, Ki-67, AR and HER2 status and TNM staging was obtained from pathological report. Of note, no patient had undergone neoadjuvant therapy.
Results: Of our 37 cases, 25 were classified as high grade, and 11 as low or intermediate grade according to the Nottingham Histologic Score. The high grade group comprised slightly younger patients (median age: 69 vs 71,5) and showed a statistically significant prevalence of HER2-amplified tumours (14/25 vs 1/12, p=0.0106) and a higher Ki-67 average score (28% vs 13% in the low and intermediate grade tumours); no difference was observed in loco-regional stage of the tumour (average primary tumour dimension: 22,7 mm vs 18,1 mm; cases with positive lymph nodes: 11/25 vs 6/12).
Conclusion: Despite being regarded as an histotype with a more indolent course, our data shows that even lower grade apocrine carcinoma has a high propensity for loco-regional spread, and should be managed accordingly; the net difference in prevalence of HER2 amplification between low and high grade tumours suggests that different, unknown molecular events underlie disease progression in the two groups, and warrants further studies to define the biology of this histotype.

OFP-10-014
Claudin-1 expression in triple-negative breast cancers (TNBCs) and its clinical significance
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Background & objectives: TNBC is an aggressive disease, lacking therapeutic and prognostic markers. Claudin-1, a biomarker with a prognostic value in several tumours, reportedly has conflicting results in TNBCs. The authors shed some light on claudin-1 expression in TNBC and its value.
Methods: We analysed the expression of claudin-1, a tight-junction protein that has a promising prognostic value in several cancers, by immunohistochemistry, in TNBC cases from the King Khaled university hospital. This expression was cross-checked against clinical-pathological criteria of TNBC patients, and against beta-Catenin expression in the same patients' sample.
Results: Claudin-1 was significantly expressed in the majority of TNBC cases. This expression was significantly correlated with lymph node metastases, tumour invasion, higher tumour nuclear grade, higher clinical and TNM staging, adverse survival outcome and failure to achieve remission following neoadjuvant chemotherapy (NAC). TNBCs' claudin-1 expression was also correlated with grade-2 abnormal expression of beta-Catenin (AEB) in the same patients' sample.
Conclusion: Most cases of TNBCs in our institution expressed the claudin-1. This expression is strongly linked to parameters of poor prognosis. The above may shed some light on the possible role of claudin-1 in TNBC; and may present an opportunity for the use of this biomarker in the management of TNBC patients.

OFP-10-015
Filamin-A expression in triple negative breast cancer (TNBC) and its clinical significance
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Background & objectives: TNBC presents a clinical dilemma with early recurrence, metastases and poor survival outcome. Filamin-A is recently discovered protein which plays a dual role as oncogene and tumour-suppressor gene in many cancers. This study analyzes the expression of Filamin-A in TNBCs.
Methods: This study analysed the expression of Filamin-A, using immunohistochemistry, in a tissue microarray of 50 cases of triple-negative, invasive ductal breast carcinomas. Filamin-A expression was cross-checked against clinic-pathological attributes of the TNBC cases including age, grade, clinical stage and TNM staging. Filamin-A expression within the cell was analysed. The TNBC cases were further categorized by the intensity of Filamin-A expression.
Results: A significant majority of this study's TNBCs exhibited positive expression of Filamin-A. All Filamin-A positive TNBC cases expressed the protein in the cytoplasm of the tumour cells. Filamin-A expression was significantly correlated with TNBC grade, clinical stage, and TNM staging. A significant majority of TNBC cases had the highest intensity of Filamin-A expression (35/45, IRS=12). This study is the first to analyse expression of Filamin-A only in TNBC cases. When compared with other studies which analysed this expression in breast cancer sets (mixed sets); it was noted that the number of Filamin-A positive cases were much higher in this study's TNBC set.
Conclusion: Given the versatile role of Filamin-A, with its numerous interactions with cytoskeleton components of tumour cells and with signalling proteins, in addition to its role in modulating sensitivity to the chemotherapeutic agent Docetaxel, make the results of this study particularly important in TNBC patients, who have few management options. This study provides evidence of the clinical significance of Filamin-A in TNBCs, and proposes additional studies to pinpoint the exact function of this protein in this subset of breast cancer patients.

OFP-10-016
Nullisomy of chromosome 17 in invasive breast cancer: characterisation of a rare and puzzling genomic event

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Background & objectives: In situ hybridization (ISH) is systematically performed for HER2 2+ invasive breast cancer. Nullisomy is a rare genomic event that may mislead the pathologist in ISH interpretation. We aimed at describe the pathological and molecular features of three nullisomy cases
Methods: Three cases of cen17 nullisomy breast cancer (BC) were retrieved from our archives. Clinical, pathological and treatment data were collected for each case. HER2 immunohistochemistry and HER2/cen17 fluorescent ISH were scored following the last ASCO/CAP guidelines. DNA was extracted from formalin-fixed paraffin-embedded samples and subjected to SNP array (OncoscanTM). A Foundation One liquid CDx analysis was available for one patient.
Results: All patients presented with metastatic BC, two of them from the outset. All tumours were high grade, oestrogen receptor positive. HER2 score was 2+ (n=2), or 3+ heterogeneous (n=1). All cases showed no signal in tumour cells with cen17 probe, whilst a signal was observed in normal cells. Two cases were HER2 amplified (HER2=7.9 and 9). All cases displayed a complex genomic profile with homozygous loss of the chromosome 17 centromeric region, associated to multiple quantitative chromosomic alterations. All cases showed chromosome 8q gain involving CCNE2 and MYC genes. Liquid biopsy sequencing of the lobular case additionally identified ESR1, PIK3CA, CDH1, DNMT3A, FAM123B, PTPN11 and TP53 mutations.
Conclusion: Nullisomy of chromosome 17 centromeric region is a poorly known genomic event that may prove puzzling for the pathologist while reading HER2 ISH in invasive BC. Our study shows that this exceedingly rare alteration is associated to BC showing a strikingly aggressive clinical course, and displaying a consistent complex genomic profile.

OFP-11 | Joint Oral Free Paper Session IT & Other Topics (Electron Microscopy / Cardiovascular Pathology)

OFP-11-001
Epidermolysis bullosa: an electron microscopy study of 6 cases

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Background & objectives: Epidermolysis bullosa (EB) is a group of rare inherited disorders characterized by skin fragility and blistering after minor trauma. This study presents the ultrastructural features of six cases of EB, highlighting the diagnostic role of transmission electron microscopy (EM).
Methods: Skin biopsies from six infants were processed for both light microscopy (LM) and EM. Five of six patients were younger than 1 month. Clinical presentation included skin fragility and blisters in all cases. Oral mucosa involvement was reported in one case. LM revealed a completely detached epidermis in all cases of dystrophic EB.
Results: EB cases were classified based on the split level as EB simplex (EBS), junctional EB (JEB), and dystrophic EB. One case showed intraepidermal cleavage, intrakeratinocyte splitting, and tonofilament clumps suggesting generalized severe EBS.
EM findings of JEB were found in one case. These included multiple microsplits through the lamina lucida and a reduced number of anchoring filaments into the lamina densa.
Ultrastructural features of both EBS and JEB were found in one case, revealing intra-lamina lucida splits, suprabasal cleavage, and intracytoplasmic fractures.
All three cases of dystrophic EB showed a split below the lamina densa, with absent or markedly reduced anchoring fibrils between the lamina densa and collagen bundles.
Conclusion: Even though TEM tends to be replaced by immunolabeling and genetic testing, ultrastructural studies are still relevant in the diagnosis of EB. Not only can EM establish the major type of EB by identifying the level of the split in the skin, but also it can provide critical prognostic information in several subtypes. Moreover, EM can detect subtle changes in the dermo-epidermal junction and was proven to be superior in diagnosing EBS in absence of evident blisters.

OFP-11-002
Clinico-pathologic correlation in cardiac amyloidosis: is there a substrate for the echocardiographic "relative apical sparing" sign?

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Background & objectives: Myocardial longitudinal strain (LS) and strain rate by speckle-tracking echocardiography play a prognostic role in cardiac amyloidosis (CA) and relative apical sparing of LS (RELAPS) is useful for early diagnosis. Our aim was to assess regional differences in amyloid burden.
Methods: Retrospective study of whole hearts from autopsy with histological evidence and immunoelectron microscopy typing of CA. Amyloid burden was assessed quantitatively by histomorphometry on sodium sulphate-Alcian Blue stained transmural slides at different levels from base to apex. The parameters of myocardial LS by echocardiography performed before death were compared to the amyloid burden and basal-to-apex distribution.
Results: Of the 29 hearts examined, amyloid typing identified 19 cases of immunoglobulin light chains (AL, 65.5%) and 10 transthyretin (ATTR, 34.5%). A prevalent interstitial deposition was found in 20 (69%) and vascular in 9 (31%). Among the latter, all but one (88.9%) were AL. A homogeneous distribution of amyloid was demonstrated, with a median of 25.38, 26.70 and 18.8 (P=NS) at the basal, mid and apical sections, respectively. In 11 patients, echocardiography during the same hospitalization showed a significant LS basal-to-apex gradient. A correlation was found between total histological amyloid burden and the reduction of LS at echocardiography, although the RELAPS didn't match to a basal-to-apex gradient of amyloid.
Conclusion: This clinico-pathological study demonstrates that amyloid is evenly distributed in the ventricular myocardium both in AL and ATTR. While there is a correlation between total amyloid burden and reduction of LS, the typical basal-to-apex gradient in LS at echocardiography does not appear to be explained by a gradient of amyloid burden in whole hearts. Our findings thus suggest that RELAPS is an epiphenomenon of complex interactions among amyloid infiltration, myocardial structure and consequent adaptation.

OFP-11-003
Acute myocarditis in COVID-19 era: pre-pandemic and pandemic periods compared

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Background & objectives: Acute Myocarditis (AM) has been much discussed as one of the most frequent cardiac complications of COVID-19. Despite serious clinical suspicion, however, there is no substantial EMB histological series.
Methods: At the S.Orsola Bologna Centre, cardiologic referral Centre for Emilia-Romagna region, we retrospectively analysed and compared two groups of patients who underwent EMB for clinical suspicion of myocarditis in the 5 years pre-pandemic (2015-2019, Group 1) and in the initial 15 months of the pandemic (April 2020-June 2021, Group 2), before the vaccine became generally available in our region.
Results: In group 1, of 65 patients who underwent EMB, 31 (47.7%) had a histological diagnosis of AM, with histotype: lymphocytic in 24 cases, giant cell in 1, toxic in 1, mixed in 1. Extension of inflammation was focal in 19 and multifocal/diffuse in 12. Month ratio in suspected cases was 1.1; in histological confirmed cases 0.5.
In group 2, of 23 patients 13 had EMB positive for AM (56.5%), with histotype: lymphocytic in 8 cases, giant cell in 1, eosinophilic in 2, mixed in 2. Extension of inflammation: was focal in 7 and multifocal/diffuse in 6. Month ratio in suspected cases was 1.5, in histological confirmed AM, 0.9.
Conclusion: In this study we analysed the frequency, clinical presentation and histological parameters of suspected AM before and during the pandemic. During the pandemic there was an increase in number of cases, in terms of both clinical suspicion and of histologic confirmation at EMB. The cases were generally more severe and showed a different range of histotypes, but there was no real correlation with SARS-CoV-2.

OFP-11-004
From conventional congenital cardiac surgery to molecular cardiac surgery: between darkness and light. New paradigms for investigations and treatments during pregnancy
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Background & objectives: We advocate new biological models and protocols for investigation and treatment of severe CHD on the light of nowadays spectacular progresses of the Molecular Biology with the Next Generation Sequency (NGS), Microarray Technologies and CRISPR-Cass9 Technique.
Methods: We reconsidered the embryogenesis and the morphology of the most severe forms of CHD, from TF to Transpositions and Univentricular Hearts, considering the diagnostic potentiality of maternal liquid biopsies in pregnancy and with emphasis on the CHD embryogenetic patterns. (Capuani et al. Ann Thorac Surg 1995, J Cardiothorac Surg 2014, Virchow's Archives 2015, 2016, 2020).
Results: We found a common morphological denominator encompassing all pathological cardiac settings: the Trabecula Septomarginalis (Leonardo's Cord) sequential counterclockwise malrotation. Several genes are involved in the process with over and under expression and network interactions. Microarray and NGS analysis applied early in pregnancy and to each single step of the malrotation may lead to a very early diagnosis and possible treatments. We present our research protocol.
Conclusion: Each malformed cardiac phenotype has a specific molecular profile. The TSM malrotation protocol encompass all cardiac pathological phenotypes and is proposed as a model for investigation and treatment of CHD early in pregnancy by NGS, Microarray and CRISPR-Cass9 technique, what we refer as Molecular Cardiac Surgery.

OFP-11-005
Reporting guidelines for pathology AI research – a review
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Background & objectives: An explosion of interest into applications of artificial intelligence (AI) is transforming pathology research. Complete reporting of research is essential for avoiding research waste and benefitting patients. The objective of this work was identifying reporting guidelines for pathology AI research.
Methods: The Equator Network library of 499 reporting guidelines and extensions was systematically searched to identify those applicable to pathology AI research. Inclusion and exclusion criteria were used and guidance was screened for utility at different stages of research and for a range of study types. Items were compiled to create a summary for easy identification of useful guidance and templates.
Results: 70 reporting guidelines and extensions applicable to stages of pathology AI research were identified. These were categorised into 5 groups: Literature & Research Priorities, Discovery, Clinical Trial, Implementation and Post-Implementation & Guidelines. A summary resource was developed for pathology AI researchers, with links to guidelines for these 5 groups, to assist in complete reporting of research. Guidelines currently in development and those useful at multiple stages of research were also highlighted. Our group recently published a study demonstrating that essential information is underreported in pathology AI studies, making replication difficult. Therefore, this summary will be shared publicly to highlight the availability of reporting guidance to the pathology AI research community.
Conclusion: Replication and research waste are recognised to be problematic in AI research. Reporting guidelines can be used as templates to ensure the essential information needed to replicate research is included within journal articles and abstracts. Reporting guidelines are available and useful for many study types, but greater awareness is needed to encourage researchers to utilise them and for journals to adopt them. This review and summary resource highlights guidance to pathology AI researchers, aiming to improve completeness of reporting.
Funding: Dr McGenity is funded by Leeds Hospitals Charity and the National Institute for Health Research (NIHR). Prof. Treanor is funded by National Pathology Imaging Co-operative (NPIC). NPIC (project no. 104687) is supported by a £50m investment from the Data to Early Diagnosis and Precision Medicine strand of the Government's Industrial Strategy Challenge Fund, managed and delivered by UK Research and Innovation (UKRI).

OFP-11-006
A holistic evaluation of three-dimensional biomarker expression and genetic alterations in non-small cell lung cancer using tissue clearing technology
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Background & objectives: The common practice of assessing programmed death-ligand 1 (PD-L1) expression based on a single section may not be representative. To overcome this problem, we developed a novel protocol that can make formalin-fixed, paraffin-embedded tissue translucent, allowing three-dimensional (3D) imaging.

Methods: Our protocol can process tissues up to 150-µm in thickness, allowing anti-PD-L1 staining of the entire tissue and producing high resolution 3D images. After 3D imaging process, the thick sections were recovered for epidermal growth factor receptor (EGFR) mutation analysis. We further developed artificial intelligence-assisted models to calculate the tumour proportion score (TPS) of the entire 3D tissue.
Results: Artificial intelligence-assisted PD-L1 quantitation of these images revealed a marked variation of PD-L1 expression in 3D. In 5 of 33 needle-biopsy-sized specimens (15.2%), the TPS varied by greater than 10% at different depth levels. In 14 cases (42.4%), the TPS at different depth levels fell into different categories (<1%, 1–49%, or ≥50%), which can potentially influence treatment decisions. The EGFR mutation analysis performed using pre- and post-processing tissue yielded identical results in all the tested cases, including 4 cases with EGFR L858R mutation, 6 cases with EGFR exon 19 deletion, 1 case with EGFR exon 20 insertion, 1 case with EGFR G719X mutation, and 8 cases without detectable EGFR mutation.
Conclusion: Our novel method has the potential to increase the accuracy of tumour PD-L1 expression assessment and enable precise deployment of cancer immunotherapy. In addition to application in PD-L1 expression assessment in non-small cell lung cancer, 3D tissue imaging can also potentially apply to the evaluation of biomarkers in other cancer types. Importantly, our technology permits recovery of the processed tissue for subsequent mutation analysis, enabling holistic evaluation of the protein-level expression and genetic alterations in small specimens.
Funding: Industry-academia collaboration grant from JelloX Biotech Inc. (grant number R-19005)

OFP-11-008
CoNIC Challenge: large scale assessment of automated methods for identification and counting of Colon Nuclei
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Background & objectives: Identification of nuclei in histology images, such as those from epithelial and inflammatory cells, enables large-scale profiling of the tumour microenvironment. To help drive forward innovation for automatic nuclear recognition, we organised the Colon Nuclei Identification and Counting (CoNIC) Challenge.
Methods: We created the largest dataset for nuclear recognition in computational pathology, containing around 550K labelled nuclei, and invited researchers to develop algorithms on the data, aimed at solving 2 tasks: 1) nuclear segmentation & classification and 2) prediction of cellular composition. Participants submitted model code to the challenge, which enabled the test data to remain completely unseen.
Results: In total, we had 323 and 50 submissions to the preliminary and full test phases, respectively. Submissions were ranked by multi-class panoptic quality (mPQ+) and multi-class coefficient of determination (R2) for tasks 1 and 2, respectively. The top segmentation and classification submission achieved an mPQ+ of 0.501 and the top cellular composition prediction submission achieved an R2 of 0.764. Best models were able to successfully identify underrepresented classes, such as neutrophils, eosinophils and plasma cells, helping them to achieve competitive mPQ+ and R2 scores.
Conclusion: Nuclear morphology and co-localisation of different subtypes have shown to be important indicators of cancer prognosis and diagnosis. However, manual assessment is not feasible as each tissue sample typically contains thousands of nuclei. We organised the CoNIC Challenge to encourage the development of automatic approaches for nuclear recognition in computational pathology. We hope that the widespread participation will motivate researchers to further develop methods on the provided data and accelerate the development of downstream cell-based models for clinical applications.
Funding: Simon Graham, Mostafa Jahanifar, David Snead, Shan Raza, Fayyaz Minhas and Nasir Rajpoot are part of the PathLAKE digital pathology consortium, which is funded from the Data to Early Diagnosis and Precision Medicine strand of the governments Industrial Strategy Challenge Fund, managed and delivered by UK Research and Innovation (UKRI).

OFP-11-009
Quantification of metabolic heterogeneity across multiple imaging modalities
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Background & objectives: Radiomics based on clinical imaging are increasingly applied to classify tumours, but often lack sufficient biological rationale, hampering clinical implementation. We developed an [18F]FDG-PET/CT signature in pancreatic cancer based on MCT4-expression, quantified by texture analyses of whole tumour cross-sections.
Methods: We developed a cross-modal image analyses pipeline using a cohort of pancreatic cancer patients (n=29) of which tumour cross-sections and PET-scans were available. We computed density maps of MCT4-expression on whole-slide images to extract texture features. Using k-means, we defined two subgroups with distinct MCT4-expression patterns. From corresponding [18F] FDG-PET scans, texture features were selected that associate with the pre-defined subgroups.
Results: Clustering techniques, based on k-means, umap and heatmap analyses, revealed two distinct MCT4-expression patterns. MCT4-expression pattern A was dominated by a higher MCT4-expression level and more local variation. MCT4-expression pattern B was characterized by less MCT4-expression. Using MCT4-expression patterns as label, we investigated which [18F] FDG-PET derived texture features associate with these tumour characteristics. MCT4-expression pattern A was linked to a specific [18F]FDG-PET signature, characterized by higher tracer uptake values and second order features correlated to local variation of tracer uptake on the corresponding clinical scans. The MCT4-based [18F]FDG-PET signatures were applied to an additional cohort (n=71) pancreatic cancer patients who received palliative systemic treatment and showed prognostic value.
Conclusion: The presented cross-modal image analyses pipeline allows to build PET-scan signatures based on a biological rationale using quantitative immunohistochemistry. As use-case we focussed on tumour glycolysis as hallmark of cancer, measured by MCT4-expression patterns on resected whole tumour sections and by [18F]FDG-PET scans. We show that a subgroup of pancreatic cancer patients with high and heterogenous MCT4-expression can accurately be identified in vivo using [18F]FDG PET-derived texture features. This MCT4-based [18F]FDG-PET-signature associated with worse prognosis.

OFP-11-010
Artificial intelligence as a potential tool for pathologists to evaluate lymphocyte infiltration in melanoma

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Background & objectives: Melanoma is one of the most frequent types of skin cancer, as well as one of the most aggressive, commonly known for having very poor survival outcomes.
Methods: Although lymphocyte presence in a tumour has been described as important, there is no standardization of the criteria pertaining to its analysis; it is highly subjective and dependent on the individual looking at the sample. Therefore, an annotation-free artificial intelligence technique, called NaroNet, was developed to identify melanoma cells and tumour infiltrating lymphocytes objectively.
Results: It was then applied to samples in order to explore the differences between biopsies at their baseline and at progression. As NaroNet's parameters determine the scope of tissue pattern learning, they were optimized to identify both cell types. Patch analysis approach (70x70 pixels) was used on 22-paired samples to detect cells of different morphologies and determine their distribution pattern. Each patch could hold one large melanoma cell and up to nine lymphocytes, which allowed the algorithm to discover interactions within their environment. NaroNet predicted baseline from progression with a 95.45% accuracy using phenotype abundances. T-distributed stochastic neighbor embedding of each phenotype showed high confidence when identifying cell types.
Conclusion: Biopsies at progression had little to no brisk infiltration of the tumour, which was significantly different (p=0.03) from baseline samples. NaroNet can be trained to detect cell types without manual annotations, and used to identify important patterns of cell interactions in melanoma that could differentiate samples at baseline and progression. With further development, the algorithm could be optimized to become a useful tool for pathologists.

OFP-11-011
Artificial intelligence-guided spatial transcriptomics in high grade serous carcinoma: toward image-analysis based precision oncology

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Background & objectives: H&E images of high-grade serous ovarian carcinoma (HGSC) may contain prognostic information detectable only by artificial intelligence (AI). We hypothesise that AI can pinpoint regions with prognostic value, and the biology of these regions can be revealed with spatial transcriptomics.
Methods: The cohort included 55 stage III-IV patients with distinct platinum-free intervals (PFI) (<6 vs >18 months). A deep learning neural network tool identified tumour regions most indicative of outcome. These high-confidence (HC) and background regions were probed with 10x Visium for FFPE spatial transcriptomics technology. Output was visualized with 10x Loupe browser and analysed using the R package Seurat.
Results: The neural network was first trained to identify tumour tissue, then to classify the tumour into short or long PFI group. Using a HC mask, regions indicative of outcome were identified. These HC regions were then used to train the final neural network. Testing a combined inference pipeline to classify an independent tumour set showed high sensitivity (73%) and specificity (91%). UMAP visualization of the spatial transcriptomics demonstrated that while data from the same patient are close to each other, HC and background regions are mostly distinct within the cluster for each patient. Transcriptomics profiles from HC regions predicted PFI group status significantly better than background regions.
Conclusion: Artificial intelligence-based image-analysis (AI-IA) of HGSC tissue can identify morphologic patterns invisible for human eye and guide selection of biologically meaningful regions for spatial transcriptomics. When combined, these novel technologies identified several signalling pathways and transcripts separating HGSC tumours with short vs. long PFI. In conclusion, AI-IA together with spatial transcriptomics offers a promising toolkit to identify biological features associated with cancer behaviour, making the AI-based diagnosis more interpretable and clinically relevant.
Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965193 for DECIDER.

OFP-11-012
Development of trial quality assurance program for digital pathology of the Korean Society of Pathologists

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Background & objectives: Digital pathology (DP) can fundamentally change the way of working in pathology. Since the Korean Society of Pathologists (KSP) published the consensus recommendation paper for DP application recently, the need for quality assurance program (QAP) for DP has been raised.
Methods: To provide standard baseline reference for internal and external QAP for DP, the Committee of Quality Assurance of KSP developed a checklist for DP QAP and started a trial QAP in 2021. After several revisions, the checklist was finalized. Five leading institutes participated the trial QAP in the first year and we gathered feedback from these institutes afterwards.
Results: The newly developed checklists of QAP for DP contains a total of 39 items (212 score) to check, 8 items for quality control of DP systems, 3 items for DP personnel, 9 items for hardware and software requirement for DP systems, 15 items for validation, operation, and management of DP systems, and 4 items for data security and personal information protection. Full text in both Korean and English is attached as appendices. Most participant institutes in the trial QAP replied that continuous education on unfamiliar terminology of new technology and more practical experience is demanding.
Conclusion: QAP for DP is essential for the safe implementation of DP in pathologic practice. Each laboratory should prepare institutional QAP according to this checklist and consecutive revision of the checklist with the feedback from trial QAP for DP needs to follow.
Funding: This study was supported by the Korean Society of Pathologists Study Group/Committee Supporting Research Grant (2020).

OFP-11-013
Detecting premalignant lesions in the Fallopian tube, using a deep-learning model. A pilot study

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Background & objectives: Serous Tubal Intraepithelial Carcinoma (STIC) is a precursor lesion to High Grade Serous Carcinoma (HGSC). Interobserver variability in STIC diagnosis is high. We aim to develop an Artificial Intelligence model that can detect STIC in digitalized whole slide images.
Methods: We collected, digitalized and annotated 91 cases of STIC/STIL and 75 control cases. Diagnosis was confirmed using p53 and Ki-67 immunohistochemical stains, when available. The cases were

split into 71 training cases and 20 test cases. A two-step deep-learning algorithm was trained: first all epithelium was detected, and next aberrant epithelium was distinguished from normal epithelium.
Results: The two-step model approach reached an area under the receiver operating curve of 0.946 on slide level. Visual inspection confirms adequate detection of the aberrant epithelium, in concordance with morphology and immunohistochemistry.
Conclusion: We present a deep-learning algorithm that can successfully detect STIC. Adequate STIC diagnosis is important to better understand the oncogenesis of HGSC, holds prognostic implications for individual patients, and is a prerequisite to safely offer alternative risk reducing surgeries, such as salpingectomy with delayed oophorectomy, currently studied in prospective international trials. We believe an AI model has the potential to aid the pathologist in this challenging diagnosis. Expanding the dataset is expected to aid further development of this model.
Funding: Supported by the Dutch Cancer Society.

OFP-11-014
Eyeballing and hot-spot counting of ki67 may misguide therapy in invasive breast carcinoma, NST and the quick fix is automated counting
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Background & objectives: Ki67 evaluation is essential in invasive breast carcinomas. This can be a very laborious process for pathologists. In this study, we aimed to compare Ki67 scores by a.)eyeballing, b.)manual-counting (MC), and c.)using an artificial intelligence based automated counting program (AIACP).
Methods: For 54 cases, three regions of interests (ROIs) (1 hotspot and 2 reflecting the first impression), each of 0.2 mm2, were selected on Ki67 (SP6) stained whole digital sections. These ROIs were counted manually and by AIACP (3D-HISTECH, Panoramic P250 Flash3, VPS3.0.2., Quant Center). Blinded to these countings, three independent observers determined Ki67 scores for the same cases, by eyeballing.
Results:
Conclusion: In this study, our findings of high agreement between AIACP and time-consuming MC shows that a standardized automated Ki67 scoring tool is very beneficial. It should also be stressed that, although interclass agreement between eyeballing and other methods seems acceptable, when Ki67 scores are grouped categorically based on International Ki67 in Breast Cancer Working Group 2021 Consensus, concordance was only moderate. Eyeballing and hotspot-only counting should not be used to determine Ki67 scores, which are critical in determining therapy options.

OFP-11-015
AI versus microscope in primary diagnosis of breast biopsies: multi-site clinical reader study
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Background & objectives: This study aimed to clinically validate the use of an AI-based solution by pathologists for reviewing and reporting breast core needle biopsies as compared with the gold standard practice, review on the microscope.
Methods: A two-arm prospective reader study comparing the performance of pathologists using an AI-based solution with pathologists using a microscope was performed at two sites (different staining and scanners). Both arms were compared to ground truth (GT) established by consensus of two breast pathologists. Rates of major discrepancies between each arm and GT, as determined by an adjudicating pathologist, were compared.
Results: Eight pathologists participated in the study and reported on 385 cases (442 HES and 330 H&E slides), each case being reported twice, once in each study arm. Pathologists first reviewed only H&E/HES slides, if requested and available, they were provided with IHCs, while the AI results were on H&E/HES only. The major discrepancy rates of the microscope arm and of the AI arm against GT were 4.42% and 3.12%, respectively, demonstrating 29.4% reduction in major discrepancies. Pathologists with AI demonstrated very high accuracy for the detection of invasive carcinoma with sensitivity and specificity of 100% for both, as well as for DCIS/ADH with sensitivity of 92.4% and specificity of 97.8%.
Conclusion: This multi-site reader study reports diagnostic accuracy improvements by pathologists performing diagnosis and reporting with the support of a first read AI solution for breast biopsies. The AI solution performed accurately and generalized well for different staining platforms and different scanners. Thus, AI solutions could be used as significant aiding tools for pathologists in clinical decision-making in routine pathology practice, enhancing the quality and reproducibility of diagnosis.

OFP-11-016
Digital score of Ki67 in prostate cancer is associated with high-grade disease and presence of metastasis
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Background & objectives: Ki67 proliferation-index (PI) has been identified as a valuable prognostic marker in prostate cancer. However, manual scoring is laborious and highly subjective. We explore the association of our digital Ki67 score with high-grade prostate cancer disease and presence of metastasis.
Methods: Diagnostic paraffin-embedded needle core biopsies were stained for Ki67 using MIB-1 antibody (DAKO, Carpinteria, CA, USA). Manual scoring used the unweighted global assessment method. Digital scores were calculated using our deep learning method. Scores were correlated with Gleason score and metastatic status.
Results: Samples from 54 patients randomised to STAMPEDE arm A (2006-2015) were assessed. There were 29 M0, 9 M1 low burden and 6 M1 high burden. Gleason score was centrally assigned with 72% classified as GG5. The correlation between manual and digital scores was calculated to be 0.7562 (p=3.78e-11). The manually assigned Ki67 score was associated with high-grade disease (GG5 and 4) ($p = 0.031$) and the presence of extra-pelvic metastases ($p<0.001$), whereas our digital Ki67 score (DigiKiPI) also showed a statistically significant association with high-grade disease and presence of metastasis ($p = 0.047$ and $p = 0.001$, respectively) with the added benefits of being objective and reproducible.
Conclusion: Ki67 PI is a robust prognostic tool in clinically advanced prostate cancer that can refine patient prognostication. However, it has not been broadly used in clinical routine due to lack of standardisation and high intra and inter observer variations. Automated deep learning based scoring offers a promising tool for better way to objectively and reproducibly quantify Ki67 PI

while reducing manual labour. We find that our DigiKiPI score is significantly associated with high-grade disease and the presence of extra-pelvic metastasis.

OFP-12 | Joint Oral Free Paper Session Molecular Pathology / Haematopathology

OFP-12-001
The Nrf2-ARE pathway: a potential novel therapeutic target in papillary renal cancer patients

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Background & objectives: Nrf2-ARE signalling, a key sensor of oxidative stress in humans, is involved in papillary renal cell carcinoma (pRCC). We characterised Nrf2-ARE pathway over-activation in pRCCs and screen pathway inhibitors to identify targeted treatment for pRCC patients.
Methods: Comprehensive characterisation of 60 formalin-fixed, paraffin-embedded pRCCs by copy number analysis and Whole Exome Sequencing allowed us to identify pRCC groups based on their genetic background. Protein expression of NQO1, the downstream target of the Nrf2-ARE pathway, was analysed in pRCCs by immunohistochemistry and activity assay. Newly established patient-derived cell models that resemble pRCC tumours were applied for drug profiling.
Results: Immunohistochemical tissue microarray analysis of 119 pRCC correlated Nrf2-ARE pathway over-activation with worse patient outcome and higher tumour grade and stage. Secondly, based on the STRING network, we identified 15 members of the Nrf2-ARE pathway of which 4 genes NFE2L2, Keap1, CUL3 and Bach1 had mutations in 12% of all samples. The investigation of 9 matched pRCC samples and patient-derived tumour cell cultures demonstrated increased NQO1 mRNA and protein expression and activity in 56% of tumours. Finally, drug screening with 18 Nrf2-ARE pathway inhibitors using 6 pRCC PDCs with deregulated Nrf2-ARE pathway activation showed Brusatol and Convallatoxin, two Nrf2 inhibitors, had the most potent responses in our PDCs.
Conclusion: pRCC is not a single disease but consists of at least two main subtypes with distinct molecular backgrounds and patient outcomes. We first characterised a subset of aggressive pRCCs with aberrant activation of the Nrf2-ARE pathway. Moreover, we showed that pharmacological inhibition of Nrf2 represents a promising therapeutic target for this tumour subtype. We anticipate that this will open up new possibilities for the clinical management of these patients.

OFP-12-002
Improving the quality of cfDNA testing – results from two years of EQA

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Background & objectives: Testing of cfDNA for biomarkers is now a recognised part of clinical practice in lung cancer. EQA plays an important role in assessing and improving standards. The results from two global EQAs testing cfDNA in lung cancer are presented.
Methods: Artificial plasma samples with cfDNA containing prescribed variants at defined allelic frequencies were distributed. Laboratories tested the samples according to their usual cfDNA protocols and reported the results in the context of specific clinical cases. Reports were peer-assessed, and feedback provided to laboratories in the form of individual reports.
Results: EQAs were provided in 2020 and 2021 with the number of laboratories submitting results increasing from 259 to 292. Both EQAs included assessment of EGFR testing and 2021 also included KRAS. The genotyping error rate decreased from 22% in 2020 to 11% in 2021. Common issues observed included the use of inappropriate methods for cfDNA testing and a lack of awareness available treatment for tumours with KRAS mutations, over-interpretation of the absence of a variant and failing to provide sufficient details of the test methodology and limitations.
Conclusion: The increase in the number of participants reflects the recognition for the need for EQA for cfDNA testing. These EQAs have shown a large variation of methodologies being used and variability in genotyping accuracy and interpretation of results being reported. This has the potential to adversely impact on patient care highlighting the clear need for education to improve testing methods and the clear reporting of the result. EQA is a key mechanism to deliver this knowledge.

OFP-12-003
Common pitfalls in interpreting fusion testing results highlighted by EQA

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Background & objectives: Testing of tumours for fusion transcripts by molecular methods is becoming increasingly widespread. GenQA has adapted to the change in testing strategies by including assessment of fusions by genomic testing into existing EQAs and the introduction of an NTRK EQA.
Methods: Fusion -testing by molecular methods is assessed in the lung, thyroid and renal cancer, sarcoma and NTRK EQAs. FFPE tissue is provided to laboratories to test for fusions according to their usual procedures and report the results in the context of the clinical case provided. Returns are assessed by expert assessors and laboratories provided with individual reports of their results.
Results: There has been a significant increase in the number of laboratories performing routine fusion transcript testing. Common reporting errors across the EQAs were identified which resulted in the incorrect interpretation of the clinical relevance of detected transcripts. Laboratories reported the presence of multiple transcripts, described transcripts incorrectly and incorrectly predicted the productive nature of transcript.
Conclusion: The introduction of molecular testing for fusion transcript has the benefit that multiple targets can be examined using the same assay compared to techniques such as FISH and IHC. EQAs for the detection of fusion transcripts in FFPE tissue from solid tumours have identified issues with both interpretation and reporting of results. This could impact on patient care and therefore there is a need for continual assessment of this testing.

OFP-12-004
The Geneva HRD test: clinical validation on 469 samples from the PAOLA-1 trial

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Background & objectives: The efficiency of the Myriad HRD test to guide use of PARP inhibitors has been demonstrated in

several phase III trials. However, its high failure rate and limited accessibility establish a need for a clinically validated laboratory developed test.
Methods: The algorithm behind the Geneva HRD test was developed on 457 high grade serous ovarian samples and 112 triple negative breast cancer samples from the TCGA. As part of the ENGOT HRD European Initiative the algorithm, applied on OncoScan(TM) CNV Assay data, was compared to Myriad with respect to the PFS on 85+384 samples from the PAOLA-1/ENGOT-ov25 phase 3 trial.
Results: The analysis of the TCGA cohort revealed that a normalization of the number of large-scale state transitions by the number of whole genome doubling events allows a better separation and classification of HR-deficient samples than the tripartite score used by Myriad or the genomic LOH score used by Foundation Medicine. On the PAOLA-1 samples, the Geneva test yielded a similar hazard ratio as the Myriad test with respect to the addition of Olaparib or placebo to the Bevacizumab maintenance treatment (HR=0.32 vs 0.31). Compared to Myriad, the test yielded a lower technical failure rate (2% vs 11%) and a positive and negative predictive value of 90% and 85%.
Conclusion: The proposed test is a viable alternative to the Myriad myChoice HRD test and can be easily deployed in a clinical laboratory. The performance is similar to the commercial test in terms of hazard ratio but the lower failure rate of the Geneva HRD test allows a 10% increase (375 vs 340) in the number of patients that will receive a conclusive laboratory result.
Funding: AstraZeneca/Merck

OFP-12-005
Clinical utility of tumour-only targeted panel sequencing in childhood tumours
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Background & objectives: Broad based genomic profiling is increasingly part of the standard workup for paediatric cancers. In this study, we evaluate the clinical utility of tumour-only sequencing in a cohort of 94 paediatric tumours using a targeted next generation sequencing panel.
Methods: 94 cases of paediatric solid tumours spanning multiple subtypes were recruited, including relapsed and refractory childhood cancers. Nucleic acid extracted from formalin-fixed paraffin embedded tissue was tested with Illumina Ampliseq Childhood Cancer Panel, which includes single nucleotide variants, copy number variants and gene fusions involving >130 genes. All clinically significant variants were reviewed at a multi-disciplinary tumour board.
Results: 94 cases of paediatric solid tumours from 87 individuals were sequenced, including bone and soft tissue tumours (n=30), central nervous system (CNS) tumours (n=17), lymphomas (n=9), sympathetic nervous system tumours (n=8), renal tumours (n=8), liver tumours (n= 5) and other tumour types.
Clinically relevant variants were identified in 57 cases (60.6%). Variants were of diagnostic significance in 54 cases (57.5%), therapeutic significance in 34 cases (36.2%), and prognostic significance in 11 cases (11.7%). A potential germline alteration was detected in 9 cases (9.3%). Based on the sequencing findings, 3 cases had a change in diagnosis: pancreatic Ewing sarcoma, myeloid sarcoma with KMT2A-MLLT3 gene fusion and metastatic colitis-associated colorectal adenocarcinoma (poorly-differentiated).
Conclusion: Paediatric tumour types that benefitted most from tumour-only sequencing were soft tissue tumours (67% of cases with clinically relevant variants) and CNS tumours (65% of cases with clinically relevant variants). Whilst changes in histological diagnoses were rare, molecular findings were extremely useful in assisting diagnosis of rare or poorly-differentiated entities, as well as tumours occurring in uncharacteristic locations.
Funding: VIVA-KKH Brain and Solid Tumour Programme

OFP-12-006
The activation of Jagged1 signalling by chemotherapeutic agents counteracts the Oxaliplatin/5Fluorouracil- mediated anti-cancer effects: a novel mechanism of drug resistance in colon cancer
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Background & objectives: Colorectal cancer (CRC) is a leading cause of mortality worldwide, characterized by metastasis and resistance to therapy. Recently, we demonstrated that Kras mutation drives the activation of Jag1-ICD oncogene, via-ERK1/2. Herein, we explore the new intrinsic drug-resistance mechanisms, Jag1-ICD-mediated.
Methods: Human CRC cell lines were treated with different chemotherapeutic compounds (e.g. OXP, 5FU and GSIs), alone or in combination, and subjected to in-vitro assays, to evaluate proliferation, metastasis and chemoresistance. CRC resistant cells were obtained by chronical treatment with low doses of OXP/5FU. The resistant cells were analysed by colony-formation assays and by qRT-PCR to assess growth and gene-reprogramming ability.
Results: Herein, we evaluate the effects of OXP, 5FU and GSIs alone or in combination, on Jagged1 processing in CRC cell lines. We demonstrate that the anticancer drugs, OXP and 5FU, lead directly to a massive Jag1-ICD activation that results in the selection of a drug-resistant subpopulation. The chemoresistance mechanism is induced by a forced Jag1-ICD accumulation that protects cells from apoptosis, under the activation of Jag1-ICD-dependent pro-survival targets. In addition, GSIs induce the proliferation of Jag1-ICD positive CRC cells, functioning as tumour-promoting agents. Finally, the Jagged1 abrogation in OXP- or 5FU-resistant subpopulations is enough to restore the sensitivity to chemotherapy, confirming that drug resistance is Jag1-ICD-dependent.
Conclusion: Overall, our data show that Jagged1 processing is directly activated by the most potent chemotherapeutic agents (OXP/5FU) or by GSIs compounds. Moreover, we unveil a new role for Jag1-ICD oncogene which controls both apoptosis and proliferation, in CRC cells upon chemotherapeutic treatments. Therefore, we demonstrate the existence of a new mechanism of intrinsic drug-resistance, where Jag1-ICD functions as pivotal nuclear effector. Finally, we suggest Jagged1 as molecular predictive biomarker for the chemotherapy-outcome in CRC patients bearing Krasmut and over-expressing Jagged1.

OFP-12-007
Ultra-fast gene fusion assessment as a reflex testing in daily clinical practice for advanced non-small cell lung cancer patients
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Background & objectives: There is an urgent need to improve the broad molecular profiling of advanced non-squamous non-small

cell lung carcinoma (NS-NSCLC) patients, notably for a rapid assessment of multiple genomic alterations.
Methods: We compared two ultra-fast gene fusion assessment assays, using a next generation sequencing (Genexus, Oncomine™ Precision Assay, Thermo-Fisher) or an RT-PCR (Idylla™, GeneFusion Assay, Biocartis) approaches, set up as a reflex testing at diagnosis.
Results: 250 NS-NSCLC patients (68 ALK, 26 ROS1, 15 RET, 6 NTRK, 11 MET positive and 125 wild type patients) from 8 centers were included. 83% of patients were stage IIIB-IV.
The sensitivity (98%) and specificity (99%) of the two approaches were analogous, when compared to gold standard methods, accredited according to the ISO15189 norm in the Laboratory of Clinical and Experimental Pathology (Nice, France).
Conclusion: Ultra-fast gene fusion evaluation using NGS or RT-PCR approaches should be developed as a reflex testing for NS-NSCLC at diagnosis in order to treat these patients according to the international recommendations and guidelines.

OFP-12-008
Nuclear markers for the diagnosis of histiocytosis
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Background & objectives: Newly described immunomarkers could bring potential benefit in the diagnosis and treatment of histiocytosis. Our objective was to analyse recently described nuclear markers and to expand the immunohistochemical panel in the diagnosis of histiocytosis.
Methods: Biopsy samples diagnosed with Erdheim-Chester Disease (ECD), Langerhans cell histiocytosis (LCH), Rosai Dorfman Disease (RDD), malignant histiocytosis, and cutaneous histiocytosis were retrieved from the files of our Pathology Department. Haematoxylin & eosin-stained slides were reviewed. Immunohistochemistry was performed with the following antibodies: PU.1(EPR3158Y, Abcam), OCT.2(EPR12482-106, Abcam), phosphoERK(Erk 1/2, Cell Signalling). Molecular biology was performed using PCR or Next-Generation Sequencing.
Results: phosphoERK was performed in 567 biopsy samples of histiocytosis. It was positive in 91%, 86%, 73%, 67%, 70% and 83% of LCH (n=118), ECD (n=198), mixed (n=22), RDD (n=119), cutaneous (n=86) and malignant histiocytosis (n=24), respectively. All the types of histiocytosis were positive for PU.1 (5 LCH, 5 ECD, 7 RDD, 4 ALK+ and 8 C group). Among the 17 cases referred as malignant histiocytosis, all the 9 confirmed cases were positive, contrasting with the 8 excluded cases that were negative. OCT.2 was positive in 42/80 cases of RDD. All 9 mixed RDD-ECD or RDD-LCH were OCT.2 positive. 18/38 cases of non-RDD had at least a low positivity for OCT.2.
Conclusion: PU.1 is a marker indicating a histiocytic origin and it is useful to exclude a tumour rich in reactive histiocytes mimicking histiocytosis. OCT.2 can be used to confirm Rosai-Dorfman Disease. phosphoERK is a nuclear and cytoplasmic marker highlighting the activation of MAPkinase pathway and it can be used to initiate targeted therapy in histiocytosis when molecular biology is not available.

OFP-12-009
Clonality analysis of Richter's transformation in CLL treated with targeted therapy
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Background & objectives: Richter's syndrome (RS) occurs in 1-10% of patients with chronic/small lymphocytic leukaemia (CLL/SLL). Clonal transformation has a poorer prognosis than de novo transformation, and benefits from more aggressive chemotherapy. We sought to characterize RS clonality in a Canadian case series.
Methods: DNA was extracted from FFPE lymph node, bone marrow, or banked cells. Targeted NGS of heavy and light chain regions was performed using the Oncomine BCR Pan-Clonality Assay (ThermoFisher). IGH, IGK, and IGL rearrangements and clonal frequencies were assessed through the Ion Reporter Oncomine BCR workflow and MiXCR. Slides and IHC were reviewed to confirm the diagnosis.
Results: We identified nine patients with 20 pre- and post-transformation samples. The median age at diagnosis was 52 (range 44-84), with median 9 years (range 1.9-15) between the diagnosis of CLL vs RS. Most cases transformed to DLBCL (n=7), and the remainder to classical Hodgkin lymphoma (n=2). 7/9 patients had received therapy prior to transformation, including ibrutinib, acalabrutinib, or venetoclax. Analysis of the heavy chain and light chain loci revealed a clonal relationship in all nine cases, including one case where the secondary DLBCL was CD5-negative. Interestingly, several cases exhibited multiple productive IGH rearrangements (2/9) or light chain rearrangements (7/9) shared between the pre- and post-transformation cells.
Conclusion: Targeted sequencing of a case series of CLL patients with RS revealed a clonal relationship in all nine cases. Multiple productive Ig rearrangements were identified in a surprising number of cases, consistent with a growing number of NGS studies supporting greater diversity in CLL clonality than previously appreciated.

OFP-12-010
Delineating the spatial compartmentalization of human follicular B cell metabolic dynamics
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Background & objectives: Despite the well-established role of germinal centers (GC) for the generation of protective B cell response, an insight on the in-situ human GC immune reactions remains unclear. We aimed to evaluate the energetic and metabolic profile of follicular B cells.
Methods: Metabolic profile of primary tonsillar B cells were characterized by applying complementary methodologies. Phenotyping and 2-NBDG uptake of relevant B cell subsets were assessed by multiparametric flow-cytometry. Ex vivo metabolic function (Seahorse) and transcriptomic signatures (bulk NGS) were investigated on cryopreserved TNMCs (tonsillar mononuclear cells). Multiplex tissue imaging was applied for the in situ B cell metabolic profiling.
Results: Seahorse analysis revealed that OXPHOS supported 70% and glycolysis 30% of total ATP produced in GCBCs. Coherently, an increased 2-NBDG uptake was observed in GCBCs. GSEA of sorted B-cell subsets showed significant enrichment of OXPHOS and mTORC1 pathways in GCBCs, with several glycolysis-related genes being significantly expressed. In-vitro treatment with UK5099 (MPC inhibitor), negatively affected the SRC, MRC, and Krebs capacity in GCBCs as compared to untreated controls. Tissue imaging of FFPE-tonsillar sections revealed a polarization of GLUT1, MCT4, HIF1a and HIF1b in Light Zone, while Opa1 was expressed within Dark Zone. Gene expression of MCT1 (lactate transporter) was increased in GCBCs, while imaging showed its distribution across the GC.

Conclusion: Despite an intense dependence of GCBCs on OXPHOS, glycolysis is a significant energy supporter too. Tissue in situ analysis suggests the coupling of massive division in DZ with OXPHOS and local exchange of lactate, while glycolysis is more frequent among B cells in LZ. Moreover, the lactate transporters' expression and the impaired Krebs cycle capacity induced by MPC-blockade point to a significant role of glucose-derived carbon atoms and monocarboxylates in sustaining the oxidative machinery.

OFP-12-011

Comparison of the accuracy of cytomorphology, flow cytometry immunophenotyping and immunohistochemistry in determining diagnostic and prognostic blast percentage groups in bone marrow in myelodysplastic syndrome and acute myeloid leukaemia cases

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Background & objectives: Bone marrow (BM) blast percentage (BP) is important in diagnosis, classification and prognosis of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). We aimed to compare accuracy of cytomorphology (CM), flow cytometry immunophenotyping (FCI), immunohistochemistry (IHC) in determining BP groups.
Methods: BM biopsy and aspiration samples from MDS and AML patients and patients diagnosed with AML underwent bone marrow transplantation (BMT) between 9/2019 and 6/2021 were analysed. CM was evaluated. CD34 positive BP was determined by FCI and IHC. Cases were divided into four groups according to BP: <5%, ≥5%-<10%, ≥10%-<20%, ≥20%. Three methods were compared with the Pearson-r correlation.
Results: A total of 68 BM materials from 55 patients were analysed. Thirty-nine of the cases were MDS (7 MDS-EB), 2 of them were AML, and 14 of them were AML patients who underwent BMT. Pearson-r correlations for absolute values in CM-FCI, CM-IHC, and FCI-IHC comparisons were 0.8865, 0.8787, 0.9670, respectively, indicating a good correlation. When CM-FCI was compared, 86.7% of the cases were in the same blast range. In the comparison of CM-IHC, 79.4% of the cases were in the same blast range. Comparison of IHC-FCI showed 88.2% correlation in blast intervals.
Conclusion: BM blast rate determination is important in MDS classification and MDS-AML differentiation. Although CM is the gold standard, reproducibility is low even with high-quality smears. In our study, we observed good correlations between CM, FCI and IHC. Correlation between FCI and IHC, which have high reproducibility and low interobserver variability, was even higher. However, this study is limited to cases showing CD34 expression. Although FCI and IHC methods have high accuracy with CM, using the three methods together is recommended.

OFP-12-012

Prevalence and impact of co-infections in patients with lymphoma and HIV

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Background & objectives: HIV infection is associated with the development of lymphomas and some other co-infections (eg., HBV and HCV). The aim of our study was to review lymphomas arising in HIV setting and linked co-infections, in a patient's cohort from our hospital.
Methods: We selected patients diagnosed with HIV and lymphoma between 2010-2020 in our hospital, from our electronic medical database. Demographic data, date of diagnosis, date of death/last contact, lymphomas types and location, serologies for hepatitis B and C, cytomegalovirus, toxoplasma and Epstein-Barr virus (6 months prior until 3 months after lymphoma diagnosis) were collected. Descriptive statistical analysis was performed.
Results: We selected 52 patients (71.2% males). HIV-1 was predominant (90.4% of the cases). Average age of HIV diagnosis was 42.38 years and of lymphoma diagnosis was 47.79 years; mean interval between diagnoses was 64 months (36.5% diagnosed within 1-year).
Laboratory data demonstrated high prevalence of chronic hepatitis C (9.6%) and B (28,8%) and low prevalence of recent EBV (1.9) or CMV (3.8) infection.
Diffuse large B cell lymphoma (40.4%), Hodgkin's lymphoma (23.1%) and plasmablastic lymphoma (11.5%) were the most frequent types. Lymph node involvement (59.6%) was predominant, followed by bone marrow (7.9%) and gastric involvement (5.8%). Mortality rate was 59.6%. Median survival was 11.71 months after lymphoma diagnosis.
Conclusion: Our patients' cohort follows the general patterns of gender, HIV type distribution and main types of lymphomas diagnosed in HIV-infection setting usually described in literature. We have a higher frequency of plasmablastic lymphoma though, not readily explained by a similar rise of frequency of EBV infection – not all patients were tested for EBV, what may account for the lower frequency observed. We hope to further investigate this point in future studies.

OFP-13 | Joint Oral Free Paper Session Neuropathology / Ophthalmic Pathology

OFP-13-001

Immunohistochemistry against RB1 is useful for the distinction between giant cell glioblastoma and pleomorphic xanthoastrocytoma

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Background & objectives: Giant cell glioblastoma (GC-GBM) displays frequent RB1 alterations, aside from TP53 mutations. Herein, we aimed to assess the value of RB1 immunohistochemistry in the differential diagnosis between GC-GBM and pleomorphic xanthoastrocytoma (PXA), which harbours better prognosis and frequent BRAF mutations.
Methods: In 34 GC-GBMs and 8 PXA (5 grade 2 and 3 grade 3), we analysed: i) mutations and copy number variations of 409 genes using NGS; ii) RB1, P53 and BRAF p.V600E immunostainings. Cases were classified P53 positive when showing at least 10% stained tumour cells.
Results: GC-GBMs were RB1-altered in 15 cases (including 4 with RB1 homozygous deletion, 5 with RB1 heterozygous deletion coupled with mutation of the other allele and 6 with RB1 mutations), TP53-mutated in 27 (including 6 with truncating mutations) and BRAF-mutated in none. At immunohistochemistry, all 15 GC-GBMs with RB1-alterations and 11 RB1-unaltered cases had RB1 loss, 21 were P53 positive and all were BRAF negative. GC-GBMs were RB1-/P53+ in 16 cases, RB1-/P53- in 10, RB1+/P53+ in 5, RB1+/P53- in 3.

PXA were BRAF-mutated in 6 cases, TP53-mutated in 3 and RB1-altered in none. All six cases with BRAF mutation were BRAF p.V600E positive; no PXA was RB1 negative or P53 positive.
Conclusion: An immunohistochemical profile consisting in RB1 loss associated with, or alternative to, P53 positivity had the same specificity (100%), but higher sensitivity (91% vs 61%) for GC-GBM than P53 positivity alone. The addition of RB1 staining in an immunohistochemical algorithm including P53 and BRAF p.V600E may be helpful to differentiate GC-GBM from PXA.

OFP-13-002
Myoepithelial neoplasia of central nervous system: a series of 4 cases
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Background & objectives: Myoepithelial neoplasms, composed of myoepithelioma and myoepithelial carcinoma, have not been documented in the central nervous system. Here we present clinicopathological characteristics of 4 neoplasms with myoepithelial differentiation involving the brain and spinal cord.
Methods: The clinicopathological findings of 4 cases were evaluated: 1) 16-year-old female with a 6-cm tumour in the right frontoparietal region.2) 24-year-old female with a 6-cm tumour in T12-L2. 3) 8-year-old female with a 3,5-cm tumour in T11-L1. 4) 20-year-old female with a 3-cm tumour in C4-T2. Spinal tumours were located in intradural-extramedullary space, and the cranial tumour was dural-based.
Results: All patients were female with a mean age of 17(8-24). Histopathologically; 3 tumours were characterized by nests/cords and sheets composed of malignant epithelioid/rhabdoid cells in myxocollagenous background at least focally, thus categorized as myoepithelial carcinoma. Case 2 was reminiscent of myoepithelioma/mixed tumour of soft tissue; however, showed a malignant behaviour. We found loss of INI1 expression in 3 of 4 cases; S100+EMA coexpression, and positivity for at least one keratin marker in all cases. SMA was positive in 3 of 4 cases. Break-apart FISH revealed *EWSR1* rearrangements in 2 of 3 cases. Two cases (cases 2 and 3) died, one of whom (case 2) with multiple recurrences and lung metastasis.
Conclusion: Myoepithelial neoplasms occur in the central nervous system of children and young adult females and should be considered in the differential diagnosis of INI1 deficient tumours, after exclusion of AT/RT, poorly-differentiated chordoma, and epithelioid sarcoma. Multiple myoepithelial marker expression and INI1 loss along with *EWSR* rearrangements favour the diagnosis of myoepithelial neoplasm.

OFP-13-003
Solitary fibrous tumour of central nervous system: a series of 23 cases
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Background & objectives: Meningeal solitary fibrous tumour is characterized by fibroblastic proliferation with hemangiopericytomatous pattern and *NAB2::STAT6* alterations. Here, we present clinicopathological features of our series with a special emphasis on the predictability of biological behaviour with the current grading schemes.
Methods: The clinical, radiological, and pathological findings of 23 cases were evaluated. Immunohistochemically, all cases were STAT6 positive. Age, sex, tumour size, location, hypercellularity, mitotic activity, presence of necrosis, hemorrhage, moderate to high-grade nuclear pleomorphism, recurrence, death, and time for recurrence were noted. Tumours were graded according to WHO2016 and WHO2021 classifications. Recurrence-free and overall survival statistics were applied.
Results: The mean age was 37 (14-51) with M:F ratio of 12:11. Tumours had intracranial (n=19) and spinal (n=4) locations; sizes ranged from 2 to 7 cm with a mean of 4,2 cm. Tumours were classified by WHO2021 as grade 1 (n = 12), 2 (n = 6), or 3 (n = 5), and by WHO2016 as grade 1 (n =4), grade 2 (n=8), or grade 3 (n=11). Necrosis was present in 7 (30%). Recurrence occurred in 10 (44%) patients within a mean of 5.6 years, 7 of which were dead during follow-up. On univariate analysis, neither of the above-mentioned parameters nor grading schemes were associated with recurrence-free or overall survival.
Conclusion: According to our data, morphological and clinical parameters, as well as WHO grading schemes, failed to stratify this family of tumours accurately.

OFP-13-004
Response to regorafenib of recurrent glioblastoma. A clinical and NGS study
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Background & objectives: Predictive factors for response to regorafenib in recurrent glioblastoma, IDH-wildtype, are scarcely recognized. The objective of this study was to identify molecular predictive factors for response to regorafenib using a clinically available platform.
Methods: We analysed a prospective cohort of 30 patients harbouring recurrent glioblastoma, IDH-wildtype, and treated with regorafenib. Next-generation sequencing (NGS) analysis was performed on DNA extracted from paraffin-embedded tissues using a clinically available platform. Moreover, MGMT methylation and EGFRvIII expression analyses were performed.
Results: Six-month progression-free survival (PFS) was 30% and median overall survival (OS) was 7.5 months. NGS analysis revealed a mutation of EGFR pathway in 18% of cases and a mutation in the mitogen-activated protein-kinase (MAPK) pathway in 18% of cases. In the remaining cases, no mutations were detected. MAPK pathway mutated patients had a poor response to regorafenib treatment, with a significantly shorter PFS and a nonsignificantly shorter OS compared to EGFR-mutated patients (for PFS, p=0.0061; for OS, p=0.1076). Multivariate analysis confirmed that MAPK pathway mutations independently predicted a shorter PFS after regorafenib treatment (p=0.0188). The negative prognostic role of MAPK alteration was reinforced when we combined EGFR-mutated with EGFRvIII-positive cases.
Conclusion: Recurrent glioblastoma tumours with an alteration in MAPK pathway could belong to the mesenchymal subtype and respond poorly to regorafenib treatment, while EGFR-altered cases have a better response to regorafenib. We thus provide a molecular selection criteria easy to implement in the clinical practice.

OFP-13-005
Digital image analysis is a powerful tool to demonstrate the prognostic impact of proliferation assessed with Ki67 and PHH3 in meningeal solitary fibrous tumours
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Background & objectives: The risk of recurrence and metastasis of solitary fibrous tumours is greatly dependent of proliferation. We aimed to determine the prognostic significance of Ki67 and PHH3 evaluated by digital image analysis in a cohort of 86 meningeal solitary fibrous tumours.
Methods: We compared eye-balling estimation, manual counting, and standardized digital image analysis using QuPath software to evaluate cellularity and proliferation based on Ki67 and PHH3, with correlation with survival in a retrospective cohort of 86 meningeal solitary fibrous tumours. The concordance between the methods was calculated and the processing time was compared.
Results: Evaluation of proliferation by digital image analysis with Ki67≥0.05 or PHH3≥0.0006 cut-off was significantly associated with worse PFS and OS in univariate and multivariate analyses, with a significantly shorter processing time for digital image analysis. Manual counting and digital image analysis were highly correlated, with a concordance correlation coefficient of 0.973 (95% CI: 0.061-0.981) for Ki67 and 0,810 (95% CI: 0.725-0.867) for PHH3. Eye-balling estimation showed less correlation with other methods.
Conclusion: Digital image analysis is a fast and accurate method for evaluating proliferation markers. Using this method, Ki67 ≥0.05 and PHH3≥0.0006 have a negative impact on PFS and OS in univariate and multivariate analyses.

OFP-13-006
Morphological analysis with morphometry of meningioma calcifications
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Background & objectives: Meningiomas are the most common non-glial tumours of the central nervous system. Differential diagnosis of meningiomas is a challenging problem due to their location. The work aims to study the morphology, structure, and phase analysis of meningiomas' psammoma bodies (PB).
Methods: The study group included 30 patients with calcified meningiomas. We use histological techniques, transmission and scanning electron microscopy with microanalysis. We captured all photos with the digital visualisation system on Zeiss Primo Star microscope with digital camera ZEISS Axiocam ERc 5s and software package "Zen 2.0". We performed the statistical analysis of the results using GraphPad Prism 7.04.
Results: All meningioma samples contained PB in the fibrous tissue of the tumour. According to the histological examination and SEM results, PB had a layered structure. They were often in the form of fragments and fragments that preserved the original structure. The number of PB in meningioma tissue varied from one to hundreds of units. In our study, the size of the PB ranged from 20.01 to 197.02 μm. We can generally divide PB by dimensional characteristics (larger formation diameter) into three groups: large (more than 100 μm), medium (70-100 μm) and small (less than 69 μm).
Conclusion: PB is a promising diagnostic marker for the prognosis of dura mater tumours, which doctors and scientists can use in radiological and histological methods. According to morphometry results, we can divide PB into three groups by size - large, medium and small.

OFP-13-007
Thalamic diffuse midline glioma, a series of cases from a single cancer centre
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Background & objectives: Diffuse midline glioma (DMG) of thalamus is rare, as thalamic tumours, in general, represent 1% of all intracranial neoplasms. It is associated with aggressive behaviours and poor prognosis. Recently, DMGs are characterized by the presence of an H3K27M gene mutation.
Methods: Eighteen thalamic DMGs are reviewed, including the age, gender, and laterality. Immunostains for GFAP, H3 K27M, and H3 K27me, IDH1 (R132H), P53. The outcome of the cases is reported.
Results: There were 11 males. The average age is 34 years (median 27.5). All cases were positive for GFAP. Eight cases were mutant for H3 K27M, all with loss of H3 K27me staining. In addition, a single case showed loss of H3 K27me immunostain in the presence of non-mutant H3K27M. There were 8 P53-mutant cases. All cases were IDH1 (R132H) wildtype. Of interest, there were 3 cases diagnosed as pilocytic astrocytoma, including a case that was H3 K27M mutant. Of those with available survival data, 10 were dead, including 4 cases of mutant H3 K27M and a single case of wildtype H3 K27M, but with loss of H3 K27me.
Conclusion: Around 50% of the cases are consistent with the diagnosis of DMG where H3 K27M is altered. However, there remains a number of cases with dismal outcomes that were non-H3 K27M altered. These should be further tested for potential other mutations.

OFP-13-008
Histone H3 trimethylated in lysine 27 (H3K27me3) immunohistochemical loss predicts shorter progression-free survival in intracranial meningiomas treated with radiosurgery
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Background & objectives: Loss of H3K27me3 has been recently associated with an increased risk of recurrence in meningiomas. In the current study, we aim to investigate whether H327 trimethylation status can predict the response of meningiomas to stereotactic radiosurgery.
Methods: H3K27me3 expression was evaluated by immunohistochemistry in 39 surgically resected, treatment-naive intra-cranial meningiomas, treated with stereotactic radiosurgery (SRS) for a residue or at recurrence. The immunohistochemical results were correlated with tumour recurrence and recurrence-free survival (RFS) after SRS.
Results: Seven meningiomas had H3K27me3 loss, 27 retained H3K27me3 expression and five has inconclusive immunostaining. The immunohistochemical loss of H3K27me3 was significantly associated with tumour recurrence (P= 0.0143) and with shorter RFS (P=0.0036) after SRS.
Conclusion: Our findings suggest that the absence of H3K27me3 in neoplastic cells may concur to a weaker response to stereotactic radiosurgery in meningiomas.

OFP-13-009
Concerted deposition of vascular basal membrane proteins laminin beta 1 and 2 supports neo-angiogenesis and contributes to vascular permeability
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Background & objectives: Expression profiling studies of glioblastomas (GBM) showed striking over-expression of laminin beta 1 (LAMB1) isoform with concomitant loss of LAMB2. Inhibition of LAMB1 expression by nanoconjugates suppresses

tumour growth in animal model of glioblastoma through unclear mechanism.
Methods: We use immunohistochemistry and in situ hybridization to identify location and cell of origin for LAMB1/2 production in human brain.
Results: In quiescent state brain the microvasculature but does not express LAMB1, but expresses LAMB2 at the sites of blood brain and CSF brain barrier. Remodelling of microvasculature in subacute stroke involves initial deposition of LAMB1 by proliferating endothelium, followed by an encasement by LAMB2. Low grade diffuse astrocytomas show no LAMB1 expression. Microvascular hyperplasia in GBM show striking deposition of LAMB1, while LAMB2 coverage trails behind. Bevacizumab induces a loss of LAMB1 and normalizes LAMB2 coverage.
Conclusion: Distribution of LAMB2 correlates with sites controlling fluid permeability. Expression of LAMB1 corresponds to endothelial cells and coincides with angiogenesis. Expression of LAMB2 lags behind LAMB1 and its deficiency in the microvascular wall correlates with increased permeability.

OFP-13-010
Molecular genetics and immunostaining of relapsing inoperable meningiomas located at the base of skull (BS) or in frontal areas, before radiotherapy
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Background & objectives: Our experience in screening for targetable molecular alterations of untreatable meningiomas led us to hypothesise that these mutations were less frequent than expected considering available studies.
Our goal to provide prospective clinic-pathological/ molecular data to support future pharmacological targeted therapies.
Methods: From 2018 to 2022, the molecular status of p-AKT and SHH activating molecular alterations was prospectively determined using NGS in the first biopsy of all relapsing patients after surgery with pathologically diagnosed meningioma located at BS or in frontal areas, before radiotherapy prescribed in our center's multidisciplinary meeting. Further evaluation of IHC prescreening using GAB1 and OTX2 was also conducted.
Results: -61 patients were included: 61.66% (N=36) in BS with median age 53 while 80.33% (N=47) were female. 62% (N=38) were grade 1, 35% (N=21) were grade 2 and 3% (N=2) grade 3.
-2 (3%) meningiomas displayed a SMO mutation and 4 (6%) meningiomas a PIK3CA mutation. Five (83%) meningiomas with SMO or PIK3CA mutations were grade I.
-Among the 8 cases (16%) that express GAB1 with a H-score >120, 2 were associated with SMO and 1 with PIK3CA mutation. OTX2 expression was contributive.
- All AKT mutated meningiomas (N=9,100%) , displayed a GAB1 H-score < 120, a score considered as negative. Conversely GAB1 was expressed in SHH activated meningiomas.
Conclusion: -In real life clinical situation we showed that SHH and mTOR activating mutations are rarer than previously described in exhaustive "molecular landscape" studies. These new data should be taken in account for future therapeutic trial designs.
-GAB1 could be a useful marker for immunohistochemical prescreening of cases amenable to sequencing for hedgehog pathway or mTOR pathway genes sequencing while OTX2 is not a beneficial marker.
-The WHO grading system has no role in predicting tumour molecular alterations of meningiomas.

OFP-13-011
miR-196b-5p and miR-107 expression differentiates ocular sebaceous carcinoma from squamous cell carcinoma of the conjunctiva
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Background & objectives: Ocular Sebaceous Carcinoma (OSC) can mimic Squamous Cell Carcinoma of the Conjunctiva (SCCC). Aim of this study was to find microRNA biomarkers to distinguish OSC and SCCC from normal tissue and from each other.
Methods: Clinical OSC and SCCC case files and corresponding histopathological slides were collected and reviewed. Microdissected formalin-fixed paraffin-embedded tumour and control tissue were subjected to semi-high throughput microRNA profiling.
Results: MicroRNA expression distinguishes OSC and SCCC from corresponding control tissues. Selected differentially expressed miRNAs were validated using single RT-PCR assays. A comparison between OSC (n=14) and SCCC (n=18) revealed 38 differentially expressed microRNAs ($p<0.05$). Differentially expressed miRNAs were selected for validation in the discovery cohort and an independent validation cohort (OSC, n=11; SCCC, n=12). At least two miRNAs miR-196b-5p ($p \leq 0.05$) and miR-107 ($p \leq 0.001$) displayed a statistically significant differential expression between OSC and SCCC with miR-196b-5p upregulated in SCCC and miR-107 upregulated in OSC. ROC analyses indicated that the combined miR-196b-5p and miR-107 expression levels predicted OSC with 90.0% sensitivity and 83.3% specificity.
Conclusion: Our findings indicate that deregulated miRNAs, identified by comparing tumour tissue with corresponding control tissue, may play a role in the tumourigenic processes in OSC and SCCC. We provide evidence that miR-196b-5p and miR-107 can differentiate OSC from SCCC. Combined testing of miR-196b-5p and miR-107, may be of additional use in routine diagnostics to discriminate OSC from SCCC in conjunctival tumour lesions.
Funding: This research was funded by SWOO-Flierenga, grant number SSWOO2018S12

OFP-13-012
Audit of outcomes for metastatic uveal melanoma patients in Ireland
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Background & objectives: Uveal Melanoma (UM) accounts for approximately 85% of ocular melanomas. The published rate of metastasis is approximately 50%, 5 years following diagnosis. This retrospective analysis investigated the percentage of patients who metastasised and their outcome over a 21 year period.
Methods: A detail review of pathology files, cancer registry files and death certs were accessioned, and results were tabulated on excel. UM patients who received enucleation were selected and further analysis was used to determine who presented with metastasis. Prior to 2011 patients were treated by enucleation. From 2011 on patients were treated by either plaque rt, proton beam or enucleation.
Results: From 194 identified metastatic cases, 93 were female and 101 male. Patient age ranged from 11-90 (average age: 62) at initial diagnosis. 10 patients were aged 20-40, 61 aged 40-60, 112 aged 60-80 and 17 aged 80-100. Youngest patient in this cohort was 11 and metastasised and died shortly after diagnosis. Primary tumour location: choroid and ciliary body. Average time for metastasis was 44 months.

Sites of metastasis included liver, lung, and skin. Metastasis rates were as follows: 116 patients metastasised 0-24 months after diagnosis, 57 patients 24-48 months and 51 exhibited late metastasis ranging from 60-216 months after initial diagnosis. Patients died on average 1.5 years following metastatic diagnosis.
Conclusion: From the analysis in our institution the incidence of metastatic disease corresponds with the European published figures. Our cohort includes a number of patients with a metastatic UM diagnosis prior to the age of 35. We found that 47.2% of patients treated for UM metastasised on average 43 months following diagnosis and the average time to death following metastasis was 1.5 years. Genetic analysis is currently underway to examine the contribution of specific genes role in early and late metastasis.

CP-02 | Computational Pathology Symposium: Abstract presentations and Best Abstract Award

CP-02-001
Swarm learning for decentralized deep learning in gastric cancer histopathology

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Background & objectives: A limitation for computational pathology is the difficulty of data exchange. Swarm learning (SL) is a protocol for decentralized training of deep learning models. We evaluate SL for the prediction of microsatellite instability (MSI) from gastric cancer histopathology images.
Methods: We collected tissue samples from four cohorts of patients with gastric cancer from four countries (Switzerland, Germany, the UK and the USA). Each dataset was stored in a physically separate computer. We trained a deep learning-based classifier to detect microsatellite instability using SL from digitized haematoxylin and eosin-stained resection slides without annotating tumour containing regions.
Results: We evaluated the patient-level performance for the prediction of MSI status in the TCGA cohort (N=334 patients). We found that local models achieved AUROCs of 0.7016 (+/- 0.0087), 0.5600 (+/- 0.0238) and 0.6638 (+/- 0.0170) when trained on local datasets. Merging the three training cohorts on a central server (merged model) improved the prediction of AUROC to 0.7508 (+/- 0.0074). This was compared to the performance of SL-trained models, and we assessed the performance of a weighted Swarm Learning model (w-chkpt) for MSI mutation prediction. In this task, w-chkpt achieved an AUROC of 0.7469 (+/- 0.0214), which was not significantly different from the merged model (p=0.7806).
Conclusion: Computational pathology problems in gastric cancer requires large datasets. Preferably, such data should be derived from different centres so as to avoid bias. However, the collection of such datasets faces practical, ethical and legal obstacles. These obstacles can be overcome using SL. In the future, this could be an alternative for sharing patient-related data across sites.

CP-02-002
BLEACH&STAIN, a novel multiplex fluorescence immunohistochemistry framework that facilitates a fast high throughput analysis of >15 biomarkers in more than 3000 human carcinomas

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Background & objectives: Multiplex fluorescence immunohistochemistry (mfIHC) approaches were yet either limited to 6 markers or limited to a small (1.5cmx1.5cm) tissue size that hampers translational studies on large tissue microarray (TMA) cohorts.
Methods: To assess more markers in a large patient cohort, we have developed a BLEACH&STAIN mfIHC approach that enables the analysis of ≥15 biomarkers in 3098 tumour samples from 44 different carcinoma entities within one week and without costly instrumentalization. An artificial intelligence-based framework –incorporating three different deep learning systems– for automated marker quantification was used to interoperate the BLEACH&STAIN data.
Results: This approach was used to study the relationship between PD-L1 expression on multiple different cell types and the relationship with various leucocyte subtypes (PD-L1,PD-1,CTLA-4,pan CK,CD68,CD163,CD11c,iNOS,CD3,CD8,CD4,FOXP3,CD20, Ki67,CD31). Comparing the automated and deep learning-based BLEACH&STAIN PD-L1 analysis framework with conventional brightfield PD-L1 data revealed a high concordance in tumour cells ($p<0.0001$) as well as immune cells ($p<0.0001$) and an accuracy of our approach ranging from 90% to 95.2%. Unsupervised clustering showed that a major proportion of the three PD-L1 phenotypes (i.e., PD-L1+ tumour and immune cells [G1], PD-L1+ immune cells [G2], PD-L1 negative [G3]) were either inflamed (G1.1, G2.1, G3.1) or non-inflamed (G1.2, G2.2, G3.2) and showed distinct spatial orchestration patterns.
Conclusion: BLEACH&STAIN mfIHC in combination with a deep learning-based framework for automated PD-L1 assessment on tumour and immune cells enabled a rapid and comprehensive assessment of 15 biomarkers across more than 3000 tumour entities that is quick and easy to establish in all laboratories. In breast cancer, the PD-L1 relative expression on tumour cells showed a significantly higher predictive performance for overall survival compared to the commonly used PD-L1 tumour proportion score.

CP-02-003
Pathologists' first perspectives on barriers and facilitators of computational pathology implementation in histopathology

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Background & objectives: Computational pathology algorithms detect, segment or classify cancer in whole slide images in histopathology. Currently, challenges have to be overcome before they can be used. We aim to explore international perspectives on the role of computational pathology in clinical practice.
Methods: We will focus on opinions and first experiences regarding barriers and facilitators, which will inform establishment of validation studies, implementation trajectories and communication activities to generate widespread stakeholder acceptance. We conducted an international explorative eSurvey study and semi-structured interviews with pathologists and pathology residents. We used an implementation framework to classify potential influencing factors.
Results: Results of the eSurvey showed remarkable variation in opinions regarding attitude, understandability and validation of computational pathology. Results of the interviews showed that barriers focused on the quality of available evidence, while most facilitators concerned strengths of using computational pathology. A lack of consensus was present for multiple barriers and facilitators, such as the determination of sufficient validation using computational pathology, the preferred function of computational pathology within the digital workflow and the appropriate timing of computational pathology introduction in pathology education.

Conclusion: The diversity in opinions illustrates variety in barriers and facilitators in computational pathology implementation. A next step would be to quantitatively determine important influencing factors among all relevant stakeholders. Simultaneously, prospective validation studies may be developed and initiated, to collect evidence on the most effective way of implementation. This will further propel the use of computational pathology into clinical practice.
Funding: This study received funding from the Dutch Cancer Society (grant number 2017-10602). This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 945358. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA.

CP-02-004

The prognostic value of deep learning based mitotic count for breast cancer molecular subtypes

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Background & objectives: Breast cancer grading was introduced decades ago and its prognostic value has not yet been studied in the context of contemporary molecular classification. This study uses automatic mitotic count to evaluate its prognostic value for different breast cancer molecular subtypes.
Methods: A previously developed artificial intelligence (AI) algorithm detected mitoses and assessed mitotic counts in H&E-stained whole-slide images from a multicentre cohort of 846 breast cancer patients. Stratified analyses based on hormonal receptor (HR) and HER2 status were performed to study potential different prognostic mitotic cut off values. Multivariable Cox regression survival models were used to study its independent prognostic value.
Results: We found that the mitotic count, assessed by AI was prognostic in univariate Cox analysis for HR positive / HER2 negative breast cancers, applying the widely used Nottingham cut-offs, both for recurrence free and overall survival. Prognostic value could be optimized applying a cut-off of 10 mitoses per 2 mm2 (recurrence free survival hazard ratio = 2.05 (1.14-3.68; p=0.02); overall survival hazard ratio = 1.84 (1.09-3.11; p=0.02) in multivariable analysis). However, for HER2-positive tumours, no mitotic cut off was found to be prognostic.
Conclusion: This study shows that automatic mitotic count yields different prognostic information for specific subtypes of breast cancer, suggesting the need for a molecular subtype specific grading assessment in clinical practice. In addition, it showed the potential of AI to automate part of the pathologists' workflow, as well as the feasibility of applying modern AI technologies to re-assess widely used histopathological features by evaluating large numbers of cases in a systematic, accurate and reproducible manner.

CP-02-005

Pathologist validation of a machine learned biomarker for risk stratification in colon cancer

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Background & objectives: Identifying new prognostic features in colon cancer may refine histopathology review. While prognostic artificial intelligence (AI) systems have demonstrated significant risk stratification in several cancer types, studies have not yet shown that the machine learned features are interpretable by pathologists.
Methods: This retrospective study utilized de-identified, archived colorectal cancer cases from 2013 to 2015 from University of Milano-Bicocca (UNIMIB). Histologic slides from 258 consecutive colon adenocarcinoma cases were reviewed at UNIMIB by two institutional pathologists. The pathologists conducted semiquantitative scoring for Tumor Adipose Feature (TAF), which was previously identified via a prognostic deep-learning model developed using an independent colorectal cancer cohort.
Results: 258 colon adenocarcinoma histopathology cases from 258 patients (median age 67 years; interquartile range 65-81; 47% female) with stage II (n=122) or stage III (n=139) cancer were included. TAF was identified in 120 cases (widespread n=63; multifocal n=31; unifocal n=26). For OS analysis adjusting for tumour stage, TAF was independently prognostic: Hazard Ratio (HR)=1.55 (95%CI 1.07-2.25; p=0.02) for TAF as a binary feature (presence vs. absence); and HR=1.87 (95%CI 1.23-2.85; p<0.005) for the highest TAF category (widespread) when evaluating semiquantitative scoring. Inter-pathologist agreement for widespread TAF vs. lower categories (absent/unifocal/multifocal) was 90%, corresponding to kappa at this threshold of 0.69 (95%CI 0.58-0.80).
Conclusion: Pathologists were able to learn and reproducibly score for TAF providing significant risk stratification on this independent dataset. While additional work is warranted to understand the biological significance of this feature and to establish broadly reproducible TAF scoring, this work represents an important milestone as the first validation of human expert learning from machine learning in pathology. This validation demonstrates that a computationally identified histologic feature can represent a human-identifiable, prognostic biomarker with the potential for integration into pathology practice.

CP-02-006

Predicting genetic variation from quantitative tissue phenotypes using explainable machine learning

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Background & objectives: Most human cancer genomes exhibit multiple mutational signatures, reflecting the complex milieu of damage and repair occurring during carcinogenesis. We used a robustly controlled, highly powered in vivo experiment to investigate genotype-phenotype correlates.
Methods: Inbred mice were exposed to a single dose of diethylnitrosamine shortly after birth. Resultant liver tumours were isolated and submitted for WGS, total RNAseq, and histopathology. This cohort was used to discover lesion segregation, which drives cancer genome evolution. We used deep learning to segment nuclei in these images, computed quantitative morphometric features, and modelled these using machine learning.
Results: We find that supervised learning of quantitative nuclear morphology robustly predicts (i) germline variation between ancestrally divergent mouse strains, (ii) germline heterozygosity within strain, and (iii) somatic mutations in driver oncogenes. We apply a game-theoretic approach to uncover morphometric features which explain the inference, identifying nuclear geometry as key to inferring driver gene mutations, and nuclear histochemical staining most

relevant for germline variation. Interestingly, we often find that statistical measures of variance in morphology are more relevant than measures of central tendency, and that the relationships are frequently non-linear and best modelled using tree ensembles. We further uncover pervasive batch effects and describe an approach to address these.
Conclusion: We defined quantitative relationships between histological phenotype and both germline and somatic genetic variation in tumour tissue using explainable machine learning. This approach has the potential to influence how clinical grade molecular inference models are optimised for generalisability in the future and allow histopathologists to gain intuition into the predictions made by deep models.
Funding: This work was supported by: the MRC Human Genetics Unit core funding programme grants (MC_UU_00007/11 and MC_UU_00007/16), MRC Toxicology Unit core funding (RG94521), Cancer Research UK Cambridge Institute core funding (20412), European Molecular Biology Laboratory, ERDF/Spanish Ministry of Science, Innovation and Universities-Spanish State Research Agency/DamReMap Project (RTI2018-094095-B-I00), and the Wellcome Trust (WT202878/B/16/Z). Edinburgh Genomics is partly supported through core grants from NERC (R8/H10/56), MRC (MR/K001744/1) and BBSRC (BB/J004243/1). J.C. is supported by a Wellcome Trust PhD Training Fellowship for Clinicians (WT223088/Z/21/Z) as part of the Edinburgh Clinical Academic Track (ECAT) programme. S.J.A. received a Wellcome Trust PhD Training Fellowship for Clinicians (WT106563/Z/14/Z) and National Institute for Health Research (NIHR) Clinical Lectureship.

CP-02-007
Successful deployment of an AI solution for primary diagnosis of prostate biopsies in clinical practice
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Background & objectives: This project aimed to validate, clinically deploy and integrate an AI decision support solution for prostate biopsies into the digital pathology workflow as a first read for primary diagnosis.
Methods: The project included a technical validation and integration phase of the AI solution into the lab workflow prior to the deployment. Seven pathologists underwent training and used the solution for prospective primary diagnosis of consecutive prostate core needle biopsies, reporting on 334 cases (1197 H&E slides). AI-assisted diagnoses were compared to the ground truth (GT = concordance of two pathologists).
Results: The AI solution demonstrated high performance when pre-classifying slides with highest likelihood to be benign or malignant, with NPV = 98.8% (331 / 335) and PPV = 99.8% (399 / 400), respectively. 32% of slides have been classified as undetermined by AI. In 4 out of 7 discrepancies that were compared subsequently to the GT, the AI classification was correct. User experience survey, as reported by pathologists, showed high satisfaction marks for the AI solution. Pathologists felt more confident to review and report both benign and cancerous slides using the AI system and prefer to continue working with the system compared to a microscope.
Conclusion: We report here successful implementation of a multi feature AI solution that automatically imparts clinically relevant diagnostic parameters regarding prostate cancer and other pathologic features. The solution demonstrated its ability to accurately triage cancerous prostate cases and improve diagnostic quality. Thus, Galen Prostate AI solution could be used as significant aiding tool for pathologists in clinical decision-making in routine pathology practice.
Funding: SBRI Centre of Excellence

MD-01 | Molecular Diagnostics Pathology Symposium: Selected Abstracts

MD-01-001
Comparison of whole genome with broad gene panel sequencing to identify actionable targets for cancer treatment
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Background & objectives: DNA mutation analysis by broad panel NGS and WGS is currently used to guide cancer treatment. WGS can detect all genetic alterations, however, its implementation in daily clinic holds practical considerations. We evaluated the potential of WGS alternatives in diagnostics.
Methods: Publicly available WGS data of lung (n=86), colon (n=118), melanoma (n=63) and ovarian (n=42) cancers was used to identify clinically relevant variants using variant interpretation software (VarSome Clinical). We compared reported variants between the whole genome and targeted panels and their clinical relevance in Dutch routine care or clinical trials.
Results: For each tumour type unique single nucleotide variants were identified (on average 1834 (likely) pathogenic variants (LPV) per tumour type). Structural variants were not included in this study. After applying *in silico* filters for commercially available cancer hotspot panel (CHP), Foundation Medicine (FMI) and TSO500 panels (50, 324 and 523 genes, respectively), of the LPV detected by WGS, an average of 12.4%, 6.6% and 3.5% was predicted to be detected by TSO500, FMI and CHP, respectively. Of the detected variants, all that were deemed clinically relevant were detected by the broad TSO500 and FMI gene panels while 15% would be missed using a smaller CHP gene panel.
Conclusion: Of the clinically actionable LPV detected by WGS in four tumour types, 100% is assumed to be identified by broad gene panels NGS (TSO500, FMI) and 85% by CHP. We conclude that in current clinical practice, the added value of WGS compared to broad gene panels is limited for clinically actionable single nucleotide variant detection in the tumour types analysed.

MD-01-002
Validation of TruSight™ Oncology Comprehensive (EU) assay
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Background & objectives: TruSight™ Oncology Comprehensive (TSO Comp) is a CE-marked comprehensive genomic profiling (CGP) assay designed to interrogate solid tumours for relevant single nucleotide variants, multi-nucleotide variants, insertions, deletions and gene amplifications from DNA, and gene fusions and splice variants from RNA.
Methods: It is an enrichment-based next-generation sequencing assay that targets 517 genes for detection of small DNA variants, 2 genes for detection of gene amplifications, 23 genes for detection of gene fusions and 2 genes for detection of splice variants. TSO Comp performance was evaluated in various analytical studies, including limit of detection/blank, accuracy, precision, utilizing FFPE-derived DNA and/or RNA samples.
Results: Performance of the assay was assessed for multiple variant classes: small variants and gene amplifications (amps) from

DNA, TMB and MSI genomic signatures in DNA, as well as RNA fusions and splice variants.
Limit of Detection was as low as 1.6% variant allele frequency for small DNA variants, 2-fold change for gene amps, 10 supporting reads for fusions, and 19 supporting reads for splice variants. Specificity was 99.9999% for small DNA variants, 99.9% for fusion variants and 100% for gene amps and MSI. Positive Percent Agreement (PPA) with whole exome sequencing (WES) for small DNA variants was 84.7% (382/451) for WES somatic and 99.8% (33,163/33,224) for WES germline variants.
Conclusion: DNA small variant Negative Percent Agreement was 99.999% (70,000,481/70,000,907). PPA for gene amps was 92.3% (337/365), for MSI status 93% (40/43). PPA for RNA fusions and for RNA splice variants was 80.5% (70/87). Qualitative precision analysis across multiple operators, instruments, reagent lots, and days showed high concordance (>90% positive percent call).
This CGP assay helps maximize the ability to find actionable biomarkers and help inform therapy decisions according to clinical guidelines that have the potential to improve patient management.

MD-01-003
Evaluation of MET amplification in lung cancer via Idylla™ GeneFusion cartridges
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Background & objectives: MET amplification in lung cancer is known as resistance mechanism to epidermal growth factor receptor tyrosine–kinase inhibitors. This retrospective study used Idylla™ GeneFusion assay (Biocartis) cartridges to develop a delta Cq cut-off for discrimination of non-amplified versus MET amplified samples.
Methods: A cohort of 70 samples including 31 non-amplified and 39 MET amplified samples was analysed. MET amplification status was previously detected by fluorescence in situ hybridization (FISH). One to five 10 µm slices with a tumour cell content (TC) between 10% and 90% of the same FFPE tumour tissues were taken for analysis with the Idylla^{TM} GeneFusion Assay.
Results: For initial data analysis a threshold of -3.0 (Delta housekeeping gene-MET) was used for discrimination between non-amplified and MET amplified samples. Hereby 27 out of 31 non-amplified samples (specificity= 87%) and 26 out of 39 MET amplified samples (sensitivity=67%) were detected. After a threshold adjustment from -3.0 to -2.0 the specificity was lowered to 74% (23/31 non-amplified samples) but sensitivity increased to 84% (33/39 MET amplified samples). No further optimization was reached by implementing a % TC cut-off since false positives and false negatives were distributed at different TC content. All top-level amplifications (copy number gain (CNG) > 10) were true positive.
Conclusion: This study showed that the Idylla^{TM} GeneFusion Assay might be a promising screening tool for top level MET amplification assessment in lung cancer samples. Nevertheless, even after threshold adjustment both specificity and sensitivity within different levels of MET amplification remained lower than 90%. Therefore, this test with our proposed cut-off is not suited to identify MET amplification at lower thresholds. This is in line with other published PCR-based approaches using for example next generation sequencing.

MD-01-004
Shallow whole genome sequencing accurately detects homologous recombination deficiency in ovarian cancer
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Background & objectives: Homologous Recombination Deficiency (HRD) predicts benefit from PARP inhibitors. MyChoiceCDx test (Myriad) is approved to assess HRD, based on *BRCA1/2* mutations and genomic instability (GIS) score. We assessed HRD by shallow whole-genome sequencing (sWGS) using Large-scale Genomic Alteration (LGA) score.
Methods: Fifteen high-grade serous ovarian carcinomas underwent sWGS on a NextSeq550 (Illumina), using FFPE-extracted DNA (tumour content ≥25%). All samples had known tumour *BRCA1/2* status (9 mutated, 6 wild-type), while 9 also had Myriad GIS score available. Raw reads were aligned to hg19 human genome assembly and analysed using shallowHRD software to compute LGA score, which was considered positive if ≥20.
Results: We successfully performed sWGS on all samples, generating an average of 22 million (M) reads per sample (11-42M) and achieving a mean coverage of 0.8X (0.3X-1.6X). LGA computation was still robust by artificially down-sampling to 5M reads (0.2X coverage). LGA score was positive in 8/9 *BRCA*-mutated cases, and negative in all wild-type cases (median 26 (11-40) vs. 6.5 (0-14), Wilcoxon rank test P=0.004). Correlation between LGA and GIS scores was statistically significant (Spearman rank rho 0.78; P=0.014), with only 1/9 cases showing discordant results. This was a *BRCA* wild-type sample with positive GIS score but negative LGA score, presumably due to low tumour cell content (25%) and low DNA quality.
Conclusion: In our series of 15 high-grade serous ovarian carcinomas, determination of LGA score by sWGS – using a predefined positivity cut-off ≥20 – was highly concordant with both *BRCA1/2* mutational status and Myriad GIS score. Despite a limited number of samples analysed so far, this preliminary cohort shows promising results, supporting further work to refine the cut-off value(s) and validate this tool as a predictive molecular biomarker for PARP inhibitor therapy, for patients with ovarian cancer or potentially other malignancies.

MD-01-005
Microsatellite instability in intestinal T-cell lymphomas
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Background & objectives: Microsatellite instability (MSI) is a consequence of defective DNA mismatch repair (MMR), leading to a hypermutant phenotype, with a high tumour mutational burden (TMB). We explored the potential impact of MSI in the oncogenesis of primary intestinal T-cell lymphomas (ITCLs).
Methods: Whole Exome Sequencing (WES) was performed on 54 ITCLs and matched non-tumour DNA: 34 MEITLs (Monomorphic Epitheliotropic Intestinal T-cell Lymphomas) and 20 EATLs (Enteropathy-Associated T-cell Lymphomas). Mutation signatures were extracted from somatic variants and compared with COSMIC reference signatures (MuSiCa package). MSI status was predicted from instability scores (MANTIS software), and assessed by PCR (5 mononucleotide markers) on 43 samples.
Results: We observed an overall median TMB of 1.8 non-synonymous somatic mutations per Mb, with a higher median in EATLs relative to MEITLs (2.3 vs 1.7/Mb). Nonetheless, the highest TMBs were detected in three MEITLs (maximum: 15/Mb). Accordingly, these three cases showed signatures associated with MMR deficiency, and high instability scores as measured

by MANTIS. Their MSI status was confirmed by standard PCR analyses, while none of the other MEITLs or EATLs showed instability. Altogether, our analyses estimated a prevalence of MSI of 11% (3/28) in the MEITL subtype. Notably, none of the MSI samples presented somatic mutations within MMR pathway genes (MLH1, PMS2, MSH2, MSH6), suggesting alternative mutagenic mechanisms.
Conclusion: Taken together, these data reveal a relatively high TMB in ITCLs when compared to other peripheral T-cell lymphomas, and an MSI status in a subset of MEITLs. This suggests a role of MMR deficiency in the oncogenesis of a proportion of ITCLs, with potential clinical implications. Alternative mutagenic mechanisms, possibly involving the intestinal environment, seem to play a role in the tumorigenesis of the majority of ITCLs.

MD-04-005
Extensive spatial characterisation of the tumour-microenvironment in a large clinical non-small cell lung cancer cohort and correlation with clinical and pathological parameters
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Background & objectives: We present an AI-driven image analysis workflow combining histomorphological and multiplex immunofluorescence data for automated, cell-level characterization of the tumour microenvironment (TME) that can facilitate biomarker identification. The workflow is utilized for the exploration of a clinical NSCLC cohort.
Methods: 340 clinical NSCLC cases from an FFPE tissue microarray were stained with a 12-plex immunofluorescence panel (IF) and subsequently with hematoxylin and eosin (H&E). All stains were scanned and co-registered with single cell accuracy. Deep learning models were developed to detect tumour regions from H&E and cell subtypes from IF and H&E. The resulting readouts were correlated with clinical parameters.
Results: Deep learning models were trained to quantify the presence of tumour cells expressing PD-L1 and lymphocyte cell subtypes. For the task of separating PD-L1+ carcinoma, PD-L1- carcinoma and other cells a balanced accuracy (BA) of 92% was reached. The task of separating FoxP3+ T-cells, CD8+ T-cells and B-cells respectively from other cells was performed with a BA of > 90%. The models were trained and evaluated using over 13,000 IF-informed manual pathologist annotations. The evaluation was performed on a held out TMA section with separate cases. The correlation of PD-L1 expression and various tumour infiltrating lymphocyte subpopulation levels with patient prognosis and other clinical parameters was computed.
Conclusion: The presented workflow allows for scalable characterization of the NSCLC TME by (1) staining the same section with H&E and multiplex IF images and registering resulting scans and (2) applying deep learning for robust cell subtype detection from both modalities at once. First results show that cells involved in the immune response within the TME can be precisely quantified and correlated with clinical parameters.

Posters

PS-01 | Poster Session Breast Pathology

PS-01-001
Insulinoma-associated protein 1 (INSM1) expression in breast carcinomas with neuroendocrine morphologies: application and future perspectives
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Background & objectives: Insulinoma-associated protein 1 (INSM1) is a zinc-finger transcription factor initially isolated from a human insulinoma subtraction library. INSM1 was recently demonstrated to be a better diagnostic and prognostic indicator for small cell lung carcinoma than the traditional neuroendocrine (NE) markers.
Methods: Herein, for the first time, we present eight cases with NE phenotype mammary neoplasms in which the NE nature of the tumours was confirmed solely by INSM1. Patients were 35–64 (mean: 48.9) year-old women with breast tumours showing characteristic NE morphologies, i.e. solid growth of polygonal, short-spindle or plasmacytoid cells with fine-granular cytoplasm and nuclei, and a well-developed vascular network.
Results: On immunohistochemical examinations, these malignancies showed diffuse nuclear expressions of INSM1 (mouse monoclonal, clone A-8: sc-271408, dilution 1:100; Santa Cruz Biotechnology, Inc., Dallas, TX), whereas chromogranin A [three sources: 1) mouse monoclonal, clone LK2H10; Roche Diagnostics, Mannheim, Germany, 2) rabbit polyclonal, dilution 1:500; Dako, Copenhagen, Denmark, and 3) rabbit polyclonal, 412751; Nichirei Bioscience Inc., Tokyo, Japan] and synaptophysin [two sources: 1) rabbit polyclonal, dilution 1:50; Dako, and 2) mouse monoclonal, clone 27G12: 413831; Nichirei] staining did not correspond to distinct NE features in the neoplastic cytoplasm. Finally, we diagnosed these cancers of luminal-like immuno-subtype as 4 neuroendocrine neoplasms (NENs), three hypercellular mucinous carcinomas, and one neuroendocrine ductal carcinoma in situ.
Conclusion: Based on the establishment of INSM1, a promising NE marker with high sensitivity and specificity, accompanied by our current immunohistochemical results, the frequency of detecting NE differentiation in systemic neoplasms, including mammary NENs as well as carcinomas with NE differentiation such as type B mucoid carcinoma and solid papillary carcinoma, is anticipated to increase. Our observations might contribute to the development of novel treatments including molecular-targeted therapies for these tumour entities.
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PS-01-002
PRAME expression in invasive breast carcinoma
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Background & objectives: PRAME (PReferentially expressed Antigen in MElanoma) is a carcinoma testis antigen expressed in numerous tumour types. The aim of this study was to assess PRAME expression in different surrogate subtypes of breast carcinoma and its correlation with other prognostic factors.

Methods: A total of 25 Luminal A like, 31 Luminal B like, 15 triple negative (TN) and 18 HER2 positive breast carcinomas were assessed for PRAME expression by immunohistochemistry (IHC) using the EPR20330 (ab219650; Abcam) monoclonal antibody. Expression of PRAME was quantified as positive (nuclear and/or cytoplasmic staining) or negative, and also as a percentage of tumour cells expressing PRAME.
Results: A significantly higher expression of PRAME was detected in HER2 positive carcinomas and TN breast carcinomas compared to ER positive (luminal like) subtype of breast carcinomas. PRAME expression was detected in 53% (8/15) TN carcinomas and 72% (13/18) HER2 positive carcinomas, as opposed to luminal A and B like breast carcinomas, where it was expressed in 32% (8/25) and 26% (8/31) of cases, respectively. Percentage of PRAME positive tumour cells showed positive correlation with tumour size, Ki67 proliferation index, HER2 status, nuclear grade and presence of metastasis, and negative correlation with ER status.
Conclusion: Previous studies on PRAME in breast carcinoma were mainly based on RT-PCR detection, with immunohistochemical studies limited to polyclonal antibody results. Our study showed that HER2 positive and TN breast carcinomas more commonly express PRAME than ER positive carcinomas and that PRAME expression shows positive correlation with certain prognostic factors. The importance of PRAME expression in breast carcinoma lies in its potential use as an immunotherapeutic target, particularly in patients with limited therapeutic options (e.g. in TN carcinomas).

PS-01-003
Alpha-methylacyl-CoA Racemase (AMACR/P504S) overexpression occurs in the early proliferative lesions of the breast irrespective of apocrine differentiation
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Background & objectives: Alpha-methylacyl-CoA racemase (AMACR/P504S) is a mitochondrial and peroxisomal enzyme involved in the branched-chain fatty acid and bile acid metabolism. We explored AMACR expression in a large cohort of patients undergoing breast biopsies to investigate its role in cancer progression.
Methods: The first, exploratory cohort of all cancer types (Caris Life Sciences) was investigated for AMACR mRNA expression followed by the second cohort of 150 patients' breast biopsies (77 with invasive carcinomas) studied for the discrete lesions' expression of AMACR using an automated IHC. The lesions were considered positive if AMACR was detected in ≥10% of the cells.
Results: AMACR mRNA expression was detected in all cancer types and in breast carcinoma, its median value was substantially and consistently lower than in prostate carcinomas. However, AMACR protein expression was detected not only in apocrine carcinomas, as recently described, but also in normal breast epithelium (6/77 samples, 8%), and with increased frequency in proliferative epithelial lesions and carcinomas: 23% of UDH, 73% of ADH and in-situ carcinomas, 60% of invasive carcinomas, including lymph node/distant metastases. LCIS and invasive lobular carcinomas expressed AMACR in 50% of cases, respectively. Apocrine lesions showed strong, nearly uniform overexpression of AMACR (100% of metaplasias, hyperplasias, and in situ carcinomas and 88% of invasive apocrine carcinomas).
Conclusion: AMACR expression in the breast is a common, early pathogenic event in the development of breast carcinoma and not exclusive to the apocrine morphology. It points to altered lipid metabolism as one of the hallmarks of breast carcinogenesis, similar to several other malignancies, notably prostate carcinoma. It may hence represent a potential target for early cancer intervention and management.

PS-01-004
Evaluation of NLRP3 immunohistochemical levels in breast cancer
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Background & objectives: NLRP3 belongs to a complex of proteins triggering proteolytic degradation via caspase-1. This molecular pathway is involved in breast oncogenesis. The purpose of our research was the investigation of NLRP3 expression in breast cancer and its association with clinicohistopathological factors.
Methods: Formalin-fixed, paraffin-embedded breast tissues from 43 patients were studied. 31 of them diagnosed with breast cancer (study group) and the other 12 (control group) diagnosed with fibroadenoma. NLRP3's expression was investigated immunohistochemically using a monoclonal anti-NLRP3 antibody. NLRP3 expression was statistically associated with various clinical and histological parameters using the SPSS program.
Results: Our results showed statistically significantly higher expression of NLRP3 in well- differentiated carcinomas G3 ($p<0.005$), a tendency for higher NLRP3 expression in carcinomas with severe Ki-67 expression ($p< 0.01$) and also with the presence of lymph node metastases ($p<0.022$). In contrast, no statistically significant correlation was observed between NLRP3 expression and patient age ($p=0.662$), expression of ER ($p=0.236$) and PR ($p=0.244$), HER2 gene expression ($p=0.342$) and the cancer type ($p=0.871$).
Conclusion: Based in our results, we conclude that NLRP3 could be a potential breast cancer biomarker as its high immunohistochemical expression is directly linked to advanced breast cancer. However, this is just a preliminary study and a more extended research needs to be conducted in order to establish these outcomes.

PS-01-005
Encapsulated papillary carcinoma. Our experience from 2005
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Background & objectives: The diagnosis of Encapsulated Papillary Carcinoma (EPC) of the breast is challenging. These lesions are staged as lesions in situ, and it is not possible to confirm EPC diagnosis until the capsule has been examined to rule out invasive growth.
Methods: All the cases treated at our institution since 2005 are reviewed. To analyse the involvement of sentinel lymph nodes, as the indication for their study is controversial. We have collected 54 patients who were treated surgically for EPC. Selective SLN biopsy was performed in 39 (72%) of them.
Results: We have observed that the mean size of EPC was 12 millimetres. The Nottingham grade was 1 in 46 cases (85.1%), 2 in 6 cases (11.1%) and 3 in 2 cases (3.7%). EPC was associated with invasive carcinoma in 17 cases (31.4%).
Of the 39 patients in whom SN was performed, only three cases (5.5%) showed invasion, whereas one was ITC, and 2 micrometastases. In these three patients, the EPC showed invasion between 3 and 8 mm.

Conclusion:
-SLN involvement is very low in our series of EPC (5.5%).
-The frequences of EPC without infiltration and invasive carcinoma are 0% and 11%, respectively.
-The presence of invasive carcinoma is only confirmed in the surgical specimen.
-Therefore, we suggest assessing the indication for SLN in those cases where invasive carcinoma is confirmed.

PS-01-006
Applicability of One Step Nucleic Acid in cytokeratin 19 negative tumours, based on a series of cases
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Background & objectives: The One Step Nucleic Acid (OSNA)is a molecular technique for the study of sentinel lymph node (SLN) in breast carcinomas. There is no general agreement on the lowest limit of detection of CK19 expression. A cut-off of 30% is proposed.
Methods: We analysed the expression of CK19 in BC diagnosed in our institution since May 2018 and selected those cases with negative or partial expression of CK19. A total of 1189 cases of BC biopsied in our hospital were reviewed, taking the cut-off value of 30%. In the selected cases, tumour type, grade and phenotype were included.
Results: 23 cases out of 1189 biopsies (1.93%) showed negative or partial CK19 expression. 19 cases (82.6%) showed less than 30% expression and four cases showed focal positivity >than 30%. 21 cases (91.3%) were invasive carcinoma-NOS with 15 (65.2%) being grade 1 and 2, one metaplastic carcinoma and one solid papillary carcinoma. The most frequent phenotype was luminal A (52.1%). In all cases with minimal and/or moderate expression (<30%), SLN study by traditional histological examination was recommended. Axillary lymph node metastasis was observed in 6 cases, in which no CK19 expression was verified by immunohistochemistry (IHC). In the 4 cases studied by OSNA, micrometastases was found in 1, CK19 negative.
Conclusion: The assessment of CK19 in tumour cells can be challenging in cases with partial positivity.
The majority of CK19-negative cases in our series are low-grade tumours, in contrast to previous evidence describing this finding in more aggressive tumours (intermediate-high grade and/or triple negative tumours).
A cut-off point of 30% in the assessment of CK19 IHC expression is considered an appropriate value in tumours with partial positivity to perform the OSNA technique, as evidenced in our series.

PS-01-007
Gross examination of post neoadjuvant chemotherapy (NACT) breast resections in resource constraint setting – how much is enough?
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Background & objectives: Post-NACT breast carcinoma gross examination poses a challenge when primary tumour is not localized with a radio-opaque wire/clip – a situation common in resource-constrained settings. We undertook a blinded study on two grossing approaches demonstrating how much sampling is adequate.
Methods: Fifty breast carcinoma cases were grossed prospectively by a single pathologist (n=50). Tumour bed was localized by clinico-radiological and visual correlation only. Tumour bed was submitted entirely in grids of multiple slices (Method 1) and one slice was marked as the one with maximum tumour bed area (Method 2). Kappa values were calculated to evaluate agreement between the two methods.
Results: Twenty patients underwent breast conservation surgery; whereas 30 patients underwent mastectomy. Mean of 8 blocks per case were prepared for a single slice (Method 2); whereas 26 blocks were prepared from sampling of entire tumour bed (Method 1). Pathological complete response (pCR) by both methods was calculated to analyse non-pCR cases missed by Method 2. Method 2 documented 23 cases with pCR of which 21 were picked up in Method 1.The two cases missed by Method 2 had minimal residual disease with <2 mm residual tumour (RCB I).The concordance of the two methods was 91.3%. Kappa value for Method 2 was 0.919 thus demonstrating very good correlation with Method 1.
Conclusion: Submitting slice of largest visible tumour bed captures 90% of pCR and RCB accurately. In resource-constrained settings, this would be a viable substitute option for primary tumour not localized prior to NACT by radio-opaque wire/clip. The average cost of 1 Hematoxylin and Eosin stained slide is INR.100 (equivalent to approximately 1$). The method 2 was shown to curtail the expenditure to 33%. RCB class could also be assigned using this technique.

PS-01-008
Clinicopathological features and response to neoadjuvant chemotherapy in triple positive breast cancer
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Background & objectives: Breast cancers with positive expression of hormone receptor and overexpression of HER2/neu, are called "triple positive breast cancers TPBC".Data is relatively limited on TPBC. We aim to characterize the clinical and pathological features associated with TPBC and study their responses to neoadjuvant chemotherapy.
Methods: Clinicopathologic data associated with TPBC from 2015 to 2021 were retrieved from our pathology database. A variety of clinicopathologic parameters, including patient age, tumour Nottingham grade, HER2 IHC status, tumour necrosis, and frequency of pathologically-determined complete response to neoadjuvant treatment (PCR).
Results: Of 123 consecutive TPBC, all cases were invasive ductal carcinomas. The mean age was 52 years with extremities of 26 and 102 years. TPBCs were more often of Nottingham grade II in 78 cases (63%). TPBC were node-positive in 63 cases (52%) and were less often IHC 3+ in 80 cases (65%). Tumoural necrosis was observed in 78% (n=96). Among the patients that underwent neoadjuvant chemotherapy, PCR was achieved in 3 of 20 (15%) TPBC.
Conclusion: In our study, TPBC are associated with Nottingham grade and higher rate of node-positivity. Notably, these tumours show lower rate of complete pathologic response to neoadjuvant chemotherapy.

PS-01-009
MMP-2 expression in BC and its association with clinicopathological features and lymph nodes status

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Background & objectives: Matrix metalloproteinase-2(MMP-2) plays a role in the invasion and metastasis of cancer through the destruction of the basal membrane and extracellular matrix. The study aimed to investigate MMP-2 expression levels in breast cancer(BC) and its relationships with lymph nodes status.
Methods: We tested the expression of MMP-2 in 358 BC specimens with immunohistochemistry (EPR1184, Abcam, USA). All cases were divided into two groups according to intensity of stained tumour cells (negative and mild vs strong cytoplasmic expression). MMP-2 positivity was detected in most cases (262, 72.2%). Nevertheless, strong positive expression (>50% tumour cells,3+) was only in every fifth case (78, 22%).
Results: Statistical significant association was found between MMP-2 overexpression(3+) and tumour size(pT2-3) (HR=34.05,p<0.001); Grade3(HR=73.08,p<0.001); ER(0-2 score, Allred)(HR=15.91,p<0.001); PgR(0-2 score, Allred) (HR=13.83,p<0.001); Ki-67≥50%(HR=68.58,p<0.001). There is loss of MMP-2 expression in most luminal A BC(93.8%). There was no statistically significant correlation of MMP-2 expression with patient's age, number of tumour nodes, its localization, histological type,HER2/neu expression. A significant relationship was found between MMP-2 expression and regional metastasis(p<0,001). In the group with lymph nodes BC metastases the number of cases with MMP-2 overexpression was higher (52 cases,66,7%) than in the group without lymph nodes metastases(26 cases,28.6%). There was negative MMP-2 expression(-) in 86 cases(38.1%) in the group without lymph nodes metastases vs the group with lymph nodes BC metastases (10cases,7,6%)(p<0,001).
Conclusion: Identification of specific biomarkers is very important for prediction of regional metastases. We demonstrated that MMP-2 expression is associated with clinicopathological parameters of BC and its lymph nodes status. Loss of MMP-2 expression is statistically significantly reduced risk of lymph nodes metastases (p<0.001). Loss of MMP-2 expression was predominant in BC with pT1, Grade I-II, ER-positive, PgR-positive, Ki-67-low parameters. These results suggest that MMP-2 plays a role in the biology of BC.
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PS-01-010
Sentinel lymph node localization with Magtrace. Our experience so far
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Background & objectives: Magtrace lymphatic tracer is a liquid non-radioactive tracer, specifically designed for sentinel lymph node biopsy, assisting surgeons to locate the first draining axillary lymph nodes. Sentinel lymph nodes (SL) are the first nodes most likely to be infiltrated by metastasis.
Methods: The cohort of our study consisted of 22 female patients aged 33-66, surgically treated (WLE or mastectomy) for breast cancer. All patients gave a written informed consent to participate in the experimental study with this lymphatic tracer. In one patient the technique was performed bilaterally. In all cases 1-6 SL were received in each patient, measuring 0,5-2 cm.
Results: Patients received the tracer 24 hours to 30 minutes prior to surgery. Macroscopically 1-6 SL were isolated and examined on frozen sections with H&E. SLN were totally enclosed and studied. Microscopically, increased presence of pigment laden macrophage aggregates was noted, found mainly in a central location in the node. Although the amount of the macrophage aggregates were striking, did not interfere with the correct diagnosis and was mainly found in one or two SL, indicating the first one or two SL. At present, common practice involves dual technique, Blue de Methylene or Patent blue in combination with radioactive technetium 99 and this technique doesn't seem to be inferior.
Conclusion: Magtrace, even though a relatively new SLN tracer method, is a standardized technique with a steep learning and teaching curve, as 2-3 applications are sufficient. The main advantages of this tracer are its safety, convenience, the non-stigmatizing technique for the patient, the significant lower allergy rates, the radiation free setting (reducing nuclear medicine dependency) and the longer half lifetime reaching up to one month. Overall, Magtrace has highly reproducible and accurate results and produces less discomfort for the patient.

PS-01-011
FOXA1 and lymph nodes status in breast cancer
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Background & objectives: Forkhead box protein A1(FOXA1) promotes the transcription of a gene that induces luminal cell differentiation and suppresses the processes of epithelial-mesenchymal transition in breast cancer(BC). In our study, we purposed to investigate the relationship between FOXA1 and lymph node BC metastasis.
Methods: We tested the expression of FOXA1 in 358 BC specimens with immunohistochemistry (SP88,Abcam,USA). FOXA1-scoring was done according to the Allred system. Scores of 3-8 are considered positive. Tumours with score 0-4 were considered as FOXA1-low, whereas tumours with score 5-8 were considered as FOXA1-high. FOXA1-negative BC was detected in 89 cases (25%). FOXA1-high expression was detected in 131 cases (36.6%).
Results: FOXA1-expression significantly correlates with clinicopathological and immunohistochemical parameters, including those that have a predictive value in the process of lymph node BC metastasis, such as the patient's age(p=0.004), tumour node size(p=0.028), Grade(p=0.001), ER(p<0.001) and PgR-expression(p=0.003), Ki-67(p<0.001). FOXA1-positive tumours were predominant in both comparing groups (with/without lymph nodes metastases-71.2% and 75.7%, respectively) (p=0.354). However, a significant relationship was found between the level of FOXA1 expression and lymph node BC metastasis(p=0.010). The intensity of FOXA1 expression was higher in the group without lymph node BC metastasis 94 cases(41.6%) compared to the group with lymph node BC metastasis 37 cases(28.2%). No significant difference was obtained in the two compared groups for FOXA1-low expression(p=0.081).
Conclusion: FOXA1 was a significant independent prognostic factor for the lymph nodes BC metastases. The intensity of the marker expression has statistical significance (p=0.01). With moderate FOXA1 expression, risk of lymph node metastasis decreases compared with weak staining of tumour cells. FOXA1-low expression reversely correlates with BC metastasis and progression and may serve as a prognostic biomarker for predicting lymph node metastasis.
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PS-01-012
SLC7A5 expression in breast cancer and its association with molecular subtypes

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Background & objectives: Solute carrier family7 member5(SLC7A5), known as LAT1, is a transporter factor delivering amino acids to cancer cells.SLC7A5 is an important prognostic marker of the breast cancer(BC) aggressive behaviour. This study aimed to investigate correlation between SLC7A5 expression and molecular subtypes.
Methods: We tested the expression of SLC7A5 in 358 BC specimens by immunohistochemistry (PA5-34215, ThermoFisher, USA). Full membranous staining in >10% tumour cells was considered as positive. Moderate/strong SLC7A5-positive expression was detected in 199 cases (55.6%). Loss of SLC7A5 expression was detected only in 56 cases(15.6%). Strong membranous staining in >50% tumour cells was determined in a quarter of cases(26.5%).
Results: SLC7A5 expression was increased in BC with HER2/neu overexpression, regardless of hormonal receptor status. Strong SLC7A5 expression was detected in 14 cases(66.7%) of luminal B HER2-positive subtype and in 12 cases (80%) of non-luminal HER2-positive subtype. There was no SLC7A5-negative BC cases with HER2/neu overexpression. In TN breast cancer and in luminal B subtypes, the transport protein was expressed more than in half cases, with approximately the same frequency in all three subtypes – 65%-66.7%. In luminal A subtype, cases with no SLC7A5 expression were 1.5 times more often (34 cases, 21%) than in luminal B HER2-negative BC (18 cases, 14.5%)($p<0.001$).
Conclusion: We demonstrated that SLC7A5-expression is associated with molecular BC subtypes ($p<0.001$). SLC7A5-negative BC positively correlates with luminal-A subtype. The largest number of cases with strong SLC7A5 expression in >50% cancer cells was detected in cases of non-luminal BC subtype with HER2/neu overexpression. These results suggest that SLC7A5 plays a role in the biology of BC.
Funding: НИОКТР АААА-А18-118053190016-7

PS-01-013
Comparison of HercepTest™ mAb pharmDx (Dako Omnis) (GE001) with Ventana PATHWAY anti-HER-2/neu (4B5) in breast cancer
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Background & objectives: For HER2 assessment in Breast Cancer, immunohistochemistry (IHC) staining is the method of choice. Here, we compare the clinical performance of the new CE-IVD-marked HercepTest™ mAb pharmDx (Dako Omnis) (GE001) with Ventana PATHWAY anti-HER-2/neu (4B5).
Methods: In total, 119 pre-selected breast cancer samples covering the entire range of HER2 IHC expression scores were tested by HercepTest (mAb), PATHWAY 4B5, and fluorescent in situ hybridization (FISH). Three pathologists independently evaluated HER2 IHC according to 2018 American Society of Clinical Oncology/College of American Pathologists guidelines. Sensitivity and specificity of both IHC assays were assessed based on FISH data.
Results: There was a high concordance between results from the HercepTest (mAb) and PATHWAY 4B5 assays for HER2-negative (IHC 0, 1+, 2+ and FISH negative) and HER2-positive (IHC 3+, 2+ and FISH positive) breast carcinomas (98.2%). Regarding individual IHC scores, complete agreement was achieved in 69.7% (83/119) of cases and all but one of the discordant cases were due to higher HER2-status scoring using the HercepTest (mAb). Thus, more tumours were scored as IHC 2+ by HercepTest (mAb) (27 versus 15) as evidenced by their lower FISH positivity rate (48.1% versus 80%). However, two amplified tumours identified as IHC 2+ by HercepTest (mAb) were missed by PATHWAY 4B5 (IHC 1+).
Conclusion: The HercepTest (mAb) detects HER2 expression with higher sensitivity in tumours with gene amplification (ISH group 1) and increased gene counts (ISH group 4) as well as in HER2-low tumours (HER2 IHC 2+ / FISH negative or IHC 1+). These findings could be critical for the identification of patients eligible to new HER2-targeting treatment options. Future studies will demonstrate whether this new assay has the capacity to provide better patient stratification, leading to better patient response rates and clinical outcomes.
Funding: This study was funded by Agilent Technologies, Inc.

PS-01-014
Phosphohistone H3 versus mitotic count in breast cancer grading: a single institution study
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Background & objectives: Mitotic index is an important prognosis marker in invasive breast carcinoma (BC). The aim of this study was to evaluate the utility of Phosphohistone H3 in grading of BC in comparison with mitotic count on hematoxylin and eosin-stained slides.
Methods: A retrospective study on a series of 40 BCs diagnosed from March 2020 to August 2021 at the Pathology Department of the Military Hospital of Tunis was performed. We compared grade variability according to the mitotic count on H&E-stained slides and on PHH3 stained slides.
Results: Although, mean average count was higher by IHC method, good correlation was observed (R^2=0.799). Using PHH3 IHC, three cases of grade I tumours were upgraded in to grade II and six cases of grade II were upgraded in to grade III. None of the tumours were downgraded.
Conclusion: In summary, we have performed the first study to explore the utility of PHH3 in breast cancer grading in Tunisia. Similar to some other previous studies, we found PHH3 a robust sensitive and practical marker for mitotic count in breast carcinoma. Especially it is helpful to identify the most proliferating area.

PS-01-015
Immune checkpoint genes expression in breast carcinoma: correlation with clinicopathological features and patients' survival
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Background & objectives: Immune checkpoints deregulation can lead to tumour progression and invasion. However, very little data is available on breast carcinoma (BC). Therefore, we analysed CTLA-4, PDCD1, CD274, PDCD1LG2, and CD276 expression in BC and their association with clinicopathological factors and survival.
Methods: We included 275 non-consecutive BC. mRNA expression was analysed by qRT-PCR using TaqMan® primers and probes. PUM1 and β-actin were used as reference genes, and healthy breast tissue served as a calibrator. The 2-ΔΔCT calculated relative changes in expression. Results were correlated with clinicopathological factors and prognosis. Significant differences were calculated with $\chi 2$ and log-rank test.

Results: Overexpression of at least one immune checkpoint was found in 95.2% of samples. CTLA-4 was overexpressed mostly in Triple-Negative/Basal-like phenotypes (p=0.046), whereas PDCD1 and CD276 were more frequently found in Luminal tumours (all p<0.023). CD274 and PDCD1LG2 showed no correlation with immunophenotype. High CTLA-4, PDCD1, CD274 and PDCD1LG2 expression was associated with a middle/high proliferation rate (all p<0.039), and presence of TILs (all p<0.011), with opposite results for CD276 (p=0.048, and 0.026, respectively). CTLA-4 overexpression correlated with better disease-free survival -DFS- (p=0.037), and specifically among HER2-enriched subtype (DFS p=0.033, and overall survival p=0.011).
Conclusion: Our data support that CTLA-4, PDCD1, CD274, and PDCD1LG2 are potential biomarkers of BC aggressiveness. Paradoxically, CTLA-4 stratified a subgroup of HER2-enriched patients with a better outcome.
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PS-01-016

The malignancy of benignancy. The malignant consequences of benign breast tumours. Is the onus on pathologists? Post-pregnancy associated infarcted fibroadenoma, a rapidly growing benign phyllodes tumour, a benign phyllodes tumour in an adolescent girl

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Background & objectives: Fibro-epithelial lesions of the breast can be difficult to assess, especially when dealing with core biopsies. In uncommon clinical settings such as pregnancy, young girls or a size that would require mastectomy, they are even more difficult to assess.
Methods: Here we report on three cases of fibroepithelial lesions, where caring clinicians were concerned about malignancy despite benign pathology reports. We discuss the difficulties of making clinicians accept a benign pathology diagnosis despite the worrying clinical presentation. Literature for similar cases confirmed that these are rare but well-known conditions usually described in single or very small series case reports.
Results: In one case, the core biopsy was reported as B2, fibroadenoma with necrosis. Despite a benign report, diagnostic surgical excision was performed. Following MDT, it was revealed that the patient was post-partum and lactating. Patient 2 had a B3 core biopsy for a spindle cells tumour, occupying most of the breast. Excision biopsy was unwelcome because the size would have required a mastectomy, not consistent with a B3 report. Additional biopsies revealing an epithelial component consistent with phyllodes tumour were required for diagnosis. Patient 3 was a 17-year-old girl with a 70mm lump in her breast. Clinical concern led to surgical resection without prior core biopsy revealing benign phyllodes tumour.
Conclusion: Benign fibroepithelial tumours simulating malignancy on clinical presentation are well known to pathologists but still create uncertainty in clinicians. Although rare, in one year we have encountered and correctly identified three such cases. Our experience, where clinicians are not prepared to accept a diagnosis of benign/uncertain tumour on core biopsies, suggests that more education of these tumour subtypes is essential if clinicians are to accept our diagnosis and organize patient management accordingly.

PS-01-018

Breast interstitium or "Hartveit's Labyrinth": morphology and relationship to disease processes

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Background & objectives: The breast stroma contains interstitial spaces (IS) supported by collagen bundles and intermittently lined by CD34+/vimentin+ interstitial lining cells (ILC) identified previously by Hartveit (Histopathology, 1990) as pre-lymphatic "labyrinth." Current study investigates morphology and role of interstitium in disease processes.
Methods: Normal breast tissue with skin and breast tissue with PASH were stained for HA with peroxidase labelled HABP (hyaluronic acid binding protein) to investigate continuity between intralobular/interlobular and skin IS. IHC multiplex co-staining for CD34 and vimentin was used to demonstrate spatial relationship of the interstitial HA with ILC (Discovery Ultra, Ventana) and IHC for Galectin/Vimentin and p63/Vimentin in PASH.
Results: HABP staining showed HA throughout the IS of the normal breast sections and demonstrated continuity of IS between intralobular, interlobular, perivascular and perineural interstitium. In samples with PASH, HABP showed expansion of IS associated with thickened collagen bundles. IHC for p16/Vimentin showed significantly increased staining in PASH comparing to normal breast tissue and Galectin/Vimentin demonstrated positive Galectin staining along cell membrane of some fibroblasts in PASH.
Conclusion: Breast IS form a continuous space permeating all stromal compartments: periductal, interlobular, nipple, and dermis. Additionally, IS are continuous between breast stroma and perivascular adventitia and perineurium, connections to a body-wide system of IS. Our data support that PASH is a keloid-type expansion and remodelling of the mammary IS, which further suggests that mammary interstitium may play roles in fibrocystic disease, gynecomastia and malignant states such as invasive lobular carcinoma and could provide a route to spread via lymphatics/perineural routes.

PS-01-019

The effect of neoadjuvant chemotherapy on histologic grade and hormone receptor status in HER2/Neu-negative Luminal-B tumours of the breast

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Background & objectives: With stratification of tumours, neoadjuvant chemotherapy (NACT) has become more common in Her2/Neu-negative Luminal-B group. Here we investigate the effect of NACT on histologic grade/hormone receptor (HR) status and tumour representation adequacy in pre-NACT core biopsies.
Methods: Her2/Neu-negative luminal-B cases between 2017 and 2020 with available core biopsy and post-NACT resection slides were retrieved. Hospital records, original sign-out reports and glass slides were retrospectively reviewed for demographic data, pre-/post-NACT histologic grade and HR status of tumours, as well as number of pre-NACT core biopsy pieces available for tumoral representation.
Results: 45 cases were identified, with a mean age of 49.8. In the pre-NACT core biopsy samples, average number of pieces and percentage of tumoral tissue in the pieces were 3.82 and 52% respectively. 40% (n=18) of cases were attributed a histologic grade different from what had been originally assigned to them with the core biopsy, while 4.4% of cases

(n=2) showed complete regression in post-NACT resection specimens. From core biopsy to resection, in terms of oestrogen receptor expression change, 8.9% (n=4) and 8.9% (n=4) of cases marked a decrease and increase, respectively. For progesterone receptor status, 33.3% (n=15) of cases demonstrated a decrease, while 11.1% (n=5) showed an increase.
Conclusion: Changes in histologic grade, increased/decreased ER or decreased PR status have been described in literature as potential effects of NACT. Yet 11.1% (n=5) of our cases showed significant increase in PR status, which can better be explained by intratumoral heterogeneity and inadequate pre-NACT representation of tumoral tissue. In fact these cases had significantly lower percentage (30%) of tumoral tissue representation in the pre-NACT core biopsy specimen.

PS-01-020
Morphological and crystalchemical features of breast cancer microcalcificates
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Background & objectives: The aim of the study is to study the main morphological and crystal chemical properties of microcalcifications of breast cancer.
Methods: In our study, we examined 30 specimens of breast carcer by histology (hematoxylin-eosin staining), histochemistry, scanning electron microscopy with EDS and TEM.
Results: Histological examination of breast cancer samples revealed the presence of microcalcifications in the form of dark blue deposits of round and irregular shape, different sizes. A positive reaction to von Koss staining indicates the presence of calcium phosphate compounds in their composition. We confirmed the presence of round calcifications using SEM. SEM with X-ray microanalysis confirmed that the biomineral part of the samples of the group consists mainly of hydroxyapatites. In 6 cases, the presence of hydroxyapatite is combined with oxalates. However, oxalates and apatites had different localizations: apatites were associated with tumour, and oxalates were in intact adjacent tissue.
Conclusion: We found the possibility of the simultaneous presence of microcalcifications of hydroxyapatite and oxalate nature in samples of invasive breast cancer. Different spatial localization of biominerals indicates different mechanisms and conditions for the formation of microcalcifications.

PS-01-021
HER-2 ISH: do we need to count?
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Background & objectives: Assessment of Her2 amplification requires counting 20-60 cells. This is time-consuming and may be unnecessary since morphological assessment can provide accurate diagnosis in a proportion of cases. We define parameters for selection of cases that can be diagnosed morphologically.
Methods: Using both glass slides and DP, we studied 200 consecutive breast core biopsies for which DDISH was requested following an indeterminate (2+) IHC result with 4B5. We assessed whole slides for presence and frequency of amplification clusters and polysomy of Ch17 by eyeballing. We separately performed formal counting and compared the time to reach a diagnosis.
Results: We identified a number of morphological groups, including tumours with large amplification clusters (regardless of the number of Ch17 signals), tumours with sparse Her-2 signals (that are clearly below a ratio of 2 per Ch17) and tumours with high prevalence of borderline/non-amplified features. We evaluated concordance between morphological diagnosis and formal counting. Concordance was high in tumours with amplification clusters and in tumours with low gene copy numbers and/or low Ch17 signals. Concordance was poor in tumours with intermediate features. Time required for morphological assessment (30-60s) was 5-6 times faster than formal counting. For these assessments, DP was comparable to glass slides.
Conclusion: Some cases will still require the formal counting approach but we demonstrate that morphological assessment can be as accurate as formal counting in selected cases. For this to become established, training will need to be provided in order to ensure concordance amongst pathologists. This training can be delivered by DP. Digital programmes of Proficiency Testing would ensure continuing diagnostic alignment. This approach would save reporting time and therefore Pathologists and Healthcare resources could be used more efficiently.

PS-01-022
Pathological features of CT-guided bone lesion biopsy specimens in breast cancer patients
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Background & objectives: Current breast cancer guidelines recommend biopsy of metastatic lesions at presentation or first recurrence. Objective is to provide a cross-sectional pathological study of CT-guided bone biopsy specimens in breast cancer patients with suspicious bone lesions.
Methods: A cross-sectional study on 56 consecutive female breast cancer patients who underwent CT-guided biopsy of suspicious bone lesion was performed. Quantity of the specimen was defined as optimal (>5% cancer cellularity), suboptimal and low (non-diagnostic). Immunophenotype of the primary tumour and matching metastasis was compared, where available. Diagnostic accuracy of CT-guided bone biopsy was determined.
Results: A total of 58 bone lesions were biopsied in 56 patients and 44 (75.9%) breast cancer metastases were found. CT-guided biopsy enabled optimal quantity of specimens in most cases (56.9%), followed by suboptimal (32.8%) and low (10.3%). In 10% of positive cases, the number of tumour cells was too low for further immunohistochemical analysis. In 36 paired cases (primary vs metastatic), a shift in immunophenotype was observed in 13 cases (36.1%), most commonly from PR-positive to PR-negative (10/13, 76.9%). Sensitivity of CT-guided biopsy for detecting bone metastases was 93.6% and specificity was 100%.
Conclusion: CT-guided bone biopsy is a method with high sensitivity and specificity for detecting breast cancer metastasis that can be used when soft tissue metastatic lesions are not obtainable. The proportion of positive cases with sufficient tumour quantity for further immunohistochemical analysis is high. Comparison of primary tumour and metastasis immunophenotype revealed discordance in more than one third of patients, with potential therapeutic implications.

PS-01-023
Luminal breast cancer subtypes and associated prognostic factors: a population-based study from Osijek, Croatia

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Background & objectives: Breast cancer is a heterogeneous disease, with a spectrum of biological features and differences in clinical outcome. The aim of this study was to examine the prognostic factors of luminal breast cancer subtypes among Croatian breast cancer population.
Methods: This is a large retrospective population-based study including 1127 primary breast cancer cases, during a six year period (2016–2020) in Osijek, Croatia. The clinico-pathologic and immunohistochemical (IHC) and in situ hybridization (ISH) data were extracted from pathology reports to examine the luminal subtypes A and B. The cross-tabulated statistics of the observed characteristics were performed between the two subtypes.
Results: Luminal cancers comprised 86.9% (980/1127) of the total cohort, including 724 (64.2%) cases of luminal B and 256 (22.7%) luminal A. Age profile of Luminal A and B cancers were similar (63.5 vs 62.3 years). Mean tumour size was higher in luminal B than luminal A cancers (19.6 vs 22.2 mm, p=0.03). Luminal B cancers were significantly associated with adverse prognostic features than luminal A cancer, including high histologic grade (14% grade III luminal B vs 3.5% luminal A, p<0.0001), vascular invasion (18% luminal B vs 7.5% luminal A, p<0.0001), and nodal metastasis (21.2% luminal B vs 15.1% luminal A, p=0.006).
Conclusion: Luminal B is the most frequent subtype of breast cancer in Croatian patients. They were associated with adverse clinico-histologic parameters such as higher grade, vascular invasion, and nodal metastasis. Our findings suggest that, despite lack of molecular studies in routine practice, IHC/ISH-based typing are sufficient for prognostic and therapeutic stratifications in breast cancers.

PS-01-024

Ki67 proliferative index in patients with early breast cancer and its association with clinicopathological factors

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Background & objectives: Standard cut-off for distinguishing low and high Ki67 index as a prognostic marker in early breast cancer do not exist. The aim of this study was to determine the role of Ki67 index and its association with other prognostic parameters.
Methods: A large population-based retrospective study including 957 primary early breast cancers (pT2 or less) was conducted during a 5-year period (2016–2020) in Osijek, Croatia. The clinicopathologic data were extracted from pathology reports. Multiple logistic regression analysis was used to evaluate the associations between Ki67 and other clinicopathological factors.
Results: The median Ki67 was 30% (range 2–98%), with 251 (26.2%) patients had a Ki67 <20%. Triple-negative breast cancers showed highest ki67 index (mean 72.7 ± 23.9%) followed by HER2-positive (mean 60.2 ± 21.3%) and luminal B cancers (mean 39.8 ± 19.9%) (p<0.0001). Metaplastic and medullary breast cancers significantly showed higher Ki67 index compared to ductal carcinoma, NOS. Using a multivariable logistic regression with Ki67 (<20% vs. ≥20%) as binary dependent variable, younger age, positive nodal status, higher grading, negative HR status, and positive HER2 status were shown to be significantly associated with a higher proliferative index (Ki67 ≥20%).
Conclusion: Ki67 index is a valuable biomarker of breast cancer as higher ki67 correlates with more aggressive tumour biology. However, definition of low and high proliferation index itself is challenging. It is essential to interpret Ki67 indices carefully with regard to the own institutional values and other clinicopathological factors.

PS-01-025

To determine the accuracy of axillary staging using ultrasound-guided fine-needle aspiration cytology in breast cancer patients: a single institutional experience

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Background & objectives: Ultrasound-guided fine-needle aspiration cytology (US-FNAC) of axillary lymphadenopathy is a helpful tool in identifying candidates for axillary dissection and neoadjuvant chemotherapy for breast cancer patients. This study investigated the diagnostic value of evaluating the axillary lymph nodes with US-FNAC.
Methods: Between 2011 and 2021, 284 cases who underwent the axillary US-FNAC procedure during the diagnosis of primary breast cancer and then underwent axillary / sentinel surgery were collected retrospectively. Cytological diagnoses and corresponding histological diagnoses were documented. Final histopathology was taken as gold standard. The diagnostic parameters, including sensitivity, specificity, positive (PPV), and negative predictive values (NPV), were calculated.
Results: Hundred-fifty-two of 284 cases were evaluated as malignant cytology in FNAC. There were no malignant histopathological findings in 4 of them. Conversely, 132 cases were evaluated as benign cytology in FNAC. While 41 of them had malignant tumour metastases histopathologically, 91 of them did not have any malignancy findings. Overall sensitivity of lymph node FNAC was 78.3% and specificity was 95.7%. Positive predictive value (PPV) was 97.3% and negative predictive value (NPV) was 68.9%.
Conclusion: Axillary FNAC is a diagnostic method that helps surgeons decide whether to perform sentinel node biopsies. This technique is favourable due to its minimally invasive nature. In addition, we suggest that FNAC can prevent unnecessary axillary dissection due to its high positive predictive value (PPV). The reason for the lower negative predictive value may be hypocellularity and micrometastasis. So FNAC has adequate sensitivity and high specificity in diagnosing axillary lymph node metastasis.

PS-01-026

Predictive factors of lymph node metastasis in breast cancer patients: a Croatian population-based study

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Background & objectives: Breast cancers are heterogeneous groups of tumours, and its subtypes correlates with therapeutic response and overall survival. In this study, we assessed whether the subtype can predict the presence of nodal metastasis in a large cohort of breast cancer patients.
Methods: A large population-based retrospective study including 1127 primary breast cancers was conducted during a 5-year period (2016–2020) in Osijek, Croatia. The clinico-pathologic data were extracted from pathology reports. The Pearson chi-square test was used to determine whether progesterone receptor (PR) status had an impact on the incidence of lymph node positivity in oestrogen receptor (ER) positive patients.

Results: Lymph node metastasis was significantly associated with HER2-positive and luminal B breast cancers, higher histologic grade, as well as higher Ki67 proliferation index ($p<0.01$). Independent predictors of nodal positivity included tumour size and vascular invasion ($p<0.0001$). There were significant differences between subtypes and nodal positivity, with luminal A cancers (23.3%) had the lowest and Her2-positive (50%) the highest rates ($p=0.001$). There was no difference in lymph node positivity between PR+ and PR- tumours amongst all subtypes ($p=.1$).
Conclusion: Tumour size and vascular invasion are independent predictors of nodal positivity in this study. HER2-positive breast cancers, higher histologic grade and Ki67 proliferation index are significantly associated with lymph node metastasis. These findings may play a role in guiding regional management considerations.

PS-01-027
GATA3 expression in human tumours: a tissue microarray study on 13,204 tumours
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Background & objectives: GATA3 is a transcription factor involved in epithelial cell differentiation. Positive GATA3 immunostaining is used as a diagnostic marker for breast and urothelial cancer but can also occur in other neoplasms.
Methods: A set of tissue microarrays containing 16,611 samples from 133 different tumour types and subtypes and 608 samples of 76 different normal tissue types were analysed by immunohistochemistry to comprehensively evaluate GATA3 expression in normal and tumour tissues.
Results: GATA3 positivity occurred in 70 different tumour types including 24 (18%) with ≥1 strongly positive tumour. Highest positivity rates occurred in non-invasive papillary urothelial carcinoma (92-99%), lobular (98%) and NST (92%) carcinoma of the breast, cutaneous basal cell carcinoma (97%), invasive urothelial carcinoma (73%), T-cell lymphoma (23%), adenocarcinoma of the salivary gland (16%), and cutaneous squamous cell carcinoma (16%). In breast cancer, low GATA3 staining was linked to advanced pT stage ($p=0.03$), high BRE grade ($p<0.0001$), HER2 overexpression ($p=0.0085$), oestrogen and progesterone receptor negativity ($p<0.0001$ each) and reduced survival ($p=0.03$). In urothelial neoplasms, low GATA3 was linked to poor grade within pTa tumours ($p=0.01$) and with advanced stage ($p<0.0001$).
Conclusion: GATA3 positivity can be seen in various tumour entities. Particularly high frequency and levels of GATA3 expression occur in breast and urothelial carcinoma. A reduced level of GATA3 reflects cancer progression and poor patient prognosis in these tumour entities.

PS-01-029
Analysis of intraoperative frozen sections of sentinel lymph nodes - a 10-year long series in a tertiary Portuguese hospital
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Background & objectives: Intraoperative frozen sections of sentinel lymph node (IFSSLN) allowed better management of breast cancer (BC) particularly in the decision to perform axillary lymphadenectomy (AL). This study reviews results of IFSSLN, their definitive evaluation and correlation with AL status when performed.
Methods: Through our department's information system, we compiled every case of BC where IFSSLN was performed along with data pertaining diagnosis and AL status, from 2010 to 2020; 929 out of 1056 cases were selected. Only cases with a diagnosis of invasive disease made in surgical specimens were chosen and AL was solely considered when referred as such by the surgeon.
Results: Median age of diagnosis was 59,4 years (range 27-95 years), with a female predominance (n=923). 695 were IFSSNL-negative with 88,9%(n=618) being true-negatives; the remaining showed signs of disease in definitive evaluation (mostly isolated tumour cells[ITC] and 2 cases with metastasis). AL was performed in 7 false-negative cases which revealed metastasis in 2 cases and micrometastasis in 1; 42 false-negatives had nodal evaluation not by AL (either satellite lymph node or axillary inspection), showing metastatic disease in 6 of these (4 metastasis, 1 micrometastasis and 1 ITC). There were no false-positive cases. Two cases were deferred. Invasive breast carcinoma of no special type was the most common diagnosis (n=725).
Conclusion: IFSSNL continues to be a useful assessment method in BC staging, showing in this retrospective study highly favourable statistical values when compared with posterior definitive evaluation (75,1% sensibility; 100% specificity; 100% positive predictive value; 88,9% negative predictive value); this results are vastly supported by our use of immunohistochemical stains during the procedure. 34,5% of true-positive cases benefited from this evaluation, since AL revealed the presence of metastatic disease; furthermore, it spared 571 patients of AL-associated complications.

PS-01-030
Determination of inter-observer agreement in the immunohistochemical interpretation of PD-L1 clones 22C3 and SP142 in triple-negative breast cancer (TNBC)
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Background & objectives: Advanced triple-negative breast cancer can be treated with immune checkpoint inhibitors, and the expression of PD-L1 is one of the biomarkers used to select patients with clinical benefit. This study analyses the interobserver agreement in the immunohistochemical report of PD-L1.
Methods: 168 cases of TNBC were previously tested and diagnosed between 1987-2016 in 3 institutions. Medical records were reviewed for clinicopathological data collection. The study was performed on 2 TMAs, using two clones. The samples were analysed by 2 breast pathology subspecialists and 2 general pathologists without training. The Kappa value was calculated to assess interobserver agreement, with $p < 0.001$.
Results: For clone 22C3, (κ) among the 4 evaluators was 0.387, with $\kappa = 0.625$ among subspecialist examiners and $\kappa = 0.264$ among general pathologists, with 73% concordant cases. Of the discordant cases, a subspecialist evaluator considered 1.7% samples as positive, while the others classified them as negative. For clone SP142, (κ) among the 4 evaluators was $\kappa = 0.331$, with $\kappa = 0.420$ among subspecialists and $\kappa = 0.285$ among general pathologists, with 109 (64.8%) cases in agreement. Of the discordant cases, in 10.1% one evaluator was inconsistent and interpreted the sample as positive, with the discordant interpretation given by subspecialists in 14 cases and by general pathologists in 3.
Conclusion: We demonstrated different rates of interobserver variability between 4 evaluators and different PD-L1 clones,

with a minimum overall level of agreement. However, in comparison with general pathologists, the agreement rate between subspecialist evaluators was higher, reaching a moderate level for clone 22C3 and pointing to the possibility of improvement with tutorials. It is noteworthy that even among trained examiners, the agreement rate did not reach optimal levels, indicating the existence of challenges in the analysis of PD-L1 expression.

PS-02 | Poster Session Head & Neck Pathology

PS-02-001

DNA methylation analysis in oropharyngeal squamous cell carcinoma – unraveling novel prognostic biomarkers in a clinico-pathological and molecular genetic study of 51 cases

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Background & objectives: Hypermethylation of tumour suppressor genes leads eventually to malignant transformation. The aim of our study was to determine DNA methylation status of selected tumour suppressor genes in oropharyngeal squamous cell carcinoma (OPSCC) and to find correlation with clinico-pathological characteristics.
Methods: A total of 101 samples were analysed in the study (31 primary tumours with 31 corresponding metastases, 20 non-metastasizing primary tumours, and 19 control samples). In every patient, classical clinico-pathological parameters were recorded. For methylation analysis, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) was performed for a set of 25 tumour suppressor genes (Probe mix ME002-C1).
Results: The study sample comprised 37 males and 14 females, aged 45–80 years (median 58 years). A total of 80% of tumours were HPV-positive. During the follow-up period (range 3–180 months; median 82 months), 10% of tumours recurred and 10% of patients died due to tumour. We observed significantly higher methylation of WT1, PAX6, and CADM1 genes in primary tumours compared to controls ($p < 0.05$). WT1 and CADM1 genes were significantly hypermethylated in HPV-positive OPSCC compared to HPV-negative OPSCC ($p < 0.01$). Kaplan-Meier survival curve showed that patients with higher methylation levels of PAX5 gene had impaired overal survival compared to patients with PAX5-unmethylated tumours ($p = 0.04$).
Conclusion: In summary, significant correlation was observed between methylation status of selected tumour suppressor genes and clinico-pathological parameters in our OPSCC study sample. Our promising results unravel novel potential biomarkers which, if confirmed by further studies, could be used as prognostic markers in the sense of tailored therapy and treatment individualization of patients with OPSCC.
Funding: This study was supported by the Ministry of Health Czech Republic conceptual development of research organization (UHHK, 00179906), by the Specific University Research Program (SVV 260396) from Charles University, Faculty of Medicine in Hradec Kralove, by the program PROGRES Q40/11, and by the project BBMRI-CZ LM2018125.

PS-02-002

Predictive gene expression model for detection of SDHx mutation in carotid paragangliomas

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Background & objectives: Mutations in *SDHx* genes occur in more than 40% of carotid paragangliomas (CPGLs). *SDHB* and *SDHD* variants are associated with the high risk of metastasis and multifocality, respectively. Identification of *SDHx* mutation is important for management of patients with CPGLs.
Methods: Whole-transcriptome sequencing on an Illumina platform and bioinformatics analysis were performed for 71 CPGLs. Based on gene expression data (CPMs), a fully connected neural network (FCNN) was constructed using Keras, Tensorflow, and KerasR libraries. The predictive model was trained and tested on a studied cohort, as well as additionally tested with RNA-Seq data for pheochromocytomas (PCCs) from TCGA.
Results: We created a two-step predictive gene expression model for identification of deleterious variants in SDHx genes. At first step, the model defines variants in SDHx genes overall based on the expression of four genes (CEP104, ERP29, EYA3, and NFRKB) and a lncRNA (STXBP5-AS1). The first gene set has the following metrics: sensitivity–0.85/specificity–1/accuracy–0.92/AUC–0.92 for the CPGL cohort and sensitivity–0.52/specificity–0.69/accuracy–0.61/AUC–0.61 for the PCC cohort. In the second round, the model predicts SDHB and SDHD mutations using data on CEP104, ERP29, and EYA3 gene expression and had the following metrics: sensitivity–1/specificity–1/accuracy–1/AUC–1 for CPGLs, and sensitivity–1/specificity–0.7/accuracy–0.77/AUC–0.85 for PCCs. This work was financially supported by the grant from the Russian Science Foundation (no.21-14-00353).
Conclusion: Clinical genetic testing of patients with CPGLs requires target sequencing of four genes (*SDHA*, *SDHB*, *SDHC*, and *SDHD*) or whole-exome sequencing, which is often long and expensive. Immunohistochemistry of *SDHB* subunit and measurement of succinate-to-fumarate ratio were recently proposed as alternative methods for primary prediction of *SDHx* mutations. However, these approaches do not detect the specific mutated gene. This model allows identifying not only *SDHx*-mutated tumours but also detect mutated genes (*SDHB* and *SDHD*) that are essential for tumour management.
Funding: This work was financially supported by a grant from the Russian Science Foundation (no. 21-14-00353) and performed using the equipment of the EIMB RAS "Genome" center (http://www.eimb.ru/rus/ckp/ccu_genome_c.php).

PS-02-003

Molecular pathways associated with SDHx mutations in vagal paragangliomas

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Background & objectives: Vagal paraganglioma (VPGL) is a rare neuroendocrine tumour occurring along the vagus nerve. Approximately half of head and neck paragangliomas are associated with mutations in *SDHx* genes. However, molecular changes associated with these mutations have not been fully understood.
Methods: Illumina whole-transcriptome libraries were prepared for 33 VPGLs with known *SDHx* status and subsequently sequenced on a NextSeq 500 at 76bp, single-end mode. Raw sequencing data were subjected to the standard bioinformatics analysis. Analysis of differential gene expression and pathways enrichment were performed using the RTrans pipeline and KEGG and GO databases.

Results: Using top-40 differently expressed genes between *SDHx*-mutated and non-*SDHx*-mutated tumours, pathway enrichment analysis was performed. Based on KEGG database, four pathways enriched with upregulated genes and seven pathways enriched with downregulated genes were found (FDR ≤ 0.05). Using GO database, we revealed 75 pathways enriched by upregulated genes (FDR ≤ 0.05) and no significant changes in pathways enriched by downregulated genes. According to both databases, *SDHx* mutations are associated with expression changes in genes related to cell adhesion, extracellular matrix, PI3K-Akt, and VEGF signalling pathways. This work was performed using the equipment of EIMB RAS "Genome" centre (http://www.eimb.ru/ru1/ckp/ccu_genome_c.php).
Conclusion: Changes in biological pathways associated with *SDHx* mutations in VPGLs were firstly detected. We showed that well-known tumour-associated PI3K-Akt pathway can potentially be activated in *SDHx*-mutated tumours. Upregulation of genes involved in the VEGF signalling pathway in *SDHx*-mutated VPGLs is possibly associated with pseudohypoxic state that occurs as a result of succinate accumulation and HIF stabilization.
Funding: This work was financially supported by a grant from Russian Science Foundation no.19-15-00419.

PS-02-004
The significance of H3K9Me3 and H3K18Ac in salivary gland neoplasms
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Background & objectives: Histone modifications had been reported in different cancers with varying prognostic implications. The objectives of this study were to examine the degree of acetylation and methylation of histone H3 in salivary gland neoplasms and their associations with prognostically-relevant pathologic characteristics.
Methods: The expression of H3K18Ac and H3K9Me3 in 70 specimens of salivary gland neoplasms, consisting of 30 mucoepidermoid carcinoma (MEC), 20 adenoid cystic carcinoma (ACC) and 20 pleomorphic adenoma (PA), were investigated immunohistochemically. The immunohistochemical scoring was calculated in each case, based on both the staining intensity and the percentage of positive tumour cells.
Results: H3K18Ac and H3K9Me3 were variably expressed in the majority of MEC, ACC and PA cases. Their expression appeared significantly correlated within this group of neoplasms. The increased H3K9Me3 in MEC was positively correlated with small nest invasion at tumour front and advanced grade pathologically. In addition, the solid subtype of ACC showed significant up-regulation of both H3K18Ac and H3K9Me3, compared with cribriform/tubular subtypes.
Conclusion: Salivary gland neoplasms differentially acquire distinct pattern of histone modification. Hyperacetylation and methylation of histone H3 could be underpinning the prognostically worsen solid type of ACC, and the trimethylation of H3K9 may be involved in aggressive pathologic characteristics of MEC.
Funding: This study was supported by Faculty Research Grant (DRF 64008), Faculty of Dentistry, Chulalongkorn University.

PS-02-005
H3K9Ac expression in salivary gland tumours: correlation with histopathologic characteristics
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Background & objectives: Acetylation of histone protein plays an important role in regulation of gene expression. Dysregulation of histone H3K9 acetylation was reported in various cancers and presented prognostic and therapeutic values. We aimed to examine H3K9Ac expression among common salivary gland tumours.
Methods: Archived paraffin-embedded tissue of 30 mucoepidermoid carcinomas, 20 adenoid cystic carcinomas and 20 pleomorphic adenomas were included in the study. H3K9Ac expression was evaluated by immunohistochemical staining. Expression of H3K9Ac were determined semi-quantitatively based on both staining intensity and percentage of positive cells. The immunohistochemical scores were then evaluated according to various histopathologic features.
Results: Mucoepidermoid carcinoma demonstrated significantly increased H3K9Ac expression compared with pleomorphic adenoma. Moreover, the solid subtype of adenoid cystic carcinoma showed significantly higher H3K9Ac expression than the cribriform/tubular subtypes.
Conclusion: High levels of H3K9Ac appear to be associated with malignant salivary gland neoplasm and a more aggressive subtype of adenoid cystic carcinoma.

PS-02-006
Predictive modeling for the diagnosis of oral and laryngeal premalignant and malignant lesions using expression of p53 and ki-67
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Background & objectives: Oral and laryngeal epithelial lesions are diagnosed based on histologic criteria of WHO classification which may appear interobserver variability. Integrated diagnostic approach based on immunohistochemistry (IHC) is required that can help the interpretation of ambiguous histological findings of epithelial lesions.
Methods: The oral cavity and larynx tissues of 118 cases from 108 patients were examined by IHC for p53 and Ki-67. Logistic regression analysis and decision tree algorithm were employed to develop the scoring system and predictive model for differentiating the epithelial lesions. The comparison between TP53 mutation and expression patterns of p53 was conducted by Next-generation sequencing (NGS) and IHC.
Results: The diffuse expression type (pattern HI) and null type (pattern LS) for p53, and pattern HI for Ki-67 were significantly associated with high-grade dysplasia (HGD) or squamous cell carcinoma (SqCC). With accuracy and the area under a receiver operating characteristic curve (AUC) of 85.3% and 85.4%, the scoring system based on p53 and Ki-67 classified epithelial lesions into two types: non-dysplasia or low-grade dysplasia, and HGD or SqCC. The decision tree model using p53 and Ki-67 classified epithelial lesions into non-dysplasia, dysplasia, and SqCC with accuracy and AUC of 64.7% and 80%. The patterns HI and LS for p53 were confirmed to be correlated with missense and nonsense/frameshift mutations, respectively.
Conclusion: The scoring system using p53 and Ki-67 may aid in the differentiation of epithelial lesions, especially when their morphologic features are ambiguous.

PS-02-007
Comparison of PD-L1 immunohistochemical assays in head and neck carcinoma

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Background & objectives: Programmed death ligand 1 (PD-L1) expression is predictive biomarker for immune checkpoint inhibitor in head and neck squamous cell carcinoma. We compared the variable immunohistochemical (IHC) assays using the tumour proportion score (TPS) and the combined positive score (CPS).
Methods: In total 56 cases of head and neck carcinoma (HNC), PD-L1 expression was evaluated for formalin fixed paraffin embedded (FFPE) blocks from biopsy and surgical resection specimens using 4 IHC assays including 22C3 pharmDx on the Dako Link 48 platform and on Ventana Benchmark Ultra platform, SP263, and SP142 by TPS and CPS using cut-offs of >1% and >50%.
Results: Overall PD-L1 positivity rates were 83.9% (47/56) with a cut-off ≥1% and 21.4% (12/56) with a cut-off ≥50%. The average of TPS scores were 18.03 ±24.83 with 22C3 on Ventana assay, 16.56±25.84 with 22C3 pharmDx, 16.76± 25.16 with SP263 assay, and 3.72±11.48 with SP142 assay, resulting in the lowest expression rate in SP142 assay. A statistically significant correlation (p=0.012) was analysed between location and PD-L1 expression using a cut-off ≥50%. When comparing different assays, 22C3 pharmDx and SP263 assay using TPS score showed good correlation with Spearman correlation coefficients calculated as 0.892 (p <0.001). However, less agreements were observed among 22C3 pharmDx, SP263 assay, and SP142 assay.
Conclusion: Overall PD-L1 positivity rate with a cut-off ≥1% was 83.9%. PD-L1 expression was statistically significant correlation with the location (P = 0.012). The correlation of PD-L1 expression between paired the biopsy and resection specimen is evaluating in this ongoing research.

PS-02-008
PD-L1 expression and its clinicopathological significance in odontogenic carcinomas
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Background & objectives: Programmed cell death-ligand 1 (PD-L1) expression has been investigated in various malignancies and is currently used for immunotherapy selection in patients with several cancers. This study aims to primarily identify PD-L1 expression and determine its clinicopathological significance in odontogenic carcinomas.
Methods: PD-L1 (clone E1L3N) immunohistochemistry was performed in 20 odontogenic carcinomas after validated compared to the 22C3 pharmDx assay. The percentage of tumour cells with membranous staining at any intensity (TPS) ≥ 1% was defined as PD-L1-positive. Associations between PD-L1 expression and clinicopathological factors were statistically analysed.
Results: PD-L1 was positively expressed in 85.7% (6/7) of ameloblastic carcinomas, 37.5% (3/8) of primary intraosseous carcinomas, 33.3% (1/3) of clear cell odontogenic carcinomas, and 50% (1/2) ghost cell odontogenic carcinomas. Positive PD-L1 expression was associated with larger tumour size (P = 0.031), whereas no correlation was observed with age, sex, and tumour location (P > 0.05). Most cases (3/4; 75.0%) of odontogenic carcinomas with metastasis showed high PD-L1 expression (TPS ≥ 50%).
Conclusion: These results suggest the possible utility of immune checkpoint inhibitors for the treatment of patients with advanced odontogenic carcinomas, which warrants further clinical investigation.

PS-02-009
Assessment of TP53 and CDKN2A status can be a predictive marker of malignant transformation of sinonasal inverted papilloma
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Background & objectives: Sinonasal inverted papilloma (IP) has the potential to transform into squamous cell carcinoma (SCC), but there are no diagnostic methods to predict it. We investigated genetic mutations involved in progression of IP-SCC and explored biomarkers that can predict malignant transformation.
Methods: 14 patients diagnosed with SCC arising in IP and six patients diagnosed with IP without malignant transformation were included. DNA was extracted from IP, IP with dysplasia, and SCC, respectively, and whole exome sequencing and immunohistochemistry (IHC) was performed.
Results: Major oncogenic mutations were observed with high frequency in the stepwise progression from IP to SCC. TP53 was the most frequently mutated gene (39%), followed by CDKN2A (27%), TTN (27%), ARID1A (21%), and PIK3CA (15%). Mutations in TP53 and/or CDKN2A were observed in 3 out of 6 IPs with malignant transformation, whereas none of the mutations were observed in IPs without malignant transformation. As a result of TP53 and CDKN2A IHC, three of six IPs with malignant transformation showed a diffuse strong or null pattern in p53, and one showed a total loss of p16 which is distinct pattern from pure IPs.
Conclusion: Our result suggests that assessment of TP53 and CDKN2A status can be a predictive marker of malignant transformation of IP and assessment of p53 and p16 status using IHC can be a surrogate marker for TP53 and CDKN2A status.

PS-02-010
Ossifying fibroma of the jaws: a clinicopathological case series study
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Background & objectives: Juvenile trabecular ossifying fibroma (JTOF) and juvenile psammomatoid ossifying fibroma (JPOF) are two rare histological variants of ossifying fibroma (OF). Theses variants are 3 distinct clinicopathological entities. Our aim is to assess clinico-pathologic features of a case series of OF.
Methods: Eleven consecutive cases of OF diagnosed in the department of pathology of Habib Bourguiba Hospital, were collected from 2011 to 2021. The clinical data and microscopic features of these cases were reviewed and analysed with the most recent diagnostic criteria for OF.
Results: Patients mean age at diagnosis was 35 years with a sex-ratio of 0,2. Eight cases were found in the mandible and three in the maxilla. Bone swelling or expansion was the most frequent clinical presentation (90%). Microscopically there was 8 cases of classic OF comprised of globulous woven or lamellar bone with rare or without osteoblastic rimming mixed with fibrous tissue and three cases of JPOF comprised predominantly of psammoma bodies mixed with a highly cellular fibrous tissue. No case of JTOF was recorded. No cellular atypia or mitosis were identified. Recurrences were recorded in two women with JPOF, aged 16 and 22 years respectively. These recurrences were surgically removed.
Conclusion: OFs occur more frequently in female patients and in those in the second to fourth decades of life. The most commonly affected site is the mandible. Most OF can be treated

by conservative and complete surgical excision. Recurrences are infrequent in classic OF but more common in Juvenile ossifying fibroma. Therefore, a complete excision with long term supervision is needed.

PS-02-011

Verification and validation of the anti-PD-L1 antibody, clone 22C3 on a laboratory developed test

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Background & objectives: PD-L1 IHC 22C3 pharmDx assay kit processed via the Dako Autostainer Link-48 platform is the licensed immunohistochemical assay and companion diagnostic test(CDT) for the assessment and thus administration of Pembrolizumab. However, laboratories may not have access to this specified CDT.
Methods: 47 whole tumour slides off head and neck squamous cell carcinomas were stained with the PD-L1 IHC 22C3 pharmDx assay kit processed via the Dako Autostainer Link 48 (CDT) and the Dako Omnis platform, referred to as a laboratory developed test (LDT). A combined positive score (CPS) were provided by 2 pathologists, with discordant cases provided with an agreed score.
Results: PD-L1 IHC 22C3 pharmDx assay kit processed via CDT and LDT showed identical staining in terms of intensity and pattern of staining. On review of concordance between the CDT and LDT, implementing a CPS cut-off of ≥ 1 showed the following: overall percentage agreement (OPA) 94%; positive percentage agreement (PPA) 100%; negative percentage agreement (NPA) 88%. A CPS cut-off of ≥ 20 showed the following: OPA 96%; PPA 95%; NPA 100%. With a CPS cut-off of ≥ 1, the intra-examiner concordance between the platforms was 89%, and the inter-examiner concordance between examiners on each platform was 92%(CDT) and 85%(LDT).
Conclusion: Firstly, the high level of concordance between scoring Pathologists illustrates with adequate training there is a reduction in the variable of scoring interpretation by examiners, which may have a therapeutic implication. Secondly, we open for discussion the deconstruction of the current practice of a compulsory CDT for a particular PD-L1 immunohistochemical assay in head and neck cancers. The implementation of LDTs as an alternative to the CDT are a novel and readily available method to surmount limitations posed.

PS-02-012

The accuracy of head and neck core needle biopsies and fine needle aspirates at a large teaching hospital

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Background & objectives: Fine needle aspirate and core needle biopsies are common techniques for diagnosis of head and neck diseases. Diagnosis can be challenging due to limited tissue for examination. Here we record the accuracy of these techniques at Sheffield Teaching Hospitals.
Methods: We accessed records of patients receiving core needle biopsy (CNB) or fine needle aspirate (FNA) at a head and neck site from 2015 to 2020. Cases without definitive diagnosis on subsequent excision were excluded. Both specific diagnosis and benign/malignant category was compared between CNB/FNA and the excision specimen. Accuracy of FNA and CNB was compared with a Fischer's exact test.
Results: A total of 79 cases were identified in which the CNB/FNA diagnosis could be compared with a definitive diagnosis made on an excision specimen. Of these, 63 cases were CNB and 16 were FNA. CNB showed 95% agreement between the benign and malignant category and 87% in specific diagnosis. FNA showed 94% agreement between the benign and malignant category and 69% in specific diagnosis. The most common diagnoses on CNB/FNA were pleomorphic adenoma and metastatic squamous cell carcinoma. A Fisher's exact test did not show a statistically significant difference in the accuracy of CNB and FNA, this may be due to the limited sample size of the FNA group.
Conclusion: CNB and FNA are both non-invasive techniques in comparison to a conventional biopsy and are often utilised in the head and neck region. The accuracy of these techniques presented here is similar to those previously reported in the literature, approximately 90% for CNB and 70% for FNA. However, where previous studies found CNB to be more accurate than FNA this difference was not observed in this cohort. This may be due to the limited sample size of the FNA group.

PS-02-013

Transcription factors profile in sinonasal neuroendocrine neoplasms (snNENs) and olfactory neuroblastoma (ONB)

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Background & objectives: snNENs are rare and mostly include neuroendocrine carcinomas (NECs). ONB is a unique sinonasal neoplasm, expressing neuroendocrine markers. We aimed to investigate transcription factors expression profile in snNENs and ONBs and to explore their role in distinguishing these two entities.
Methods: GATA3, SATB2 and CDX2 expression were investigated in a series of 26 ONBs and 7 snNENs diagnosed and treated in our Institution. ONBs were graded according to Hyams' system (2 grade 1, 13 grade 2, 8 grade 3 and 3 grade 4) and epithelial NENs were reclassified into 5 NECs, 1 mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs) and 1 amphicrine carcinoma.
Results: Hyams' grade 1-3 ONBs stained diffusely and intensely for SATB2. Grade 4 ONBs and NECs were globally negative, including the NEC component of the MiNEN. The intestinal-type adenocarcinoma (ITAC) component of the MiNEN, like the amphicrine carcinoma, was intensely positive. GATA3 was heterogeneously expressed in Hyams' grade 1-3 ONBs, whereas grade 4 ONBs, all NENs and the amphicrine carcinoma were completely negative. CDX2 was only expressed in the amphicrine carcinoma and, as expected, in the ITAC component of the MiNEN.
Conclusion: Our study expands the spectrum of SATB2 and GATA3-positive neoplasms and identifies, for the first time, SATB2 and GATA3 expression as features of Hyams grade 1-3 ONBs, suggesting that Hyams grade 4 ONBs are not only clinically but also biologically different from low graded ONBs. These results are useful in diagnostic daily practice, as highlight that the joudicious employment of transcription factors may help in correctly diagnosing rare but clinically relevant neoplasms.

PS-02-015

Cervical lymph node extemporaneous assessment by confocal microscopy during surgery: an alternative to frozen section examination?

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Background & objectives: To evaluate the value of the Ultra-fast Confocal Microscopy (UFCM) imaging of cervical lymph nodes in

patients with squamous cell carcinoma, compared to conventional histology. This technique would be considered interesting if it is more accurate than frozen section examination.
Methods: We carried out an ex vivo study on lymph nodes from patients N0. The two parts of fresh lymph nodes were marked with acridine, then imaged with the Histolog Scanner (SamanTree Medical, Switzerland) during one minute. In post processing, all acquired and anonymized UFCM images were read independently by two pathologists and the "UFCM diagnoses" were compared to conventional histology.
Results: We included 11/44 patients, i.e. 64 lymph nodes. 8/64 lymph nodes were metastatic (N+) on conventional histology. On Ultra-fast Confocal Microscopy images, one pathologist (PT1) was in accordance with conventional histology in 93.75% (95% CI= 84.8-98.3%) and the other (PT2), in 95.3% (IC95=86.9%-99%). PT1 considered as negative one patient, who was finally N+. The errors were as follows: the metastatic area has escaped the screening of the Histolog Scanner image (n=3), and a metastasic area has been analysed as «suspect », but not identified as carcinomatous (n=1)
Conclusion: Inclusions have now reached 44 patients and 206 lymph nodes, allowing a robust statistical analysis, which is in progress. At this stage, the analysis by Ultra-fast Confocal Microscopy seems to be a very promising technique. It could eventually replace the frozen section examination, because its diagnostic reliability seems at least equivalent. Furthermore, its speed processing (5 minutes) constitutes a major asset.
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PS-02-016
Laminin is a useful marker in the differentiation between actinic cheilitis and invasive squamous cell carcinoma in oral biopsies: new insights
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Background & objectives: Oral cancer can be life-threatening if not diagnosed early. Precancerous lesions, such as actinic cheilitis, can transform into oral cancer. Laminin is a fundamental component of basement membrane (BM), its degradation can contribute to mucosal malignant transformation.
Methods: Formalin-fixed and paraffin-embedded biopsies from 46 patients with oral lesions (37 males and 9 females, mean age = 67 years) were histologically analysed by hematoxylin and eosin staining to diagnose the entity of actinic cheilitis and to classify epithelial dysplasia and invasive cancer. Immunohistochemical (IHC) analysis was performed to evaluate laminin expression in biopsies.
Results: Histological analysis revealed 34 patients with actinic cheilitis and 12 patients with squamous cell carcinoma (SCC) of the lip. Three patients with actinic cheilitis had concomitant in situ carcinoma. IHC analysis for laminin revealed intense and continuous staining of the BM in all cases of actinic cheilitis with low dysplasia, while loss of laminin expression was observed in invasive SCC cases. Interestingly, intracellular expression of laminin in parabasal layers of the epithelium was noted in cases of actinic cheilitis with high-grade dysplasia/in situ carcinoma.
Conclusion: Laminin expression, by IHC analysis, could be useful in the differential diagnosis between actinic cheilitis and invasive squamous cell carcinoma, as well as actinic cheilitis with low and high-grade dysplasia. Findings from this study provide new insights into the mechanisms involved in the process of progression of actinic cheilitis into SCC of the lip, encouraging in vitro and in vivo studies that may document the mechanistic role of laminin in this process.

PS-02-017
Exploration of the transcriptomic landscape of HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma upon development of cisplatin resistance
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Background & objectives: Oropharyngeal Squamous Cell Carcinoma (OPSCC) has seen a dramatic increase over the past few decades. OPSCC is frequently treated with a chemoradiotherapy regime including cisplatin, but resistance can develop in some patients which may be difficult to treat.
Methods: To develop a cisplatin resistant cell line model, a HPV-positive (UDSCC2) and a HPV-negative (UMSCC89) cell line were treated over several months with increasing cisplatin concentrations. Single cell clones were selected and assessed using clonogenic survival assays. Following RNA-Sequencing the reads were quantified using Salmon and differential expression analysis was conducted using the package DESeq2 in R.
Results: Clonogenic survival assays revealed the selected clones were more resistant to cisplatin compared to the parental cells. One HPV-positive and one HPV-negative resistant clone were selected for RNA-Sequencing alongside their parental counterparts. Differential expression analysis between parental and resistant cells revealed there were 1234 differentially expressed genes in the HPV-positive group and 1521 differentially expressed genes in the HPV-negative group. 243 of these genes were seen to be differentially expressed in both the HPV-positive and HPV-negative resistant clones. Using gene pathway analysis, multiple pathways were seen to be involved upon development of cisplatin resistance, including epithelial to mesenchymal transition and apoptotic signalling.
Conclusion: This study provides an insight into the transcriptomic landscape of HPV-positive and HPV-negative OPSCC upon development of cisplatin resistance. Following validation, expression of selected markers will be assessed in tumour samples to explore their potential as a prognostic biomarker.
Funding: Funded by a Cancer Research UK (CRUK) and the Pathological Society Joint Predoctoral Research Bursary and Wellcome Trust Clinical PhD Fellowship (4Ward North Programme)

PS-02-018
"Molecular" resection margins in squamous cell carcinoma of the oral cavity – report of the first results of the multidisciplinary view
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Background & objectives: The therapy of squamous cell carcinoma of the oral cavity has significantly intensified in the last decade. Here, we focused on sensitive mutation analysis of resection margins that could improve the prediction of relapse and/or sensitivity to specific drugs.
Methods: DNA was isolated from 26 patients (tumour, peripheral blood and margins in total 3 samples/patient). We performed Illumina sequencing using a panel of 88 cancer genes. Only

non-synonymous variants in tumour margins that were reported in the ClinVar database as "pathogenic", "likely pathogenic" or "uncertain significance", and were simultaneously not present in the peripheral blood, were selected for further analysis.
Results: In total, we found 21 mutated genes, among them mainly tumour suppressor genes involved in DNA repair. We detected mutations in DNA isolated from 22/26 tumours, and in 5/26 tumour margins. Gene TP53 was the most commonly mutated gene followed by BRCA1/2 and CDKN2A. The median tumour load was 2 pathogenic mutation per patient on average (range 0-9). This parameter did not correlate with the presence of histological markers like perineural invasion probably due to small cohort size. Similarly, we did not observe association of mutations in resection margins and probability of disease relapse.
Conclusion: The spectrum of the tumour mutations is similar as in other studies with the exception of mutations in the BRCA genes, which were not found frequently mutated in OSCC (12-19%). The data in the literature suggests BRCA mutation in OSCC examined by imunohistochemistry technique ranges from 44% (139patients) to 63% (60patients). Variants identified in our dataset are often introducing stop codons leading to truncated and non-functional proteins. The potential application of BRCA(PARP) inhibitors for OSCC needs to be elucidated.

PS-02-019
Keratinising pleomorphic adenoma of parotid salivary glands: analysis of three cases from practice
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Background & objectives: Pleomorphic adenoma (PA) of parotid salivary glands (PSG) with squamous metaplasia, keratin cysts formation (keratinizing PA) is not common and causes difficulties in diagnosis. The objective was to analyse three cases from practice of keratinizing PA of parotid salivary glands.
Methods: Surgical material from two women, one man with keratinizing PA was studied. The mean patients' age was 36.3±2.1 years. In two cases, primary surgical treatment was performed, in one case – secondary, due to relapse. During examination it was noted in PSG a painless nodule of dense consistency in diameter from 1.5 to 4.5 cm. Histological, histochemical methods were used.
Results: Macroscopically in three cases the nodes on the cut were of whitish-pinkish colour with cyst formation. Microscopically, the tumour was characterized by the predominance of the parenchymal (epithelial) component over the mesenchymal (stromal) one. The epithelial component was represented by epithelial, myoepithelial cells. Epithelial cells were of basaloid, spindle-cell, squamous, clear-cell type. They formed nests, strands with numerous foci of squamous metaplasia and keratinous cysts lined by squamous epithelium and containing eosinophilic keratin substance. The stroma was represented by connective tissue, vessels and myxoid, chondroid, osteoid, mucoid zones. In two cases, the tumour was surrounded by a distinct fibrous capsule with tumour invasion; in one case the capsule was absent.
Conclusion: Morphological diagnosis of keratinizing PA causes certain difficulties for pathologists and requires a differential diagnosis with mucoepidermoid carcinoma, necrotizing sialometaplasia, squamous cell carcinoma. In the studied cases, morphological examination revealed a keratinizing PA of PSG with a predominance of the epithelial component over the mesenchymal one. The presence the relapse in one case in anamnesis; tumour invasion into the capsule in two cases, absence the capsule in one case indicate that keratinizing PA is prone to recurrence.

PS-02-022
Frequency of SDHx variants in middle ear paragangliomas
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Background & objectives: Middle ear paragangliomas (MEPGLs) are rare neuroendocrine tumours occurring on the medial promontory wall of the middle ear. MEPGLs are highly hereditable, being susceptible to mutations in driver genes, such as *SDHx* coding for succinate dehydrogenase subunits.
Methods: Total of 28 MEPGLs were subjected to genetic testing on the presence of *SDHx* variants using Sanger sequencing on an ABI PRISM 3500xL (Thermo Fisher Scientific) based on designed specific primers for all exons of target genes.
Results: Four pathogenic mutations (4/28, 14%) were found among studied MEPGLs: missense and nonsense variants in the *SDHB* gene, [NM_003000.3:c.689G>A (rs587782604) and NM_003000.3:c.79C>T (rs74315369)], respectively, as well as two missense mutations in the *SDHD* gene, [NM_003002.4:c.305A>G (rs104894302) and NM_003002.4:c.274G>C (rs80338845)]. This work was performed using the equipment of EIMB RAS "Genome" centre (http://www.eimb.ru/ru1/ckp/ccu_genome_c.php).
Conclusion: According to the literature on head and neck paragangliomas, *SDHB* variants are most frequent (33%), followed by *SDHD* variants (21%). This research showed low and close frequencies (7%) for variants both in *SDHB* and *SDHD* genes for Russian patients with MEPGLs. These results are similar to those for patients with MEPGL in other populations. Thus, development of MEPGLs may be linked with prevalence of mutations in other PGL susceptibility or cancer-associated genes.
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PS-02-023
Sinonasal inverted papillomas with multiples recurrences: revision of our experience and HPV status
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Background & objectives: Inverted Papilloma (IP) is a rare sinonasal tumour with local destructive potential and risk of malignant transformation. The aim of this study is to compare clinicopathologic features of a multirecurrent IP group and a none-multirecurrent IP group and its HPV status.
Methods: We reviewed clinical and pathological data of patients diagnosed of IP during the period of 1978-2020 in our institution and selected the recurrent cases. The IP group with more than one recurrence, treated by diverse surgical procedures, was compared with another group of IP with one recurrence. We performed p16 IHQ (Dako) study and HPV Genomic PCR.
Results: The study included 152 patients from which 22 had recurrent IP.13 patients had multirecurrent IP,9 were males with a median age of 59, 11tumours were localized in ethmoid-sphenoid sinuses. Four patients were smokers,2 had allergy and 2 had toxic exposures. Three IPs in the multirecurrent group showed low-grade dysplasia and one SCC.p16 was positive in 8cases, in 2 PCR showed presence of HPV, one determination negative and 10 not valuable. Nine patients presented with none-multirecurrent IP,8 were males with a median age of 56, 6 were localized in ethmoid-sphenoid sinuses. Five patients were smoker and 1 had toxic exposure. They had not dysplasia or SCC associated.p16 was positive in 3cases but PCR were not valuable.

Conclusion: IP is a benign sinonasal tumour with malignant potential. In our series, 1/22 had squamous cell carcinoma transformation and 13/22 had more than one recurrences. The aetiology is yet unknown and probably multifactorial with a main role of HPV infection. Our findings suggest that the HPV status may be associated with a higher risk of recurrences and dysplastic transformation, but further investigation is needed.

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PS-03-001

MarrowQuant 2.0: clinical application of a user-friendly digital hematopathology tool for human bone marrow trephine biopsies

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Background & objectives: Bone marrow(BM) assessment is a multiparametric evaluation of which cellularity constitutes one parameter. In diagnostic practice, the assessment is based on a semi-quantitative estimation which is time-consuming. In this study, we validated MarrowQuant2.0, within QuPath software, a digital hemopathology tool.
Methods: MarrowQuant2.0 quantifies four compartments within the BM (hematopoietic cells, adipocytes (using Stardist), interstitiumμvasculature, and bones) and measures the cellularity of human BM trephine biopsies. We calculated the cellularity in a series of retrospective biopsies (training set n=36; experimental set n=157H&E). Using intraclass coefficient of correlation(ICC), specificity and sensitivity tests, we measured the agreement between MarrowQuant 2.0's quantification and clinical reference.
Results: Our algorithm was capable of accurate, rapid, and robust segmentation (average accuracy 0.86, n=36). There was an excellent agreement between MarrowQuant 2.0 and the clinical reference (ICC=0.978(95% CI0.955-0.989), R2=0.93). MarrowQuant 2.0 performed in a comparable way as to the clinical reference when used on a set of BM trephine biopsies from clinical routine diagnosis(n=42). We found reciprocity between the hematopoietic and adipocytic compartments in the context of an extreme case of BM remodelling, except for cases with stromal expansion. MarrowQuant2.0 can also leverage an adipocyte-based StarDist model, a deep-learning-based segmentation algorithm, implemented as an extension in QuPath, offering an accurate segmentation of individual adipocytes and a size-based classification.
Conclusion: Our tool may represent a useful adjunct for experimental and clinical hematopathology. We will use MarrowQuant 2.0. to link output with clinical parameters using dimension reduction and clustering methods to visualize and explore a potential prognostic value in myeloid malignancies.
Funding: PHRT-Personalized and Health-Related Technologies

PS-03-002

Convolutional neural network-based algorithm for the detection and quantification of the components of the histologic grading of breast ductal adenocarcinoma - the first results

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Background & objectives: The current grading system for ductal adenocarcinoma NOS of the breast (DAC-NOS), is prone to low reproducibility, subjectivity, and is overall time-consuming. Here, we trained a convolutional neural network-based algorithm (CNN-bA) to detect and quantify the components for grading DAC-NOS.
Methods: 100 whole slide images (WSI) of diagnostic slides and 10 training slides (TS) with DAC-NOS were selected from the TCGA-BRCA dataset and subsequently uploaded to a WSI management server (Aiforia Technologies Oy, Helsinki, Finland). Briefly, the CNN-bA (Aiforia version 4.8, Aiforia Create, Aiforia Technologies Oy) was trained on the 10 TS to detect and quantify the components for grading DAC-NOS.
Results: After a successful model was established, the model was used to detect and quantify the histological components of DAC-NOS: tumour tissue (TT), tubule and gland formation (T + GF), solid tumour (ST) aspect, nuclear pleomorphism (NP) and mitotic count (MC). Next the results were exported and interpreted. Here, we report the first results of this pilot program. Successful training for TT, T, and GF or ST aspects was achieved after 3 iterations of the model. Unsuccessful training for NP and MC was reported and this represents the limitations of the results, and the baseline for future improvements that need to be addressed for the subsequent improved artificial intelligence (AI) model.
Conclusion: AI in digital pathology represents the successful evolution of diagnostic pathology. While at times difficult, this transition is successfully implemented in *in vitro* diagnostics (IVD) platforms. Complex diagnostic algorithms used by pathologists like grading DAC-NOS are laborious to translate into an AI model. We report preliminary data (successful and unsuccessful data points) for a CNN-bA AI model that detects and quantifies components of the histologic grading of DAC-NOS with the aim of constructing the framework for a future IVD model.
Funding: Aiforia Aiforwarding Program

PS-03-003

Refining pre-analytic deficiency reporting and capture in the anatomical pathology laboratory: a quality improvement initiative

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Background & objectives: Pre-analytic, notably pre-laboratory, deficiencies are estimated to account for ~70% of laboratory errors. Herein, we reviewed pre-analytic deficiency (PAD) data at our institution to develop strategies for improved PAD documentation, allowing for identification of PADs and improvement of quality performance.
Methods: We retrospectively reviewed 12 months of data at an academic, tertiary referral centre, which was captured from three sources: Laboratory information system (LIS), corporate risk management reporting system and manual paper logs. We also interviewed accessioning staff to determine barriers to data recording.
Results: 237 PAD were recorded in one year. Of these, 72% (n=171) were pre-laboratory and 28% (n=66) were in laboratory. Specimen procurement accounted for 79% (n=134) of all pre-laboratory PAD followed by deficient requisitions, 12% (n= 21). Failure to adhere to specimen handling protocols accounted for 37.5% (n=25) of in-laboratory PAD with accessioning errors contributing to 23% (n= 15). Barriers to incident documentation were: time required, multiple systems being used and free-hand

data entry under 92 separate headings with no protocol to determine categories of incidents. Therefore, the following consensus categories were created: specimen collection, requisition, packaging, transportation, reception, accessioning, specimen preparation and missing histology alerts.
Conclusion: To streamline PAD documentation, manual logs were eliminated, all reporting was moved to LIS under the above eight categories and accessioning staff was trained on data entry under the new categories. Mandatory deficiency check has been implemented in LIS for the accessioning bench, before the specimen is further processed. Deficiency entry protocol for the grossing bench and histology lab are also currently being optimized for LIS integration in the next phase of the project.

PS-03-004
NLP in diagnostic texts from nephropathology
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Background & objectives: Nephropathology is a sub-discipline with complex diagnostic patterns and terms. In addition, reporting in a structured manner is a special feature.
Against this background, we investigate whether predicting the final diagnosis based on the written description is possible.
Methods: For his work, 1,185 unlabelled nephropathological reports were included. (i) First, the diagnosis sections were clustered unsupervised to <20 diagnosis groups. Therefore, bag of word-based and embedding-based text-vectorization methods were used. (ii) Second, different natural language processing (NLP) methods for classification were trained to predict based on the descriptive report section the diagnosis group.
Results: Regarding text clustering (i), the silhouette-score and the classification performance of a support vector machine were used to measure clustering accuracy. For both, embedding-based approaches (best is a Bidirectional Encoder Representations from Transformer (BERT)) performed slightly better compared to bag of word-based (best is latent Dirichlet allocation) approaches. Analysing the clusters for keywords shows that some clusters can be mapped to diagnostic groups. For example, there is a cluster for IgA-nephropathy or one for diseases with glomerular necrosis.
Again, the BERT-based approach worked best regarding diagnosis prediction based on the histological description (ii). Notably, there are classification quality differences between the diagnostic clusters. Only some groups are almost perfectly predicted.
Conclusion: For nephropathological reports, the morphological description alone enables retrieving the correct diagnosis for some entities. For other entities, this associative approach does not work well. This is in accordance with a previous study on glomerular change patterns, where some diagnoses are associated with one pattern, and for others, there is a complex pattern combination.
Mapping every diagnosis cluster to a diagnosis group (or a chapter in a textbook) is still under investigation while writing this abstract.

PS-03-006
A multi-feature AI solution for diagnosis support in gastric biopsies: a multi-site clinical study
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Background & objectives: This study aimed to clinically validate the performance of a multi-feature AI-based solution on the detection of gastric carcinoma, high-grade dysplasia and high-grade lymphoma, and Helicobacter pylori against rigorous ground truth (GT) established by multiple blinded pathologists in gastric biopsies.
Methods: The Galen™ Gastric algorithm was examined in a prospective stand-alone performance study using retrospectively collected histopathology slides from two sites. We compared GT diagnosis of adult gastric biopsies with the algorithmic results on H&E. GT was reached by concordance between two pathologists (original report and a new blinded diagnosis by pathologist reviewing slides/WSIs). Discrepancies were adjudicated by an expert pathologist.
Results: The AI algorithm demonstrated very high accuracy for the detection of gastric adenocarcinoma, high-grade dysplasia and high- grade lymphoma, with AUC of 0.986. Analysing 544 cases (82 positive), demonstrated sensitivity of 96.34%, specificity of 88.74%, and NPV of 99.27%. Additionally, the algorithm achieved an AUC of 0.966 for the detection of H. pylori in analysis of 525 cases (112 positives), with sensitivity of 91.07%, specificity of 90.56%, and NPV of 97.40% %. We will further report on additional pathologies, e.g., low-grade lymphoma, low-grade dysplasia, and Adenoma.
Conclusion: This study reports the successful clinical validation of the Galen™ Gastric multi-feature AI solution in the accurate detection of a broad range of pathological features, including gastric adenocarcinoma, H. pylori, neuroendocrine neoplasms and more, offering an important tool for computer-aided diagnosis in routine pathology practice, supporting pathologists in their diagnostic work.

PS-03-008
Computer aided iron quantification on liver biopsy whole-slide images
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Background & objectives: Iron overload disorders diagnosis currently relies on blood tests and genotyping. However, liver biopsies remain an invaluable tool for prognostic purpose. We developed a pipeline to quantify iron deposits in whole-slide images (WSI) of liver biopsy marked with Perls stain.
Methods: The study is based on 10 WSI of liver biopsies with different amount of iron. WSI were analysed on different scales to quantitatively and objectively reproduce the standard clinical procedure followed by pathologists. The cells stained by Perls stain (PS) were segmented and quantified by exploiting two methods: Optical Density (OD) colour thresholding and a custom spectral phasor approach.
Results: Our pipeline is able to quantitatively retrieve: the percentage liver biopsy covered by PS, the mean intensity of PS stain, the density and dimension of PS granules, PS heterogeneity. Different background properties of WSI were buffered using a colour correction procedure. Moreover, heatmap overlays are generated to address statistically significant tissue patches (i.e., more densely stained, higher/lower intensity areas, PS deposits dimensions). Data generated by the pipeline had < 5% of error from pathologist's evaluation.
Conclusion: Our pipeline warrants a rapid and objective method for the evaluation of hepatic iron. Moreover, it can also be tuned and applied to different staining protocols (for example Picro-Sirius Red, used for the quantification of liver fibrosis). Finally, the estimated parameters are coupled to heatmap overlays in order to obtain intuitive graphical representations of parameter differences in the WSI.

PS-03-009

AI-aided assessment of HER2 status in primary and metastatic breast carcinoma

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Background & objectives: Re-evaluation of HER2 receptor status is recommended following metastatic transformation of invasive breast carcinoma to assess for receptor status conversion. We examine the performance of artificial intelligence in the determination of HER2 status in metastatic compared to primary breast carcinoma.
Methods: 60 slides of matched primary and metastatic invasive breast carcinoma were selected from our digitalised cohort of 476 cases (Roche Ventana DP200 Scanner). HER2 IHC scoring was performed by 3 pathologists, and followed with ISH when IHC score $\geq +1$. Results were compared to those from uPath HER2 4B5 and Dual ISH algorithms for IHC and ISH respectively.
Results: Overall, there was moderate agreement between pathologist and AI results (Cohen's κ 0.43, 95CI 0.25-0.61), with higher concordance on metastatic (κ 0.48, 95CI 0.24-0.73) versus primary cases (κ 0.36, 95CI 0.07-0.64). Breakdown analyses revealed the lowest concordance with ISH on metastatic lesions (κ 0.23, 95CI 0.04-0.49) where unedited AI overestimated the number of positive and equivocal cases. Inter-observer-variability of HER2 IHC scoring among pathologists was similar for primary (Fleiss' κ 0.77, 95CI 0.68-0.86) and metastatic lesions (κ 0.73, 95CI 0.58-0.89). Conversion of HER2 status between primary and metastatic lesions was observed in one case, confirmed by pathologists and AI on IHC and ISH.
Conclusion: Moderate concordance was observed between AI and pathologists in the assessment of HER2 status on primary and metastatic breast carcinoma. Concordance between AI and pathologists was notably higher with IHC compared to ISH. Examination of larger cohort with a diverse range of metastatic sites, combined with increased operator input at the time of digital analysis, may help to determine the feasibility of an automated digitalised HER2 workup for metastatic breast carcinoma.

PS-03-010

Evaluation of Ki67 by image-analysis-enhanced quantitative digital pathology

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Background & objectives: Assessment of prognosis of breast cancer by Ki67 immunohistochemistry is an important element of personalized treatment strategies. A precise assessment is crucial for clinically relevant therapy decisions. We aimed to evaluate a Ki67 quantification tool using whole slide images (WSI).
Methods: 61 Ki67 stained, pre- (preTx) and intra-therapeutic core biopsies, as well as corresponding surgical residual disease tissue from neoadjuvant GBG trials, were digitalized. Manual Ki67 scoring was performed by five individual pathologists on WSI (multi-observer), while semi-automated Ki67 scoring was done using VMscope's Scan Connect (multi-tumour-area). Scan Connect analysed up to four 600x600dpi areas on WSI, followed by pathologist supervision.
Results: The Pearson correlation between manual (man.) and computational (aut.) Ki67 assessment was r=0.781, with no significant differences in overall scoring or global precision (p=0.333, p=0.070). Semi-automated multi-area analysis on preTx tissues had a significantly lower variability than manual assessment (n=29, p<0.001), while showing no differences on intra-therapeutic samples (n=29, p=0.885). Using predefined cut offs, we observed that in Ki67 low and intermediate (int.) groups standard deviations (sd) were lower, while being higher for Ki67 high group, irrespectively of the assessment method (man. & aut.: low sd=±3.4 & ±2.0; int. sd=±4.3 & ±3.9; high sd=±18.2 & ±12.7). In comparison with full-automated assessment, the supervised semi-automated assessment improved the precision significantly (p=0.008).
Conclusion: We found strong correlation between manual (multi-observer) and supervised semi-automated (multi-tumour-area) Ki67 assessment. In comparison to inter-observer variance in manual Ki67 assessment, improved precision was seen in semi-automated assessment considering intra-tissue variance. VMscope's Scan-Connect software could be a useful tool in pathological cancer diagnostic. As a next step, results should be validated in a larger cohort and survival data could be included to examine prognostic differences between the two methods.
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PS-03-011

Leveraging deep learning-based mitosis detection models for supporting automated breast cancer grading

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Background & objectives: The mitotic figure count within 10 HPF in a mitosis-dense region is the only mitosis-based metric used for tumour grading in breast cancer. We present an innovative spatial statistical analysis of mitoses driven by an automatic mitotic figure detection method.
Methods: Mitotic figure candidates are detected using a detector neural network and are then filtered by a classifier neural network with customised architecture. The density and spatial distribution of detected mitotic figures and their relationship to tumour grade are investigated, using G-function that characterises probability distribution of nearest neighbour distances and Getis-Ord Gi statistics that detects local hotspots.
Results: A mitotic figure classification model with 83.06% validation accuracy, was applied on 131 test slides including 18, 47 and 66 slides with tumour grade I, II and III, respectively. Mitotic density showed 0.3987 Pearson (0.4660 Spearman) correlation with tumour grade. The area between observed and theoretic G-function suggested that nearest neighbours of mitotic figures were closer when tumour grade is higher. Group comparison p-values for tumour grade I vs II, II vs III, were 0.0069, 0.019 respectively. The hotspot ratio suggested more hotspots present in higher tumour grade. Group comparison p-values for tumour grade I vs II, II vs III, were 0.015, 0.0036 respectively.
Conclusion: Automatic mitosis detection models enable identifying regions of highest mitotic activity and quantification of the tumour proliferation and aggressiveness based both on the presence of mitotic figures and their relation to their neighbourhood. Our spatial analysis identifies metrics that quantify the mitotic figure spatial distribution and have statistical power to differentiate between low, intermediate, and higher grade tumours. Future work will focus on assessing whether these spatial metrics provide additional information over the current standard and ideally better prognostic value.

PS-03-012

Computer-aided algorithm and 3D imaging technology are sensitive methods in the diagnosis of HER2 expression-low breast cancers

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Background & objectives: The developed antibody-drug conjugates (ADC) show promising results especially in HER2-low expression breast cancer defined as immunohistochemically 1+ or 2+ with no gene amplification. More sensitive methods can be helpful in HER2-low samples diagnosis compared with traditional light microscopy examination.
Methods: Two approaches were used to determine HER2 expression. The computer-aided algorithm on digital pathological slides can determine HER2 expression levels. The 3D (three-dimensional) imaging approach used 100-μm thickness slide labelled by HER2 antibody with fluorescence and acquiring image under confocal microscopy with optical clearing method. Both methods can be successfully applied to retrospective and forward clinical studies.
Results: In computer-aided approach, we developed a workflow including tumour recognition and HER2-positive cell counting based on 70 WSIs (Whole slide imaging) training dataset. Using 68-ROIs (Region of interest) cropped from 15-WSIs as validation, this method reached 86.7% accuracy and 94.34% sensitivity. 2 ROIs originally categorized as HER2-negative were reclassified as HER2-low by this method.
In 3D imaging approach, HER2 fluorescent stained slides from the same 15 validation cohort were acquired under confocal microscopy. One of four HER2-negative specimens originally categorized by IHC report was reclassified as HER2-low. Using 3D image, 2 of 15 specimens showed heterogeneous HER2 expression in different depth of their thick slides.
Conclusion: This study demonstrated both computer-aided algorithm and 3D imaging technology were able to identify more HER2-low samples than light microscopy. These sensitive methods can detect cases with very low HER2 expression which are considered as HER2-negative by traditional light microscopy. For patients with very low HER2 expression identified by these sensitive methods, more studies are needed to see their clinical response to HER2 antibody-drug conjugates.

PS-03-013

Differential diagnosis of Crohn's disease and Ulcerative Colitis with deep learning based on hyperspectral infrared images

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Background & objectives: Differential diagnosis of inflammatory bowel disease (IBD) can be challenging but is important for treatment decisions and follow-up strategies. We aimed to establish label-free quantum cascade laser (QCL)-based infrared imaging combined with deep learning as a tool for differential diagnosis.
Methods: Infrared imaging was used to analyse IBD and non-IBD cases. It is based on the interaction of electromagnetic waves with molecules within the tissue creating specific molecular fingerprints. A two-step deep learning approach, based on a modified U-Net (CompSegNet), was applied. The first instance differentiates IBD from non-IBD. The second instance differentiates between Crohn's disease (CD) and Ulcerative Colitis (UC).
Results: The cross-sectional sample set consisted of formalin-fixed, paraffin-embedded (FFPE) tissue sections from biopsies of CD (n=102), UC (n=52), and control cases (n=70). These cases were equally separated in the sub-cohort train (n=99), test (n=66), and validation (n=59). With the first instance CompSegNet, we achieved a validation area under receiver operating characteristic (AUROC) of 0.99 (sensitivity 95%, specificity 91%) in distinguishing between non-IBD and IBD. The subsequent second instance differentiation between CD and UC provided a AUROC of 0.89 (sensitivity 93%, specificity 83%).
Conclusion: Our approach provides an objective and label-free tissue diagnosis in IBD distinguishing between CD and UC. With an increased number of patients and longer training phases, we expect a more accurate and robust classification. The combination of spatial and biochemical information encoded in the infrared images allows to track changes on the molecular level. Overall, this approach has the potential to become a widely applicable diagnostic tool for IBD and maintains intact tissue for further molecular analysis.
Funding: This work was founded by a synergy award of the Kenneth Rainin Foundation.

PS-03-014

Generalisation of deep learning for breast cancer metastasis detection

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Background & objectives: For clinical adoption of AI, models must be robust when applied to new settings. Objective of this study was to test the generalization potential of a pretrained deep learning (DL) model to unseen data and to a new diagnostic domain.
Methods: Whole slide images from Linköping, Sweden, with exhaustively annotated tumour regions, and publicly available CAMELYON data were used. Previously developed DL for breast cancer metastases detection in sentinel lymph nodes, developed using CAMELYON data, was used as baseline. The model was tested on sentinel nodes and lymph nodes from axillary dissections (n =51 and n=17, respectively; both Linköping).
Results: Base model showed decreased performance on Linköping data (AUC 0.929; 95%CI 0.800-0.998 and FROC 0.744; 95%CI 0.566-0.912), compared to the performance on CAMELYON data. A large FROC decrease was found for the base model applied to axillary nodes. The model was retrained, using both CAMELYON and Linköping WSI, resulting in increased performance for both sentinel nodes and axillary nodes (both AUC $p<0.05$). Pathologist qualitative evaluation of the outputs of the retrained model showed no missed positive slides and in 21 of 24 positive slides slide-level diagnoses matched the clinical ground truth. False positives and false negatives were observed. One previously undetected micrometastasis was identified as a result of using DL.
Conclusion: The study highlights the generalization challenge (even when using DL trained on multi-centre data), both as a result of applying DL in a new diagnostic setting for the initial indication, but even more remarkably, a slight change in indication impacted the model´s performance even more. Retraining the model, including data from target application, could mitigate the problem. Further studies are required to explore strategies to overcome the generalization challenge and evaluate what model performance is needed for different clinical applications.

PS-03-015

The use of digital pathology and artificial intelligence in the assessment of multiple myeloma

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Background & objectives: Plasma cell quantification in bone marrow trephines is an essential part of the diagnosis of multiple myeloma. Artificial intelligence (AI) is ideally suited for classification and quantification tasks but has not yet been employed in analysing the full myeloma microenvironment.
Methods: Twenty-two trephines from patients with myeloma were retrieved from the archives and whole slide imaging performed at 40x (Objective Imaging). Using a deep learning convolutional neural network (HALO-AI, Indica), the algorithm was trained to segregate and quantify bone marrow tissue and cellular phenotypes. In addition, spatial analysis was performed to assess the relationship of plasma cells within the marrow microenvironment.
Results: The trained classifier showed excellent segregation of marrow tissue elements as well as quantification of the different cell phenotypes on a Haematoxylin & Eosin stain. The mean number of plasma cells across the cases was 60,300 and mean density 1,637/mm2, occupying an average of 67% of the cell constituents. It was also noted that eosinophil numbers were increased (mean 4,900/trephine; 7% of all cells). Analysis of other marrow constituents demonstrated an inverse correlation between increasing plasma cell numbers and other cell types. Spatial analysis revealed a higher plasma cell density/mm2 with increasing distance from bone, although at a distance of 200uM, overall plasma cell numbers were reduced.
Conclusion: In this study, we have successfully applied AI to the classification of tissue types in multiple myeloma bone marrow biopsies. Using cellular phenotyping, it was possible to quantify plasma cells without immunohistochemistry, as well as other cell types in the marrow microenvironment in a more reproducible manner. This is a useful diagnostic adjunct for Pathologists and enables us to further study the relationship between the pattern of disease burden and overall prognostic indicators for patients with this disease.

PS-03-016

Optimization of automated tissue classification in histopathological images: use of a deep transfer learning approach on a pancreatic cancer cohort

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Background & objectives: Neuronal networks (NNs) can assist with the analysis of digitalized histological slides. However, training of NNs can be hampered when training samples contain not one, but several tissue types. Our aim was overcome this problem by using deep transfer learning.
Methods: Image tiles were extracted from tissue microarrays with samples from 223 pancreatic cancer patients. Tiles contained pancreatic cancer, healthy pancreas, lymph nodes, but also confounders such as adiopse tissue. To purify the training data, we performed a data clean-up step using two communicating NNs (communicators). Subsequently, data was used to train NNs, which were then validated using an independent dataset.
Results: By feeding pre-existing datasets containing confounders such as adipose tissue as well as our own training datasets into two communicating NNs (communicators), we received a selection of unequivocal tissue tiles for NN training. A ResNet-18-based NN re-trained with these data achieved a higher weighted accuracy over all tissue classes (94%) than after training with raw data (90%). Additionally, we tested 72 NNs using an independent dataset created from H&E-stained whole-slide images. NNs were able to distinguish between pancreatic cancer, healthy pancreas, lymph nodes and adipose tissue following training with purified data. Performances varied and depended on various factors, such as the learning rate and the optimizers used.
Conclusion: Automated classification of histological tissue types in a pancreatic cancer cohort can be optimized by using communicator-driven data pre-processing. In the future, we aim to explore whether a similar approach can also be used to optimize other classification tasks, e.g., the distinction between pancreatic ductal adenocarcinoma and cholangiocellular carcinoma on digitalized H&E slides.

PS-03-017

Inter-rater agreement of pathologists on determining cell-level PD-L1 status in non-small cell lung cancer

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Background & objectives: Artificial intelligence (AI) based quantification of cell-level PD-L1 status enables spatial analysis and allows reliable and reproducible assessment of the tumour proportion score. In this study, we assess the cell-level inter-pathologist agreement as human benchmark for AI development and validation.
Methods: Three pathologists manually annotated the centres of all nuclei within 53 regions of interest in 12 whole-slide images (40X magnification) of NSCLC cases and classified them as PD-L1 negative/positive tumour cells, PD-L1 positive immune cells or other cells. Agreement was quantified using F1 score analysis, with agreement defined as annotations less than 10 um apart and of the same class.
Results: An average of 9044 nuclei (1550 negative, 2367 positive tumour cells, 1244 positive immune cells, 3881 other cells) were manually annotated by the three pathologists. The mean F1 score over pairs of pathologists at dataset level was 0.59 (range 0.54-0.65). When split across classes, the mean per-pair F1 scores stay approximately the same, indicating the readers perform similarly regardless of cell type. Besides human variability in manual point annotations with respect to the centre of nuclei, lack of context contributed to disagreement: readers who reported they solely examined the ROIs tended to disagree more with readers that reported they also looked outside the ROIs for additional (morphological/density) information.
Conclusion: Agreement on determining the PD-L1 status of individual cells is only moderate, suggesting a role for AI. By quantifying the inter-rater agreement of pathologists, we have created a human benchmark which may serve as an upper bound (and could be combined via majority vote) for the validation of AI at cell level, something not done previously. Cell-level AI-based assessment of PD-L1 may supersede slide level scoring, adding significant information on the heterogeneity and spatial distribution over the tumour.
Funding: VIDI (F. Ciompi)

PS-03-018

Nuclei detection with YOLOv5 in PD-L1 stained non-small cell lung cancer whole-slide images

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Background & objectives: Nuclei detection in histopathology images is an important prerequisite step of downstream research and clinical analyses, such as counting cells and spatial interactions. In this study, we developed an AI-based nuclei detector using the YOLOv5 framework in whole-slide NSCLC cases.
Methods: Our dataset consisted of 42 PD-L1 stained cases (30 training, 12 test). Four trained (non-expert) readers manually annotated all nuclei (both positive/negative) within regions of interest (ROIs) viewed at 40X magnification. We trained a YOLOv5(s) network on annotations of one reader. Performance was measured using F1 score analysis; hits were defined as being less than 10 um away from annotations.
Results: We evaluate YOLOv5 on the test set by pairing it against all four readers separately. There, YOLOv5 performs excellently, falling within the interrater variability of the four readers: the mean F1 score over algorithm-reader pairs is 0.84 (range 0.76-0.92) while the mean F1 score over pairs of readers is 0.82 (range 0.76-0.86). When we determine the cell count (number of annotations/predictions) per ROI in the test set, agreement of algorithm-reader pairs and reader pairs is equally well aligned: 0.93 (range 0.90-0.97) versus 0.94 (range 0.92-0.96). Visual inspection indicates YOLOv5 performs equally well on PD-L1 positive and negative cells.
Conclusion: We have trained a nuclei detector that performs within the interrater variability of four human readers. In future work, we could extend this detector to additional tissues and immunohistochemistry stainings. Moreover, this detector could be used as a AI-assisted manual point annotation tool: while human readers perform the (context-driven) task of delineating homogeneous regions (e.g. clusters of PD-L1 positive stained cells), the detector performs the (local, yet laborious) task of identifying individual nuclei within these regions, providing labelled point annotations.
Funding: VIDI (F. Ciompi)

PS-03-019

Automated annotation of digital H&E/SOX10 dual stains generates high-performing convolutional neural network for calculating tumour burden in H&E-stained cutaneous melanoma

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Background & objectives: Deep learning for analysis of H&E stains requires a large annotated training set; a labor-intensive task that often involves highly skilled pathologists. We aim to develop and evaluate computer-assisted annotation based on digital dual stains of the same tissue section.
Methods: H&E stains of primary (n=48) and metastatic (n=48) melanoma were digitized, re-stained with SOX10, and re-scanned. Images were aligned, and automated annotations of SOX10 stains based on thresholding and a trained convolutional neural network (CNN) were thus directly transferred to H&E stains of the training set (n=37). Training of the final CNN for calculating tumour burden included 1,221,367 annotated nuclei.
Results: For primary melanomas, nuclei-annotation precision was 99.7% (95%CI=99.4%;99.9%) for tumour cells and 99.2% (95%CI=97.7%;99.7%) for normal cells. With a mean difference of 7.9% (95%CI=6.1%;9.7%), precision for normal cells was markedly reduced for metastases compared with primary melanomas (p<0.001). Associated false-positive annotations were predominantly related to SOX10-negative tumour cells. Correspondingly, mean SOX10 intensity (red chromaticity) was 0.37 (95%CI=0.35;0.39) for primary melanomas and subcutaneous metastases but 0.32 (95%CI=0.30;0.34) for lymph-node and organ metastases (p=0.002). Accuracy of trained CNN for calculating tumour burden in primary and subcutaneous lesions was 92.6% (95%CI=83.6%;96.8%). Compared with stereological counting, mean difference in tumour burden was 5.8% (95%CI=-1.2%;12.9%, p=0.10) for CNN and 16% (95%CI=3.7%;28.3%, p=0.02) for routine eyeballing.
Conclusion: With this annotation technique, a large annotated H&E training set with high quality was created within a reasonable timeframe for primary melanomas and subcutaneous metastases. For these lesion types, the training set generated a high-performing CNN for calculating tumour burden, which was superior to routine eyeballing. Yet, due to low or missing tumour-cell SOX10 positivity, advantages were limited in lymph-node and organ metastases. To include other cancer types or objects of interest, immunohistochemistry of the technique may easily be modified.
Funding: Health Research Foundation of Central Denmark Region

PS-03-021

Collaborative web platform: lab organisation, research and digital pathology practice

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Background & objectives: Digital pathology has become increasingly important in Pathology laboratory practice. The combination of whole-slide-based imaging techniques and machine learning has been greatly applied to develop visual analytics tools, with great contribute to a more accurate and time-effective practice.
Methods: A consortium between BMDSoftware, Computer Graphics Center and Institute of Anatomical Pathology and Molecular Pathology - Faculty of Medicine/University of Coimbra, is developing a collaborative Web platform for digital pathology. It is a three years project that began in January of 2020 and joins the efforts of pathologists, computer science researchers and software developers.
Results: The result is a cloud-based platform known as iPATH. It allows the visualization of whole-slide images, easy navigation through the images, annotations, delimitation of areas of interest, and a wide range of measurements. It aims the informatization of laboratory routine, tracking of all steps, from the reception of samples to the final pathologic report, including the management of response time. The platform allows the management of the datasets annotation process for production but also for supporting the development and integration of artificial intelligence tools. Currently, Helicobacter pylori identification and quantification instrument to apply to gastric biopsies and mitoses identification in different neoplasms are the challenges being considered as case-study.
Conclusion: Digital pathology is already a reality in many Pathology labs across the world, perhaps driven by Covid-19 pandemic crisis, as it allows remote work. We believe that digital pathology is just the beginning and a platform for the creation of decision aid tools through artificial intelligence and deep

learning technologies, that will improve the speed and quality of diagnosis processes.
iPATH is a multidisciplinary project aiming to create useful solutions for pathologists and Pathology labs.

PS-03-022
Upconversion nanoparticles as labels for histopathological tissue evaluation
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Background & objectives: H&E staining and DAB-labelling are the gold standard in pathology, suffer from narrow dynamic range, difficulties in quantification and limited possibilities regarding multiplexing. We present an upconversion-nanoparticle (UCNP)-based technique that allows to overcome problems associated with commonly used labelling techniques.
Methods: Formalin-fixed paraffin-embedded breast cancer cell line and human breast cancer tissue were sectioned and labelled. Upconversion imaging of the human tissue sections was conducted in our prototype device and compared with a standard DAB-based IHC. The combination of UCNP and haematoxylin counterstaining on the same slide was investigated.
Results: Images obtained with our novel device demonstrate that our UCNP bioconjugates are excellent labels for the detection of cancer markers in tissue sections. Brightfield images prove that UCNPs do not interfere with the standard tissue evaluation by a pathologist. Additionally, brightfield and luminescent images can be merged to provide a better understanding of tissue morphology.
Conclusion: The emerging field of UCNP-based labelling techniques provides new possibilities for more accurate diagnosis. Staining solutions and a novel device developed by us keep the advantage of H&E staining and combine it, in one image, with the UCNP luminescent data. The high-contrast images of the UCNP labelling – generated by our scanning device – set the foundation for generating ground truth for machine learning algorithms.

PS-03-023
Computer-assisted diagnosis of early-stage lung adenocarcinoma using deep learning
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Background & objectives: Early-stage lung adenocarcinoma growth patterns strongly associate with disease progression. Tumour biopsies are subtyped regarding microenvironment alterations and growth patterns: lepidic, acinar, papillary, micropapillary, and solid. We developed a deep learning (DL) pipeline to sub-classify adenocarcinomas to improve pre-operative assessments.
Methods: We developed a multi-class DL classification model for the prognostically relevant patterns. A retrospective cohort of 129 whole-slide images of needle-biopsy sections of stage I and II lung adenocarcinomas stained with haematoxylin and eosin and their corresponding annotations for the regions of interest were used to train and validate our DL classification models.
Results: In preliminary experiments, we designed a three-class DL model to classify normal tissue, tumour area of combined growth patterns, and tumour microenvironment. Compared to the ground truth, we reported a high overall accuracy of 0.86. Next, we designed a nine-class DL model to individually classify all patterns, yielding an overall accuracy of 0.77 and a Dice similarity coefficient of 0.66. We believe the results are influenced by class imbalance, introduced by dominant normal tissue, stroma, lepidic and solid patterns. Furthermore, high intra-class variability and inter-class similarity might have also influenced the results. For example, acinar patterns cover heterogeneous morphologies ranging from glandular to cribriform patterns, that may resemble lepidic patterns.
Conclusion: Our results indicate the potential aggressiveness of early-stage lung adenocarcinomas from small biopsy samples by sub-classifying growth patterns using DL. As we have a limited cohort, further training of the model on enriched datasets is required. This analysis can guide the extent of the surgical approach to maximise the preservation of healthy adjacent tissue and increase the patient's quality of life. However, biopsies might misclassify the dominant growth pattern due to sampling error.

PS-03-024
A novel machine learning pipeline to analyse unstained liver biopsies and automatically quantify tumour-related structures
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Background & objectives: Tumour diagnosis is usually performed through the visual inspection of stained biopsies. Here, we propose a pipeline to support the pathologists' clinical routine: it avoids staining procedures and provides novel quantitative insights to improve the diagnosis accuracy.
Methods: Images of unstained liver biopsies, acquired by a whole-slide scanner, are virtually H&E-stained through a convolutional neural network (CNN). Relevant biological structures (e.g. dead hepatocytes, cell nuclei, collagen) and tissue dis-architecture (e.g. steatosis) are retrieved by exploiting semantic segmentation and texture analysis procedures, coupling the phasor approach with clustering and semi-supervised machine learning techniques.
Results: The pipeline accuracy has been evaluated on 20 liver murine biopsies (10 affected by hepatocarcinoma and 10 healthy controls) by comparing the algorithm output with the pathologist's quantification. In each biopsy, the amount of dead hepatocytes, cell nuclei and the extension of steatosis-affected regions have been automatically provided, with a mean accuracy > 95%. Moreover, the CNN performance in the virtual staining procedure has been evaluated for H&E samples. 2000 real and virtually stained tissue patches have been pixelwise compared, resulting in a colour content discrepancy < 5%.
Conclusion: These preliminary results demonstrate the capability of the proposed pipeline to extract quantitative and objective information, expanding the tumour feature dictionary, assisting pathologists with a more accurate diagnosis and overcoming the limitations due to inter-observer variability. Moreover, time and resources consumptions due to staining procedures are avoided by the H&E virtual colouring provided by the CNN in the images pre-processing steps.

PS-03-025
Segmentation of anthracosis – a needed first step in digital analysis of lung tissue
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Background & objectives: Anthracosis, the black granular pigment in lung tissue, is often wrongfully detected as nuclei by image analysis algorithms, leading to high false positive rates in immunohistochemical slides. Here, deep learning models for preemptive removal of anthracosis were evaluated.
Methods: From n=8 CD8 stained whole slide images, 128 tiles (256x256 px at 0.2431 µm/px) were manually selected and annotated to reflect expected lung tissue heterogeneity. Tiles were used in 4-fold validation to comparatively evaluate a traditional U-Net vs. Xception-based U-Net model (31e6 vs 2e6 parameters). For image augmentation, we focused on colour augmentation. Model performance was assessed by Dice score.
Results: The traditional U-Net outperformed the Xception-based model (0.78 ± 0.22 vs. 0.74 ± 0.22), with its unaugmented version performing the best (0.85 ± 0.16). Qualitative assessment showed that the models were more precisely segmenting individual granules versus the coarse annotations provided in the ground truth, suggesting superior performance over those suggested by quantitative metrics. Faint anthracotic pigments on darker background (condensate macrophages) and intensively stained CD8-postitve lymphocytes were common sources of error, with the dark combined hematoxylin and DAB at the nuclear membranes being detected as false positive anthracosis.
Conclusion: We show that simple U-Net-based models are powerful tools for localization of anthracosis. These models should likely be included in image analysis pipelines to help eliminate biologically irrelevant artifacts, thus improving specificity of downstream analyses. Augmentation methods did not appear to improve the model in identifying potentially relevant morphological features, suggesting that colour is insufficiently discriminatory in many instances. Next steps will include the refinement of our anthracosis model, including more targeted augmentation methods, and combination with nuclei segmentation.
Funding: MD-PhD scholarship 5088-06-2020 of Cancer Research Switzerland

PS-03-027
Deep learning neural networks for real-time discrimination between osteosarcoma and fracture callus on conventional histological (H&E) sections
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Background & objectives: Histopathological discrimination between osteosarcomas and fractures can be extremely challenging. Herein, we aimed at developing a novel Machine Learning architecture (Convolutional Neural Network) for real-time discrimination between osteosarcoma and fracture callus based on conventional H&E sections under brightfield microscopy.
Methods: We collected 2136 H&E images from 1154 osteosarcomas and 982 fractures from our archives (n=925) and the web. With the data collected, we trained a Convolutional Neural Network (CNN) based on the mobilenet version 3 architecture. Training set included 2021 images (1086 osteosarcomas, 935 fractures), and test set 115 images (68 osteosarcomas, 47 fractures) from new/unknown to the system cases.
Results: We created a web application that allows microscopes to directly connect to either desktop/laptop computers or mobile phones, in order to facilitate easy access to the Neural Network classifier.
The proposed system is simple to use and delivers real-time high accuracy classification regarding the separation of osteosarcoma from fracture, with sensitivity 91.3% and specificity 93.75%. Four (4) osteosarcomas were falsely classified as fractures; among them 2 were postchemotherapy osteosarcoma cases with 100% necrosis. Two (2) fractures were falsely classified as osteosarcomas.
Conclusion: CNN trained on conventional H&E sections can significantly decrease the pathologist's workload and serve as an additional tool towards accurate diagnosis of several pathologies in everyday-routine practice. Since this tool is based on conventional H&E images and not on WSI, it can be easily used by pathologists from remote areas and small hospitals for the diagnosis of osteosarcomas, but also for virtually every pathologic condition, after specific training.

PS-03-028
Novel approach for adaptive colour normalisation based on tissue thickness and biological tissue type variability
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Background & objectives: Colour variation in H&E and IHC slides poses a huge challenge for computational pathology algorithms. We present a novel method for colour normalisation based on tissue thickness and biological tissue variability to achieve significantly improved performance over existing methods.
Methods: 30 H&E slides of endometrium tissue were scanned using Pramana WSI scanner (inline analysis of tissue thickness and colour) and data was collected for colour and tissue thickness variation using colour distribution map and tissue thickness graphs. Colour normalisation was done based on tissue thickness, biological tissue variability and colour differences between thick and thin tissue areas in the slide.
Results: Visual evaluation by histopathologist revealed that our method yielded better results in comparison to existing methods. Our method does selective normalisation in the AOI as per the requirement after consideration of vectors for tissue thickness, biological tissue variability and colour distribution of the target AOIs instead of adopting the generic approach uniformly across the slide like existing methods. Reference pairing based on close matching of the colour distribution range of different colour in the target AOI to the reference AOI has improved the performance when biological tissue variability vector was also considered. Selective application of this approach based on tissue type and thickness reduces the over and under colour saturation.
Conclusion: Inline analysis of tissue thickness variation and colour hue distribution for all the AOIs in a WSI can help in achieving better colour normalisation when biological tissue variability is taken into consideration. Target to Reference AOI pairing done on the basis of biological tissue type and colour distribution graph allows for selective colour normalisation in the target AOI if needed. Both tissue type and thickness variation across the AOIs determine the need of selective colour normalisation for optimal results.

PS-03-029
Digital image analyses applied to HSIL cervical biopsies
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Background & objectives: Pathology has been integrating technology into its workflow and there are several algorithms we can runout to generate reliable information.
We aimed to determine if nuclear features of cervical HSIL differ among patients infected with distinct HPV genotypes.
Methods: We randomly selected 57 HSIL (CIN II and CIN III) cervical biopsies with previous HPV genotypification and scanned one

representative slide of each. We then used a built-in algorithm on Aperio ImageScope software [12.4.3.5008] to estimate the average nuclear size and the nuclear chromasia of cervical epithelium with HSIL and used statistical software to compare the data.
Results: Our sample comprised 18 cases of HPV16, 26 cases of HPV-HR and 13 cases of HPV16 and HPV-HR coinfection.
The presence of HPV16 genotype, alone or together with HPV-HR, was associated with CIN III (chi-squared = 5,28; p = 0,02).
When comparing the HPV16 group to coinfected 16+HR, we found that HPV16 alone had significantly larger nuclei than the coinfection group (t-test = 2,3; p = 0,03). However, these groups showed no difference regarding the nuclear chromasia.
Conclusion: Digital image analysis applied to pathology seems a promisor field since it can provide us with essential information about our specimen that human eye simply can´t measure. In our study, the stronger association was between HPV 16 and CIN III but the clinical value of that is uncertain and may need a larger study. The same applies to the fact that HPV16 specimens have larger nuclei than coinfected 16+HR.

PS-03-030
Using a digital platform to organize and manage pathology residents curricula in Portugal
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Background & objectives: In Portugal, for yearly and national board exams (NBE),a formal curriculum must be written down. In order to organize the registry of routine cases signed out during residency, a free internet platform dedicated to curricula organization and management (XERPA-MD) has been working together with Portuguese residents.
Methods: Members of the residents' committee of the Portuguese Society of Pathologists (NiSPAP) and an independent pathologist (coordinator of Anatomic Pathology for XERPA-MD) met regularly over a period of 12 months. A database, with neoplastic and non-neoplastic entities, was built according to the most recent editions of the WHO Classification of Tumours books, as well as other well-known bibliographic references in the field of surgical pathology.
Results: The database follows the Portuguese College of Pathologists curricular guidelines. After three rounds of work (data input, data correction, and data review), a total of 5500 entities were organized. Users are now able to access the database online and to register all their curricular activities in a structured and systematic way. All inserted records can be reviewed, organized, managed, and exported automatically, saving several hours of work.
Conclusion: Pathology residency is a critical period in the lives of all pathologists worldwide, with lots of study, routine cases and diverse scientific activities to be performed. The formal curriculum must include, among several other extensive registries, a thorough and organized list of all routine cases signed out during residency. Quite understandably, this becomes a daunting, exhaustive and stressful task, to be done every year, until the NBE. Automatization of curricula creation and management greatly decreases the time spent by Portuguese Pathologists writing down and organizing data.

PS-03-032
AI(H): deep learning model for standing and grading autoimmune hepatitis from histology
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Background & objectives: Autoimmune Hepatitis(AIH) is one of the most challenging diagnoses in liver pathology. We aim to develop a deep learning model, Artificial Intelligence for Hepatitis[AI(H)] that evaluates liver biopsies, to provide granular, quantifiable, and rapid analysis of histological features of AIH.
Methods: One hundred twenty-five pretreatment liver biopsies with AIH diagnosis from the biobank of the University Hospital Basel were selected and split into training (80%) and test (20%) datasets and utilised to train several convolutional neural network models in the Aiforia platform. Manuel annotations of target regions were created by a hepato-pathologist, and used to train and test AI models.
Results: The liver microstructure detection model was trained to segment liver tissue into portal or, lobular areas and central vein compartments, while the necroinflammation model was trained for focal necrosis, interface hepatitis, or confluent necrosis. The immune cell classification model can detect, classify, and quantify lymphocytes, plasma cells, macrophages, eosinophils, and neutrophils. The bile duct model was trained for detecting the damaged bile duct.
The four AI models are accurate and efficient in diagnosis of various morphological components of AIH biopsies. When evaluated on a separate test set(ratios of correct predictions) of 92.9%, 97.1%, 84.5%, and 99.5% on liver microstructures, necroinflammation features, immune cell classification and bile duct damage detection, respectively.
Conclusion: AI(H) is a novel diagnostic tool for AIH histology. It demonstrates comparable results to manual hepato-pathologist assessment for several specific diagnostic tasks on AIH biopsies and classifies cell/tissue types a much shorter time. AI(H) is an intelligent, fast, accurate, and efficient diagnostic tool. Further planned development of AI(H) will allow for more functionalities such as portal and lobular necroinflammation, specific inflammatory cells, fibrosis, and bile duct damage.
Funding: Study was partially sponsored by Novartis.

PS-03-033
An assisting deep learning tool for accurate detection of colorectal cancer lymph node metastasis
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Background & objectives: Histopathological evaluation of lymph node metastasis (LNM) for colorectal cancer (CRC) patients can be laborious and time-consuming. We propose an assisting deep learning method for CRC-LNM detection by leveraging transfer learning with an ensemble model on hematoxylin and eosin slides.
Methods: The proposed deep learning method consists of an LN segmentation (UNet) and an ensemble (Xception, Vision Transformer) metastasis detection models. LN segmentation model was trained on one hundred annotated CRC slides. An ensemble metastasis detection model was trained first on the public breast cancer dataset, PatchCamelyon and then fine-tuned on CRC data.
Results: The proposed method was validated on an internal and external CRC cohort by analysing AUC, sensitivity, and specificity on a whole slide level. The method achieved an AUC of 98.1% in the internal validation cohort (2803 slides) with a sensitivity of 99.5% and specificity of 96.7%. Around 0.5% of positive slides were incorrectly classified as negative due to small isolated tumour

cell clusters (<100um). About 3.3% of negative slides were falsely detected as positive, mainly due to tissue folds and active germinal centres. In the external validation cohort (1033 slides), the method correctly classified 100% of all slides.
Conclusion: The deep learning method developed in this study showed excellent performance, making it suitable as an assisting tool for CRC-LNM screening. Future studies should include other histological subtypes (mucinous adenocarcinomas, signet ring cell carcinomas), investigate the application for other solid tumour types next to breast and CRC, as well as improve sensitivity for more challenging cases (isolated tumour cell clusters). The specificity could be improved by detecting and excluding tissue folds and germinal centres before applying the metastasis detection model.
Funding: Rising Tide Foundation for Clinical Research (CCR-18-295800) and Swiss Cancer Research Foundation (KFS-4427-02-2018)

PS-03-034
The creation of a virtual pathology department: a novel solution to a modern crisis
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Background & objectives: There are several well-known global challenges confronting Pathology that translate into poor TATs, lack of expertise/access and ultimately poor patient care. Our aim was to alleviate these pressure points to improve patient management.
Methods: A multitude of challenges are currently faced in Pathology resourcing. To this end, we developed an AI-empowered digital pathology system using a proprietary, customizable, scanner agnostic, cloud-based, LIS integratable, state-of-the-art pathology PACS. We then recruited and validated a team of recognized subspecialists to constitute the world's first CQC/CLIA accredited virtual pathology department.
Results: Across our pathologist network we currently have 56 pathologists in funnel across 12 subspecialities. The team is geographically distributed across Europe, UK, Canada and the US. We have fully validated our pathologists according to RCPath/CAP guidelines and have shown over 97% concordance for glass versus digital cases. Only minor discordances occurred, and a discordance remediation process was put in place whereby blind review of the discordant case was performed again and diagnostic accuracy recorded. We are currently producing successful turnaround times of <2 days in pilot trials. Pathologist efficiency has improved with the use of measuring and mitoses counting tools, including Ki-67 quantification.
Conclusion: Overall Client hospital satisfaction is highly evident with TAT decreased, no mailing of slides required, MDT ready reports not being re-typed, and going into LIS directly, saving both time and overheads. Pathologist satisfaction, quality control and efficiency are evaluated for this disruptive workflow, with net promoter score systems and tools employed to ensure optimal pathologist experience and high-quality reporting achieved.

PS-04 | Poster Session Nephropathology

PS-04-001
Morphometric analysis of lysosomes in the renal tubule in monoclonal gammopathy using transmission electron microscopy: 'mottled appearance' and beyond
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Background & objectives: Lysosomal 'mottled appearance', or uneven electron-dense contents related to monoclonal gammopathy (MG), has been described in light chain proximal tubulopathy (LCPT). We aimed to determine the ultrastructural characteristics of lysosomal mottled appearance in kidney biopsies and its association with LCPT.
Methods: Seventy-seven biopsies were grouped into LCPT (n = 5), MG conditions other than LCPT (n = 43), and non-MG conditions (n = 29). The mottled lysosomes in the renal tubules were evaluated using transmission electron microscopy and morphometric analysis.
Results: Mottled lysosomes were more prevalent (% of present cases) and frequent (no. of mottled lysosomes/20,000x ultramicroscopic field) in the LCPT group (100% and 8.20 ± 4.15/field) than in the MG (41.9% and 1.13 ± 2.05/field) and non-MG (37.9% and 0.80 ± 1.44/field) groups. In morphometric analysis of all mottled lysosomes (n = 520) detected from the 34 biopsies (5 LCPT, 18 MG, and 11 non-MG), we found that mottled lysosomes were larger, more irregular, and more electron-dense for the LCPT group than for the MG and non-MG groups.
Conclusion: Mottled lysosomes can be present in disorders other than LCPT or even without MG. The morphological characteristics of mottled lysosomes could provide objective guidance for the diagnosis of LCPT.

PS-04-002
Gene expression characteristics of T-cell-mediated alloimmune response in HIV-infected kidney transplant recipients
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Background & objectives: The graft survival of HIV-infected renal transplant recipients are comparable to that of non-HIV infected referents. However, the frequency of first-year T-cell-mediated rejection (TCMR) in the former group is higher. We assessed the molecular characteristics of TCMR in HIV-infected individuals.
Methods: We studied formalin-fixed paraffin-embedded (FFPE) renal biopsy samples from 68 transplant recipients (34 HIV+, 34 HIV-). The diagnostic groups were normal, borderline changes, and TCMR. We applied gene expression analysis on the FFPE material by using a panel of 760 targets that included immune-response-related and HIV genes. We performed differential gene expression (DE) analysis and pathway analysis (PA) (reactome database).
Results: DE analysis revealed multiple genes with significantly increased expression in the diagnostic groups of HIV+ borderline changes and HIV+ TCMR relative to their HIV- counterparts. PA of these genes showed gene enrichment in the following pathways: toll-like receptor cascades, MYD88:MAL cascade, cytosolic sensors of pathogen-associated DNA, and NLR-signalling among others. HIV genes were not found to be present in the biopsy material of HIV-infected patients.
Conclusion: Upregulation of the innate immune pathways in the biopsies of HIV+ patients with borderline changes and TCMR may indicate the enhanced involvement of natural immunity during T-cell-mediated alloimmune response in this patient group. This can potentially stem from immune dysregulation caused by HIV infection.

PS-04-003

Chief renal medullary osmolytes NaCl and urea differentially modulate tubular cellcytokine expression and monocyte recruitment

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Background & objectives: Extreme electrolyte concentrations characterize the renal medulla. Renal immune cells are sentinels against ascending bacteria but also promote detrimental inflammation. Here, we investigated how the renal main osmolytes, NaCl and urea, regulate tubular cell cytokine expression and monocyte chemotaxis.
Methods: Normal kidneys, transplant surveillance and minimal change biopsies were stained for macrophages, monocytes and cytokines using immunofluorescence and RNA in situ hybridization. Tissue cytokine concentrations were measured with ELISA. Clinical data, immunosuppressant and diuretic medication were extracted from the records. Human renal tubular cells (HK2) were exposed to NaCl, urea or mannitol. Gene expression was assessed by gene array analysis.
Results: In the healthy human kidney, more monocytes were detected in medulla than cortex. The monocyte gradient was attenuated in patients with medullary NaCl depletion by loop diuretic therapy and in nephrotic syndrome. Renal tubular epithelial cell gene expression responded similarly to NaCl and tonicity control mannitol, but not urea. NaCl significantly upregulated chemotactic cytokines, e.g., CCL2 and CSF1. This induction was inhibited by ROS scavenger n-acetylcysteine. In contrast urea, the main medullary osmolyte in catabolism, dampened tubular epithelial cytokine expression. NaCl-, but not urea stimulated tubular epithelium or cytokine combinations promoted human classical monocyte migration. Consistently, gene array data revealed renal medullary chemokine and monocyte marker decrease in catabolic mice.
Conclusion: Our results depict two different renal medullary scenarios depending on whether NaCl or urea is the main osmolyte: The energy intense state with tubular cell cytokine production and recruited myeloid cells in the presence of elevated NaCl may aid antibacterial host response. Less cytokine production and stable myeloid cell populations in presence of elevated urea concentrations may benefit organisms with limited energy supply which may also limit detrimental inflammation. This could be a basis for additional management strategies of patients.
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PS-04-004

Adverse renal effects of immune checkpoint inhibitors: presentation of 12 patients undergoing renal biopsy

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Background & objectives: The immunomodulatory activity of immune checkpoint inhibitors (ICIs) often elicits a broad spectrum of immune-related adverse effects (IRAEs), in multiple tissues, including kidney. We present a case series of renal IRAEs with various clinical and histological manifestations.
Methods: Twelve patients, bearing a wide range of solid malignancies, received either PDL-1, or a combination of PDL-1 and CTLA-4 inhibitors. Following ICIs administration, clinical signs indicative of renal toxicity included acute kidney injury (AKI), proteinuria, nephrotic syndrome and/or haematuria. All patients underwent renal biopsy, which was processed for light microscopy, immunofluorescence, and when tissue sufficed, electron microscopy.
Results: The most frequent clinical presentation was AKI and the most frequent pathologic alteration was tubulointerstitial nephritis (TIN) encountered in six cases. In one of these cases, TIN was accompanied by IgA glomerulonephritis. Two patients, presenting with nephrotic syndrome, exhibited a secondary "lupus-like" membranous glomerulopathy. In one of the latter patients, there was TIN as well. Among the remaining three patients with AKI, two displayed acute tubular injury as the most prominent finding, while in the third, a combination of membranoproliferative glomerulonephritis and thrombotic microangiopathy was identified. The last patient developed nephrotic syndrome and a secondary renal amyloidosis was detected, on a rheumatoid arthritis background presenting after the initiation of ICIs.
Conclusion: Our findings harmonize with bibliographical data that identify TIN as the most frequent histological lesion related to ICIs administration. The preferential involvement of tubulointerstitial tissue could be associated with the higher expression levels of PD-1 on tubular epithelial cells, compared to glomeruli. On the other hand, both secondary "lupus-like" membranous glomerulopathy and secondary amyloidosis upon rheumatoid arthritis, are postulated to emerge as a consequence of a systemic immune system reconstruction, induced by immune-checkpoints inhibition.

PS-04-005

Compensatory and regenerative potential in kidneys of newborns from mothers with complicated pregnancy by preeclampsia and iron deficiency anaemia

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Background & objectives: Preeclampsia (PE) and iron deficiency anaemia (IDA) are pregnancy complications that have a negative effect on women health, their offspring. The objective was to reveal the compensatory and regenerative potential in newborns kidneys that developed under maternal PE, IDA conditions.
Methods: The study material was the tissue of kidneys of newborns from mothers with physiological pregnancy (n=28) (group (G) 1); complicated pregnancy by PE of varying degrees of severity (n=78) (G 2), IDA of varying degrees of severity (n=85) (G 3). Histological, immunohistochemical, morphometrical, statistical methods were used.
Results: In newborns kidneys of G 2-3 it was revealed a deficiency of nephrons with the presence of alterative changes in them, hypertrophy of glomeruli with hyperplasia of capillary loops mainly in G 3. Proliferative activity of nephrons structural elements increased in G 2 (Ki-67 proliferative index (PI) – (21.3±2.1)%), G 3 (Ki-67 PI – (38.9±2.7)%) compared with G 1 (Ki-67 PI – (12.5±1.9)%), however, was more pronounced in G 3. In G 2 and especially G 3, there was compensatory angiogenesis activation, as evidenced by an increase in the number of vessels in stroma in these groups (G 2 – 8.3±1.2, G 3 – 11.4±2.1) compared to G 1 (5.6±0.9).
Conclusion: In kidneys of newborns from mothers whose pregnancy was complicated by PE and IDA, compensatory and

regenerative processes characterized by hypertrophy of glomeruli with hyperplasia of capillary loops, activation of proliferative potential of nephrons cells, angiogenesis activation. The latter were more pronounced in kidneys of newborns that developed under maternal IDA conditions. The data obtained by the authors indicate a more pronounced damaging effect on the newborns kidneys of maternal PE compared to IDA.

PS-04-006

Renal amyloid deposition limited to glomeruli in caveolin-1 knockout mice

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Background & objectives: Caveolae are invaginations of the plasma membrane involved in many different disease processes, such as cardiovascular diseases, infections, diabetes, drug sensitivity and cancer. The objective of this study was to assess the renal pathological abnormalities in cav-1 knockout ageing mice.
Methods: Renal tissue from 6 and 18 month-old cav-1 knockout mice was processed for paraffin and plastic embedding in order to be examined using light microscopy (LM) and electron microscopy (EM). Slides with paraffin embedded tissue were processed for immunofluorescence microscopy (IF) and examined using the following markers: IgA, IgM, IgG, C3, C1q, fibrin, kappa and lambda light chains.
Results: LM showed normal structure of kidney from 6 month-old mice and large amorphous deposits located only in the glomeruli from 18 month-old mice. There was no endocapillary hypercellularity, fibrinoid necrosis or crescents in the glomeruli. The tubulo-interstitial and vascular compartments of the kidney had a normal structure. IF was negative in the glomeruli and there were no extraglomerular deposits on any marker examined. EM showed non-branching, randomly arranged fibrils, with a diameter between and 7 and 12 nm located only in the glomeruli.
Based on the findings observed by LM, IF and EM, a diagnosis of amyloidosis limited to the glomeruli in the kidneys of aged mice was made.
Conclusion: There are several experiments in animal models and HEK cells that demonstrate a connection between cav-1 levels and amyloid precursor proteins. In humans, variations in the CAV1 gene have been reported in association with metabolic disorders and cardiovascular disease.
This study represents the first report of amyloid deposition in the kidneys of cav-1 knockout aged mice, further strengthening the evidence that cav-1 and caveolae are implicated in disease pathophysiology.

PS-04-007

Clinical and pathohistological characteristics of COL4A3 c.2881+1G>A variant causing Alport spectrum disorders in Croatian population

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Background & objectives: Alport syndrome (AS) and thin basement membrane nephropathy (TBMN) are kidney disorders caused by mutations in COL4A3, COL4A4, or COL4A5 genes that encode polypeptide chains of collagen IV, the major structural component of basement membranes.
Methods: We identified 13 patients from 12 unrelated families with a pathohistological diagnosis of AS or TBMN who tested positive for a heterozygous variant COL4A3 c.2881+1G>A on conducted next-generation sequencing (NGS). Subsequently, their family members were recruited for genetic counselling, urinalysis, and blood sampling for targeted NGS. A correlation of clinical and pathohistological data and genealogy study was also performed.
Results: Overall, 34 patients (58.8% male) were found positive for heterozygous, disease-causing variant COL4A3 c.2881+1G>A. Haematuria was present in 33 patients (97.1%), while 19 (55.9%) had proteinuria. Follow-up data showed that four more patients developed proteinuria (23 total; 67.6%) and 6 (17.6%) developed chronic kidney disease, started dialysis or underwent kidney transplantation by the median age of 51 years. There were 6 (17.6%) patients with hearing loss (3 confirmed with audiogram) and 4 (11.8%) with ocular lesions. Among 13 patients who underwent kidney biopsy, 12 had glomeruli available for electron microscopy. Five patients had classic AS morphology and 7 had TBMN (3 of them with focal lamellation).
Conclusion: The suspected founder variant COL4A3 c.2881+1G>A is disease-causing. There is variability among these patients not only in clinical presentation but also in pathohistological findings. Interestingly five out 12 heterozygous patients had classic AS morphology on kidney biopsy. It is essential to conduct a detailed analysis of each collagen IV variant to optimize the affected patients' prognostic and therapeutic approach.

PS-04-008

Ursolic acid prevents the dysregulation in the expression of histone methylation-related epigenetic enzymes in diabetic kidney

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Background & objectives: Histone methyltransferases (KMTs)/demethylases (KDMs) play a major role in the pathology of diabetic kidney disease (DKD). We aimed at investigating the potential role of ursolic acid (UA), a pentacyclic triterpenoid, to modulate the expression of archetypal KMTs/KDMs in diabetic kidney.
Methods: Non-diabetic and streptozotocin-induced diabetic C57BL/6J mice were randomized to receive via intraperitoneal injection 1 mg/kg UA, or its vehicle for 4 weeks. Human endothelial cells (EA.hy926) were exposed to normal (5 mM) or high (25 mM) concentrations of glucose in the absence/presence of UA (5 μM). Hematoxylin-eosin staining, fluorescence microscopy, real-time PCR and Western blot were employed.
Results: No significant changes in blood glucose levels and body weights were detected following UA administration to diabetic mice as compared with vehicle-treated diabetic animals. Glomerular hypertrophy and enhanced accumulation of extracellular matrix proteins were detected in diabetic kidney. The mRNA and protein levels of KMT (DOT1L, SETD7, EHMT1, EHMT2, EZH1, EZH2) and KDM (KDM1A, KDM2A, KDM3A, KDM4A, KDM5A, KDM5B) subtypes were found significantly elevated in the kidney of diabetic mice as compared with non-diabetic animals. Treatment of diabetic mice with UA suppressed the up-regulation of KMTs and KDMs. High glucose-induced increased expression of the archetypal KMT and KDM subtypes was significantly reduced by UA in cultured endothelial cells.
Conclusion: Selective triterpenic acids are generally acknowledged as potential medicines for the treatment of a wide range of human pathologies. In this study, we provide evidence that ursolic acid prevents the alterations in gene and protein expression levels of archetypal KMTs and KDMs in the kidney of diabetic mice. Ursolic acid or its pharmacologically active chemical derivates may become important therapeutic tools to prevent epigenetic

instability and the ensuing gene expression and phenotypic alterations in DKD.
Funding: Work supported by UEFISCDI (PN-III-P4-ID-PCE-2020-1898, PN-III-P1-1.1-TE-2021-0180, PN-III-P2-2.1-PED-2019-2497, PN-III-P2-2.1-PED-2019-2512).

PS-04-009

A multihierarchical terminology for non-neoplastic kidney biopsies: kidney biopsy codes for pathologists

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Background & objectives: A kidney biopsy is often the only option to correctly diagnose a kidney disease and to gain information about prognosis and possible treatment. However, an international standardized system for coding morphological findings and diagnoses has been missing.
Methods: An expert workshop defined the principles for the Kidney Biopsy Codes for Pathologists (KBC) system. Based on experience, literature review, and 60 nephropathology reports, a terminology with synonyms and parent-child relationships was established. Then, a project-internal review process and a second workshop were carried out. Several visualisations of the system have been developed using R/Shiny.
Results: The aim of the Kidney Biopsy Codes for Pathologists project (KBC, https://kibico.org/) is to establish a comprehensive coding system for non-neoplastic kidney biopsies. KBC currently consists of 576 active concepts, of which 168 belong to a compact and 408 to a detailed set of terms. The KBC structure is multihierarchical with a pattern of injury (276 concepts) and a disease concept axis (266 concepts) as well as attributes (43 concepts) including qualifiers for certainty (3 concepts). Concepts are further grouped according to kidney compartments. For each concept, a preferred term and synonyms have been defined.
Conclusion: A comprehensive coding system for non-neoplastic kidney diseases is established. In order to provide governance and to promote use within existing frameworks, the KBC team aims to collaborate with SNOMED international to make a subset in SNOMED CT. Finally, an international review process will be conducted.

PS-04-010

Association of amyloid deposits with C4d immunohistochemical staining in kidney allografts on the onset of AA amyloidosis recurrence

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Background & objectives: Serum amyloid A protein-related AA amyloidosis can lead to ESRD,therefore renal transplantation. Surveillance of allografts with C4d immunohistochemical staining assesses humoral rejection.Immune complex-mediated diseases and amyloidosis describe positive staining.We analysed the C4d immunohistochemical staining pattern in allograft biopsies with recurrent amyloidosis.
Methods: This retrospective analysis included allograft biopsies performed in our centre that were previously positive for amyloid with congo red and C4d evaluation. Amyloidosis scoring and description of C4d immunohistochemical pattern staining (glomerular, vascular, interstitial and/or capillary peritubular) were evaluated, and C4d staining was correlated with congo red staining.
Results: 41 biopsies belonging to 22 patients were analysed. Among the indication of biopsy were graft dysfunction (n=9; 40,9%), non-nephrotic proteinuria (n=5; 22,7%) and nephrotic proteinuria (n=8; 36,3%). During the investigation 12 graft cases had preserved function, 6 cases had graft dysfunction and 4 patients died. Amyloid deposits were frequently founded in arteriolar vessel walls (N=12; 54,5%) and combined glomerular/vascular staining (n=6;45,4%). There was one biopsy with C4d insufficient staining, in 5 cases the amyloid deposits were small and the evaluation of C4d and congo red at the same time was necessary. In the other cases, C4d staining highlighted amyloid deposits within blood vessels and glomeruli.
Conclusion: Amyloid deposits in recurrent AA amyloidosis in kidney allografts show a distribution over blood vessel walls. This nonspecific finding at the walls of the arterioles is seen as well in arteriolar hyalinization, in contrast, glomeruli staining with arteriolar staining seems to be more specific for amyloidosis. C4d can be used as a marker for amyloid using mass spectrophotometry identifying C4d protein as part of the AA amyloid component.

PS-05 | Poster Session Ophthalmic Pathology

PS-05-001

Conjunctival Melanoma in Ireland – a sixty year review

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Background & objectives: Conjunctival melanoma is a rare ocular neoplasm with an unpredictable pathological course. Reported incidences vary from 0.1–0.9/1,000,000. Lack of population studies coupled with the rarity of the tumour has resulted in poor understanding of risk-factors and limited therapeutic options.
Methods: A retrospective review of all cases of conjunctival melanoma accessioned in the largest eye unit in Ireland over a 60 year period (1961 – 2021) was performed. The age, sex, eye laterality, size of tumour, development of metastasis and/or recurrence was determined. Genome sequencing was performed on a select number of samples from the cohort and any mutations found recorded.
Results: 72 cases of conjunctival melanoma were diagnosed since 1961. There was a female preponderance (n = 42, 58.3%). Median age of diagnosis was 77 (Range:32-91). Tumour size varied from 5–56mm in maximum dimension. Thirty-five (48.6%) have died. Time of death ranged from 1 month to 12 years post diagnosis.
28 (40%) developed metastases (brain, lung, liver, kidney, bowel, thyroid, prostate, parotid, lymph nodes), 20 (28.6%) developed recurrences. The left eye was more commonly affected (n=36, 50%).
14 of 70 specimens dating back to 1996 were sent for analysis with either Sequenom or Oncomine platforms. Mutations were detected in 12 patients. These included PIK3R1, M326I, PIK3CA, MET, N3755, BRAF and NRAS.
Conclusion: Conjunctival melanoma is a rare neoplasm with only 72 cases diagnosed in Ireland in the last 60 years. Recurrence and metastases are common.
Options for treatment of conjunctival melanoma include excision, cryotherapy, corneal epitheliectomy, radiotherapy and topical mitomycin C. Adjuvant therapy is limited, with conjunctival melanomas showing intermediate sensitivity to immunotherapy.
Extended follow up of patients will allow identification of risk factors for the disease, while further genetic sequencing will enable identification of potential therapeutic targets.

PS-05-002

Uveal melanoma: ten years of experience and behaviour in the Principality of Asturias. A retrospective analysis

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Background & objectives: Uveal melanoma (UM) is the most common primary intraocular neoplasm in adults, arising from melanocytes located in the iris (4%), ciliary body (6%), or choroid (90%). It represents 2 cases per million per year in Spain and Italy (Southern Europe).
Methods: We performed a descriptive and retrospective analysis for ten years (2011-2021) on patients diagnosed of UM from different public medical institutions from the Health Service of the Principality of Asturias (SESPA). The information was obtained through the Hospital Registry of Tumours in Asturias.
Results: Twenty-five patients were included in this study with a median age of 62-year-old. Predominant histologic subtype was epithelioid melanoma (28%), followed by spindle cells (24%) and mixed (24%), subtype was not available in 6 patients (24%). Most of them presented as local stage (64%) and underwent radical surgery (88%). Most cases affected the choroid (80%) and a smaller group the ciliary body (20%). We found no cases with iris involvement. A small percentage (8%) required radiotherapy and immunotherapy respectively. Four patients died with a mean of 4,43 years after diagnostic, three of them with metastatic disease. The other patients are being followed-up at the referral hospital.
Conclusion: In recent years, numerous advances have been made in genetics and behaviour of UM. However, despite these efforts, survival has not been improved and once metastatic disease progresses, the prognosis is poor and therapeutic options are very limited. The heterogeneity of the molecular pathways involved in this pathology has hindered the development of a specific drug for advanced disease. Therefore, more studies are needed to achieve this.

PS-05-003

Retinoblastoma in Ireland; the next generation sequencing molecular profiles of selected enucleation cases with a special focus on non-RB1 mutations and a comprehensive review of the retinoblastoma caseload in Ireland over the past 20 years

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Background & objectives: Increasingly, retinoblastoma has been linked to somatic gene abnormalities beyond RB1, especially BCOR, a BCL-6 co-repressor gene. Our aim is to assess the molecular profile of selected retinoblastoma specimens and to review 20 years of retinoblastoma in the Irish population.
Methods: Using the hospital database of the national ophthalmic centre, all enucleation specimens for suspected retinoblastoma performed in Ireland over the past 20 years (2001 – 2020) were analysed under various headings, including age at surgery, sex, laterality, diagnosis, and histopathological features including tumour differentiation, extent and stage. 6 selected cases were sent for somatic molecular analysis using next generation sequencing.
Results: 65 enucleations were performed on 63 children. 61 specimens showed retinoblastoma. On average 3.2 surgeries were performed per year. 41% were female, 59% male. The average age at surgery was 2.72 years. 8% of the patients had undergone neoadjuvant therapy prior to the enucleation procedure. 75% of the tumours were moderately to poorly differentiated, 61% had optic nerve invasion and 5% had a positive optic nerve margin. 5 of the cases referred for molecular profiling had a somatic RB1 variant. The remaining case, a 3 year old patient with a left sided, high grade, poorly differentiated retinoblastoma was found to have a mutation in BCOR, with no associated RB1 mutation.
Conclusion: Our review shows that the rate of performance of enucleations for retinoblastoma in the Irish population over the past 20 years has remained stable. We identified a non-RB1 BCOR mutated retinoblastoma, associated with a high pathological grade. This supports the literature in highlighting BCOR as the most common non-RB1 gene to be mutated in retinoblastoma, and the importance of molecular profiling to identify non-RB1 somatic mutations and potentially higher grade, more aggressive tumour types to improve patient treatment.

PS-05-004

Histopathologic findings of lens capsule and persistent hyperplastic primary vitreous of Korean juvenile cataract patients

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Background & objectives: Persistent hyperplastic primary vitreous (PHPV) is a rare congenital anomaly in which the regression of the hyaloid vessel fails and primary vitreous persists after birth. The purpose of study was to determine the histologic features of congenital cataract and PHPV.
Methods: Histopathologic examination of a total of 142 lens capsules from a retrospective cohort study of 106 consecutive unilateral and bilateral Korean juvenile cataract patients was conducted. Retrolenticular membranes of the 12 PHPV patients were reviewed for histology and immunohistochemistry with antibodies of CD31, CD34, Von Willebrand factor, Cytokeratin, Vimentin and TGF-β1 were performed.
Results: 1) The frequency of PHPV in unilateral and bilateral Korean juvenile cataract patients was 11.3% (12/106). 2) Characteristic histologic features of PHPV, hypercellular membrane tissue consisting of either vascular structures and/or mesenchymal cells, were found in 75% (9/12) of cases at an age younger than 123 months. However, the hyaloid arteries and endothelium-lined blood vessels in the retrolenticular membranes were found only in 3 cases. 3) Six cases, including one case of bilateral PHPV, showed only mesenchymal cells. Three cases of clinically diagnosed PHPV did not show fibrovascular membranes by histology. 4) Endothelial cells of the vessels but not mesenchymal cells expressed TGF-β1 by immunohistochemistry.
Conclusion: 1) Not all cases of PHPV have vascular structures in the retrolenticular membrane tissues. 2) Mesenchymal cells with or without vascular structures are found in most of cases (80%), which suggests that the vascular mesenchymal transformation could be one of the possible mechanisms in the process of vascular regression of PHPV. 3) Mesenchymal transition of remnant foetal vascular structures in PHPV is independent of the patient's age at the time of operation, or the size of retrolenticular membranes.
Funding: This work was supported by a grant from Research year of Inje University in 20150684.

PS-06 | Poster Session Paediatric and Perinatal Pathology

PS-06-001

Paediatric soft tissue malignant tumours: a 16 year experience with literature review

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Background & objectives: Paediatric soft tissue tumours are rare heterogeneous group. Although most tumours are benign, developing an appropriate diagnosis requires knowledge of clinical and radiologic characteristics. The objective of our study is highlight the clinico-pathologic characteristic of paediatric soft tissue malignant tumours.
Methods: A total of 25 cases of soft tissue malignant tumours diagnosed in children under 16 years at the Department of Pathology of Farhat Hached University Hospital in Sousse, over a period of 16 years (from 2005 to 2020). A review of clinical, paraclinical, pathological and evolutionary data was performed in all cases.
Results: These were 9 female and 16 male, with an average age of 9 years. The average diagnosis time was 7 months. The main clinical presentation was abdominal mass. The main tumour size was 7,15 cm. 7 tumours were in upper limbs and 18 were in lower limbs. MRI was an essential exam for the diagnosis. There were 8 Ewing sarcoma/PNET (32%), 5 rhabdomyosarcoma (20%), 3 fibrosarcoma (12%), 2 dermatofibrosarcoma protuberans (8%), one inflammatory fibroblastic sarcoma (4%), one low grade fibromyxoid sarcoma (4%), one kaposi sarcoma (4%) and one myxoid liposarcoma (4%). Treatment is a combination of chemotherapy, surgery, and radiation. 5 patients were dead and 20 are still alive.
Conclusion: Evaluation of paediatric soft-tissue tumours can be challenging. To formulate a differential diagnosis and, ultimately, diagnose a presenting lesion, the clinician should have an organised and systematic approach to the evaluation. Biopsy is a relevant and indolent exam for the diagnosis. Sarcomas represent the most common paediatric soft tissue cancers. To optimize their management and survival, patients should be treated at specialised centres to provide appropriate therapy and follow-up.

PS-06-002
The role of preeclamptic stem villi obliterative angiopathy in the prognosis of newborn status
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Background & objectives: The prevention of ischemic changes in the placenta, where obliterative angiopathy of the villus vessels plays a leading role, requires the development of an objective prognosis tool. 70 placentas from women with preeclampsia of varying severity, 20 from healthy women.
Methods: Morphometry was carried out using the Leica Application Suite module, Leica DM4000B. Micromorphometric indicators were determined: the area of the stem villi, the area of the lumen of the arterioles; diameters and areas of arterioles, including their wall thickness; measurements were made in 20 stem villi, the arteriole obliteration degree was calculated according to the coefficient Kco = Saт\Sa.
Results: Foetal distress manifestation in preeclampsia depends on the severity of obliterative angiopathy. The normal significance of the obliteration coefficient for arterioles1-2 the order of stem villi was 1.18-1.34, for the 3rd -1.19-1.37. With an increase in the obliteration coefficient of arterioles of the 1st and 2nd order of villi more than 1.34, and of the 3rd order more than 1.37, the frequency of chronic intrauterine hypoxia increased to 61.0%and 59.4%, respectively. The increase of this indicator in the combination of preeclampsia with extragenital pathology over 1.89 for villi of 1-2orders and 1.92 of 3rd was accompanied by the addition of an increase in intrauterine growth restriction to 31.3% and 29.6%, respective.
Conclusion: The coefficient of arteriole obliteration is directly proportional to the incidence of chronic intrauterine hypoxia. When the placental villi arteriole obliteration coefficient exceeds critical value, the frequency of chronic intrauterine hypoxia and intrauterine growth restriction occurring in combination increases significantly. The significance of obliterative angiopathy in preeclamptic placentas in the functional state of the foetus and newborn was confirmed, and a prognostic model was created to calculate the probability of its occurrence.

PS-06-003
Immunohistochemical characteristics of the vessels of the supporting villi of the placenta during preeclampsia
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Background & objectives: Morphological changes in the vessels in preeclampsia are not sufficiently reflected in the literature, especially for the stem villi and their branches. There are no clear morphological criteria for assessing the severity of hypoxia of a newborn.
Methods: Studied 70 placentas from women with preeclampsia of varying severity, 20 placentas from healthy women. A macro- and microscopic examination of the placenta was carried out according to the generally accepted method. Immunohistochemical markers were used: CD34 (clone QBEnd\10), VEGF-A, eNOS. The level of expression of immunohistochemical markers was assessed in points: 0-no reaction, 1-weak reaction, 2-moderate reaction, 3-pronounced reaction.
Results: Immunohistochemical markers detailed the cells producing these factors in the vessels and stroma of supporting villi. Using the CD34 marker, hyperplasia and desquamation of endotheliocytes were revealed with a pronounced formation of reticulate structures in arterioles (placental endotheliosis) and its "palisade" location in venules. A decrease in the expression of eNOS and VEGF-A was clearly accompanied by the presence of rheological disorders in the vascular bed, there was a progression of collagenization of the supporting villi stroma with the formation of perivascular sleeves and obliteration of the lumen of their vessels with signs of reduction of the paravascular bed.
Conclusion: Morphological changes in the supporting villi are most pronounced in pregnancy complicated by preeclampsia. The lack of conditions for the implementation of compensatory reactions at the tissue level in the presence of preeclampsia exacerbates the severity of placental insufficiency, the development of obliterative angiopathy of the vessels of the stem villi, a decrease in blood flow in the capillaries of the terminal villi, which significantly worsens the prognosis for foetal development, increases the risk of adverse perinatal outcomes.

PS-06-004
Foetal autopsy: causes of foetal death
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Background & objectives: Perinatal mortality remains globally unacceptably high with up to three million stillbirth every year. Intrauterine foetal death and stillbirth are crucial part of perinatal mortality. Autopsy, correlated with clinical data, remains the “gold standard” for identifying causes of foetal death.
Methods: A cross-sectional study, during the 2018 year, was performed by reviewing autopsy reports from the Institute of Pathology, Faculty of Medicine University of Belgrade. It was 1171

autopsies generally, among them 146 foetal. Based on autopsy findings, we identify the most common causes in perinatal death. Data were analysed using methods of descriptive statistics.
Results: The clinical diagnoses were: anomalies 45, intrauterine death 42, chromosomal aberrations 18, placental and umbilical lesions 10, spontaneous abortion 2, tumour 3 and multiple causes 26. Autopsy confirmed anomalies are the most frequent primary disease and cause of death (56%), where CNS anomalies were leading lesions (41%). Based on patohistology general asphyxia is the following cause of foetal death in 47%. Asphyxia was associated mostly with placental lesions (37%) as a result of vascular placental changes, followed by inflammation in women older than 35 years. We found the highest association of chromosomal aberrations in the same mother's ages. Foetal anomalies were mostly found in women younger than 25 years.
Conclusion: Anomalies and asphyxia are the most frequent cause of foetal death between 26-35 gestation weeks. Foetal asphyxia as a result of placental ischemic lesions, umbilical cord pathology is mostly seen in mothers older than 35 years. In the same age group were mothers of foetuses with chromosomal aberrations. Foetal anomalies are mostly found in mothers younger than 25 years.

PS-06-005
The association of mir-204 and mir-483 5p expression with clinicopathological features of Wilms tumour: could provide foresight?
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Background & objectives: Wilms tumour(WT) is the most common neoplasm of the kidneys in childhood. With the improvement of up-to-date treatment protocols, an increase in survival rates in WT was observed. However, metastases or local relapses are still observed in 15% of patients.
Methods: The evaluation of genetic and epigenetic features such as miRNA analyses might allow us to comment on the behaviour of the tumour and the treatment response. For this purpose, expression levels of mir-204 and mir-483-5p were evaluated in tumoral and normal tissue by qRT-PCR. The relationship of miRNA expression levels with clinicopathological, histological features, and survival was also investigated.
Results: This study recruited 24 WT cases who had paraffin blocks available for the study. Anaplasia (focal and diffuse) was identified in six patients(12%) based on the distribution of anaplastic changes. The result of the study indicated that the relative expression levels of mir-204 in WT tissues were significantly lower than that in adjacent normal tissues(mean value0.11). In contrast, tumour tissue had higher miR-483-5p expression than corresponding normal tissues. A statistically significant association between miR-204 expression level with age and the presence of anaplasia was observed in this study. Significantly high levels of miR-483-5p expression were found in cases who underwent preoperative CT compared to those who did not receive CT.
Conclusion: According to the literature data, decreased expression of miR-204 is associated with a poor prognosis. Our findings also suggest that poor prognostic data are accompanied by a downregulation of miR-204. In our study mir-483-5p expression level was found to be higher in patients who underwent preoperative CT compared to patients who did not receive CT. Of particular interest is the finding that the mir-483-5p can be a promising biomarker in the early detection of CT response in WT.

PS-06-006
Histopathological assessment of placenta in maternal SARS-CoV-2 infection
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Background & objectives: The placenta represents an important witness of pregnancy and its related complications in SARS-CoV-2-infected mothers. We aim to evaluate specific histopathological placental changes associated with maternal SARS-Cov-2 infection and their correlation with pregnancy dynamics.
Methods: The study includes 36 pregnant women, with pregnancy age ranging from 11 to 42 weeks, admitted between September 2020 and February 2022 with positive nasopharyngeal RT-PCR for SARS-CoV-2. All placenta specimens were macroscopically and histologically examined, the slides being conventionally stained with Hematoxylin and Eosin and immunohistochemically stained for CD8, CD68, and CD20.
Results: Of the 36 women, 34 (94.44%) had singleton pregnancies, one (2.77%) had twin pregnancy, and one (2.77%) had quadruplets. 28 (77.77%) pregnancies were term deliveries, with one (2.77%) placenta accreta and one (2.77%) marginal placenta praevia, two (5.55%) were miscarriages, and 4 (11.11%) were foetus exitus. The histopathological assessment revealed chorioamnionitis in 9 (25%) cases, foetal vascular malperfusion in 15 (41.66%) cases, villitis and chronic intervillositis in 8 (22.22%) and 4 (11.11%) cases, chronic deciduitis in 4 (11.11%) cases, hematomas in 7 (19.44%) cases, infarction in 11 (30.55%) cases. All placentas showed an association of these abnormalities, the local inflammatory response being underlined by positive immunoexpression of studied markers.
Conclusion: SARS-CoV-2 infection in pregnant women is associated with an increased frequency of placental histopathological abnormalities, especially foetal vascular malperfusion, various inflammatory lesions, infarction, and hematomas. In complicated pregnancies of patients with SARS-CoV-2 infection, histopathological evaluation of the placenta, supported by a specific panel of antibodies, may help elucidate the pathological mechanisms that occur at the foetal-maternal interface associated with COVID-19 infection, providing additional data in the obstetrical management of this pathology.

PS-07 | Poster Session Digestive Diseases Pathology - GI

PS-07-001
Podoplanin expression in neoplastic cells and cancer-associated fibroblasts in colorectal cancer predicts unfavourable clinicopathological features
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Background & objectives: The pattern of activity of the cellular elements that compose the tumour microenvironment influences tumour behaviour. To analyse the activity of cancer cells (CCs) and cancer-associated fibroblasts (CAFs) in colorectal cancer (CRC), based on the expression of podoplanin stratified by tumour-stroma ratio.
Methods: We performed immunohistochemistry for podoplanin on tissue microarrays from 357 cases of colorectal adenocarcinoma (CRA). The tumour-stroma ratio (TSR) was evaluated: stromal percentage ≤50%- stroma low; >50%-stroma-high. The expression of podoplanin was evaluated in different areas: TSR, most invasive, centre of tumour, tumour budding, and desmoplastic stroma. The

association between the markers and clinicopathological parameters, including TSR, was evaluated.
Results: Immunostaining of podoplanin was detected in CCs and CAFs, with positivity of 36.8% and 70%, respectively. Higher positivity of podoplanin in CCs was observed predominantly at TSR area: 64.3% of cases. Status podoplanin CAFs+ was higher in the desmoplasic region (71.6%). Stroma-high tumours showed increased expression of podoplanin in CCs and CAFs in comparison with stroma-low tumours. The status of podoplanin in CCs was observed in association with women (p=0.042), angiolymphatic involvement (p=0.021; p=0.047) and distant metastasis (p=0.014).
Conclusion: In the CCR microenvironment, CAFs and CCs express podoplanin. Our research found an increase in podoplanin expression in high stromal tumours, known to be more aggressive than low stromal tumours, and an association with angioinvasion and distant metastasis. The expression of this marker, in CRA stratified by tumour-stroma ratio, contributes to aggressive behaviour. It may represent a patient stratification tool, in the prediction of possible outcomes.

PS-07-002
IgG4 as a biomarker for inflammatory bowel disease
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Background & objectives: Inflammatory bowel disease (IBD) is a non-specific inflammatory condition affecting the gastrointestinal tract. The pathogenesis of IBD is insufficiently understood, but a key role is attributed to immune dysregulation. Our objective was to approach the IgG4 contribution to mucosal injury.
Methods: We conducted a case-control study comprising 12 patients with IBD with different stages of disease activity (remission, mild, moderate, severe), and we focused our research on immunohistochemical identification and quantification of IgG4+ plasma cells found in lamina propria. The infiltration of IgG4+ plasma cells in patients with IBD was compared with plasma cells level of 12 healthy control individuals.
Results: Patients with IBD had higher intestinal mucosal IgG4 counts than normal colonic mucosa (over 10 times more plasma cells IgG4+ in IBD per 10 HPF). Cases of ulcerative colitis (UC) showed higher numbers of IgG4+ plasma cells in lamina propria, compared to patients with Crohn disease (CD) for the same stage of activity. Mucosal infiltration of IgG4+ plasmocytes in active disease was higher comparative to remission stage of disease, as it follows: 5 IgG4+ per 10 HPF when CD is remitted and up to 25 IgG4+ in severely active CD, in contrast to 13 IgG4+ in remitted UC which goes up to 33-41 IgG4+ in moderately to severely active UC.
Conclusion: Our study led to the following conclusions:
The potential pathogenic involvement of B cell lineage in the pathogenesis of IBD deserves further research and in-depth studies, as it may contribute to personalized therapy.

PS-07-003
MMR proteins and PD-L1 status: impact on gastric adenocarcinoma's prognosis
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Background & objectives: Deficient MMR proteins and PD-L1 expression have been shown to be prognostic factors[H1] and predictive biomarkers for anti-PD-1 immunotherapy in gastric adenocarcinoma(GA). We aimed to assess the expression of MMR proteins and PD-L1 in GA with clinicopathological features and survival.
Methods: This was a retrospective and descriptive study including 143 GA diagnosed at the Department of Pathology of Habib Thameur hospital (2001-2018). Evaluation of MMR proteins and PD-L1 status was carried out by immunohistochemistry. The combined positive score (CPS) was calculated for PD-L1 with a threshold of 1.
Results: The frequency of deficient MMR proteins (dMMR) GA was 30.1%. There was no significant association, in univariate and multivariate analysis, between MMR proteins and clinicopathological parameters. dMMR GA were PD-L1+ in 24%. The frequency of PD-L1+ GA was 21.7%. Medullary histological subtype according to World Health Organisation classification (p<0.001), intestinal subtype according to Lauren classification (p=0.014), lymphoid stroma reaction (p=0.004) were predictors of PD-L1+ status. Median survival was 16 and 18 months for patients with dMMR and PD-L1+ GA, respectively, with no significant association. PD-L1- status was associated with a poor prognosis.
Conclusion: One third of patients with GA have dMMR status. PD-L1- status is a factor of poor prognosis. Prognostic value of dMMR status should be investigated in a larger series.

PS-07-004
Pathomorphological and molecular genetic features of serrated colorectal lesions
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Background & objectives: Morphological diagnosis of serrated neoplasms today is based on the identification of a specific structure of formations in histological preparations. Therefore, the aim of our study was to identify molecular and biological features of serrated colorectal lesions (CSL).
Methods: We studied 481 cases of CSL (GP - 238, SSL - 201, and TSA – 42), stained with H&E and PAS-AB. For molecular-biological analysis, 69 observations of CSL were selected: SSL- 26, GP - 26, TSA - 17. The immunohistochemical panel included: CK20, Ki67, MUC2, MUC5AC, MUC6, MLH1, PMS2, MSH2 and MSH6. KRAS/BRAF/NRAS gene mutations were determined by real-time PCR.
Results: CSL show immunophenotypic signs of both colorectal differentiation (expressed expression of more than 50% of all cells of the markers MUC2 and CK20) and gastric differentiation (appearance of MUC5AC and MUC6 expression, focal positive PAS-AB staining). MUC6 expression is characteristic only for SSL. The malignisation pathway of SSL was associated with the presence of a BRAF gene mutation (53.8%) and high grade microsatellite instability (34.8%), while that of TSA was associated with a KRAS gene mutation (47.1%) and MSI-H (40%). The KRAS (15.4%), BRAF (38.5%) and MSI (60%) gene mutations detected in HP confirm their role in serrated carcinogenesis. The NRAS gene mutation was not detected in serrated colorectal lesions.
Conclusion: CSL show immunophenotypic signs of both colorectal differentiation and gastric differentiation. The malignisation pathway of CSL was associated with the presence of a BRAF gene mutation and MSI-H. Genetic mutations found in hyperplastic polyps, in combination with immunophenotype confirm their role in serrated carcinogenesis

PS-07-005

Tumour infiltrating lymphocytes (TILs) relate to PD-L1 expression and provide prognostic value in stage II and III colon cancer patients

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Background & objectives: Tumour-infiltrating lymphocytes (TILs) and PD-L1 expression have been suggested as markers of immune-response in colon cancer also providing prognostic value. The aim is to assess TILs in the invasive primary tumour front, its relationship with PD-L1 expression and clinical outcomes.
Methods: In a cohort of 140 patients with stage II/III colon cancer, TILS were assessed according to the TILs Working Group standardized methodology and underwent automatic immunohistochemical staining for PD-L1. Clinical outcomes assess were disease-free survival and overall survival. The percentage of TILs score was categorized into low (≤ 5%), intermediate (≤ 10%), high (≤ 20%), and highest (> 20%).
Results: Assessment of TILs in the intermediate category and above in the tumour sample was statistically significantly related to PD-L1 expression. The higher percentage of TILs found, the stronger association with PD-L1 expression ($p<0.001$). There was no significant difference between TILs assessment and Stage II or III nor any other baseline characteristic. Category high TILs showed statistical significance for disease free survival HR=0.40 95%CI [0.23-0.95] independent of sex, age, TNM stage and localization.
Conclusion: Our results suggest that TILs and PD-L1 expression are closely related. In addition, the presence of TILs in the tumour microenvironment seem to provide a positive prognostic value in early stage colon carcinoma. Immunotherapies that aim to stimulate an immune response may benefit from TILs assessment as a predictor for PD-L1 expression, in addition to its prognostic value.

PS-07-006

Novel patterns of V-set and immunoglobulin domain containing 1 expression in gastric cancer

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Background & objectives: V-set and immunoglobulin domain containing 1 (VSIG1) is an intercellular-adhesion molecule expressed in the membrane of the normal gastric mucosa. The aim of this study is to report the possible significance of VSIG1 cytoplasmic translocation in gastric cancer.
Methods: Based on VSIG1 immunohistochemical (IHC) expression in tumour core and front in 94 cases, three patterns were established: homologous type I (membrane/membrane), homologous type II (null/null) and heterologous cases (membrane/cytoplasm or cytoplasm/null). VSIG1 status was correlated with clinico-pathological features (TNM stage and Dukes-MAC-like stage, molecular phenotype) and survival rate.
Results: From the 94 cases, 21.27% showed homologous type I expression, with the same percentage for cases with heterologous patterns. The rest of 57.46% demonstrated homologous type II pattern. Heterologous patterns were indicators of aggressive behaviour, such as advanced Dukes-MAC-like stage ($p=0.02$), lymph node metastases ($p=0.03$) and mesenchymal tumour phenotype, with loss of E-cadherin expression ($p=0.004$) and nuclear translocation of β-catenin ($p=0.0007$). Cytoplasmic expression was more frequently seen in poorly differentiated/undifferentiated carcinomas. In cases with heterologous pattern, overall survival was significantly poorer, compared to that of cases with homologous expression ($p=0.0005$).
Conclusion: In gastric carcinomas, VSIG1 cytoplasmic positivity might be an indicator of mesenchymal phenotype, and thereby, a marker for dismal prognosis, aggressive behaviour and shorter overall survival.
Funding: This work was supported by the Romanian National Authority for Scientific Research, Project no. 20-PCCF/2018

PS-07-007

Serum and mucosal CD30 in paediatric inflammatory bowel diseases (IBD): useful biomarkers for diagnosis and disease activity monitoring?

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Background & objectives: The underlying immune pathophysiology of IBD is incompletely understood, rendering quick diagnosis followed by tailored therapy difficult. The TNF superfamily receptor CD30 has been proposed as potential marker of ulcerative colitis (UC), and has been associated with elevated Th2 cells.
Methods: In this study we evaluate a cohort of 94 paediatric patients with UC and Crohn's disease (CD) for serum soluble CD30 (sCD30) using ELISA, and expression of CD30 and subpopulations of Th1/Th2/Th17 lymphocytes in the gastrointestinal mucosa using flow cytometry (FCM). The dataset is supported by endoscopic and microscopic activity of disease and basic laboratory markers of inflammation.
Results: sCD30 was not associated with diagnosis of CD or UC. However, sCD30 levels correlated with levels of CRP, ESR, faecal calprotectin and albumin and also with clinical activity of the disease in both UC and CD patients. FCM was not helpful in evaluation of mucosal CD30, which was lowly expressed and not associated with diagnosis or disease activity. We show augmented Th2 and Th1/17 response in the terminal ileum and right-sided colon and decreased Th1/17 response in left-sided colon of UC patients. T lymphocyte subsets were also affected by anti-TNF treatment and patients' age.
Conclusion: Neither sCD30 nor FCM evaluated mucosal CD30 were helpful in the diagnosis of paediatric UC. sCD30 seems to be marker of systemic inflammation and clinical activity of the disease.
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PS-07-008

Assessment of immune T cells expression in colorectal cancer

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Background & objectives: Colorectal cancer(CRC) is the second most deadly cancer worldwide. CRC recurrence is at the origin of this high mortality.Resistance to chemotherapy remains one of the greatest challenges causing recurrence. Our study specifically addressed the expression of immune Tcells in CRC.

Methods: Immunohistochemical analysis was performed on a total of 23 patients with CRC and 18 adjacent normal tissues. Membranous expression of CD4, CD8 and nuclear expression of FOXP3 were analysed in T cells infiltrating the tissues in three different fields of the stained slides. Clinico-pathological characteristics were recorded.
Results: Patients mean age range was 63.9 years. CD4, CD8 and FOXP3 markers were significantly expressed in CRC tissues compared to normal tissues (Mann Whitney U test: CD4 p=0,0034 ; CD8 p<0,0001 ; FOXP3 p=0,0019). Interestingly, high percentage of CD8 positive expression was reported in CRC (near 30%) compared to CD4 and FOXP3 (not exceeding 4%) suggesting a high cytotoxic T cell infiltration. CD8high expression was found mostly in CRC without perineural invasion versus those with perineural invasion (p=0.042).
Conclusion: Altogether, our results showed the high expression of T cells infiltrating the tumour in CCR. Perineural invasion should be taken into consideration to design crucial strategies for CRC treatment.

PS-07-009
HLA-E proteins expression and clinical relevance in colorectal cancer
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Background & objectives: Human leukocyte antigen(HLA)-E is a non-classical HLA class I molecule implicated in immune cells modulation. Many studies proposed HLA-E molecule as a predictive biomarker for cancers' outcome. We aimed to characterize the HLA-E expression in colorectal cancer(CRC) according to clinicopathological characteristics.
Methods: HLA-E expression was studied in tumour tissues and adjacent normal tissues from 22 CRC patients by immunohistochemistry. HLA-E expression was found at the surface of cells. Labelled tumour cells percentage determined semi-quantitatively was correlated to clinico-pathological parameters.
Results: Patients mean age range was 64 years. HLA-E expression was significantly expressed in CRC tissues compared to normal tissues (100% and 86.6% respectively; Mann-Whitney U test: $p < 0.0001$). Moreover, high expression of HLA-E was revealed in patients exceeding 63 years, in those with early tumour stages (stage I and II), in those without lymph nodes metastasis, and in those with well differentiated tumours without significance.
Conclusion: Our results suggest that HLA-E is implicated in CRC promotion and could be proposed as a candidate biomarker for CRC. Its prognosis value remains to be confirmed through a wider study population.

PS-07-010
Epstein-Barr virus infection in chemoradiotherapy-naïve gastric adenocarcinoma: relationship with PD-L1 Expression and survival
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Background & objectives: EBV has emerged as a prognostic biomarker in gastric adenocarcinomas (GA). EBV associated GA (EBVaGA) accounts for 10% of GA and comprises amplification of PD-L1.We aimed to assess EBV status and PD-L1 expression in GA with clinicopathological features and survival.
Methods: We performed tissue microarray slides from 143 GA patients treated with radical gastrectomy. PD-L1 expression was evaluated through immunohistochemistry (Combined Positive Score ≥1) and EBV status through chromogenic in situ hybridization. Differences in overall survival (OS) were assessed using the Kaplan-Meier method, log-rank test and Cox proportional hazards regression model.
Results: EBVaGAs accounted for 33.6%. They were associated with male gender (70.8%; p=0.020). The tumours were in the antrum (54.2%) with tumour size > 6 cm (52.2%). According to WHO classification, they were classified as poorly cohesive adenocarcinomas (43.8%). According to Lauren classification, they were classified intestinal subtype (45.8%), diffuse (43.8%) and indeterminate (10.4%). Perineural invasion was observed in 68.8% of cases and vascular emboli in 85.4%. EBVaGAs were associated to pT1/pT2 stage (p=0.031), low rate of lymph node metastasis (p=0.029) and PD-L1+ status (p=0.016). EBV+ status was predictor to PD-L1+ status (p=0.018). Median survival was 17 months in patients with EBVaGA compared to 16 months in EBV negative GA.
Conclusion: The prevalence of EBVaGA is high in Tunisian population (33.6%). It is more frequent in poorly cohesive than tubular adenocarcinomas. EBVaGAs were more common in the antrum which does not fit reports in the literature. EBV+ status was a predictive factor to PD-L1 expression which suggests that patients infected with EBV may respond to PD-1 checkpoint inhibitors. This incites to further investigation of EBV carcinogenesis for therapeutic targets to select high-risk patients.

PS-07-011
Ckit mutations in patients with gastrointestinal stromal tumours
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Background & objectives: CKIT mutations are oncogenic drivers for gastrointestinal stromal tumours (GISTs). They also function as predictive markers for response to imatinib. We studied various histologic types of GISTs, risk stratification, types of Ckit mutations and correlated with survival.
Methods: Histology and immunohistochemistry of 98 patients diagnosed with GIST were reviewed retrospectively. Histologic risk stratification was derived using CAP protocol. Sequencing results for Ckit exons 9,11, 13 and 17 were documented. Histologic and molecular parameters were correlated with survival. Clinical data was derived from electronic medical records.
Results: Immunohistochemistry for Ckit and DOG1 was positive in 98% of tumours; 2% being positive for DOG1 only. The histological risk groups were not associated with statistically significant differences in PFS (p=0.6) or OS (p=0.7). Ckit mutation rate was 73%, Exon 11 mutations were found in 75% of patients, exon 9 in 19%, exon 13 in 4.1 % and exon 17 in 5.5 % respectively. All patients with exon 9 mutations had consistent duplication c.1504_1509dupGCCTAT. Decision of dose escalation of imatinib or change to second line TKI was made in all patients with ckit exon 9 mutation. No statistical difference could be demonstrated among different mutational types when correlated with survival.
Conclusion: Overall Ckit mutation rate was lower (73%) than reported in literature, thus concluding that incidence of ckit mutations could be lower in Indian population. Ckit exon 9 mutations had consistent duplication while deletions and substitutions were found in in exon 11. Exon 9 mutations guided treatment decisions. However, no statistical difference could be demonstrated among histological risk stratification and different mutational types when

correlated with survival which might be attributed to low numbers of low and intermediate category GISTs.

PS-07-012

Molecular landscape of rectal cancer patients up to 5th decade – the preliminary results

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Background & objectives: An availability of modern molecular solutions provided us a new insight into cancer genetic variations. In the current study we intended to perform a molecular screening of rectal cancer in young patients and then numerical analysis of cancer stem cells.
Methods: The ruling in criteria were the patient's age before 50years old, no previous radio- and chemotherapy, and eligible DNA for the next generation sequencing. The DNA was isolated from FFPE tissue. We used a Hot-Spot Cancer Panel by Illumina harbouring 50 genes (700 amplicons). To assess stem cell population we intend to use CD133, SOX-2, and Lgr5 antibodies.
Results: The average patient's age was 43-year-old. The female/male ratio was 1.4:1. The mean follow up time is 38 months. We observed a following mutation frequency: TP53 61%, KRAS 58%, APC 47%, PIK3CA 19%, SMAD4 11%, FBXW7 11%, NRAS 9%, BRAF 7%, NRAS 5%, CTNNB1 4%, MLH-1 1%. We noted the co-occurrence KRAS/BRAF/NRAS mutation ($p<0.05$). Two cases did not present any mutation in the used panel. The immunohistochemistry and a statistical analysis is still in progress.
Conclusion: Our preliminary results indicate a rising number APC independent rectal cancer in a group of young patients. 40% of them presented multigene abnormality, where three to four mutations occurred the most common. Interesting is the fact of the evident contribution of the PIK3CA pathway and also 11% of SMAD4 which worsens the prognosis.

PS-07-013

Evaluating PTEN expression using immunohistochemistry in neuroendocrine tumours of the digestive tract and correlations with tumour grade and location - a seven-year retrospective study

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Background & objectives: Neuroendocrine tumours (NET) of the digestive tract are heterogeneous tumours, which despite similar morphology and grading have often distinct behaviour. We propose the use of PTEN immunohistochemical (IHC) expression for neuroendocrine tumours of the digestive tract as a prognostic factor.
Methods: 25 samples from patients diagnosed with neuroendocrine tumours from 2012 until 2018 were selected. All tumours were reclassified and graded based on 2019 WHO classification. Representative tissue sections were stained for Synaptophysin (clone 27G12; Leica), Chromogranin A (clone 5H7; Leica), Ki-67 (clone MM1; Leica), and PTEN (clone 6h2.1; Dako) using Leica BONDMAX fully automated staining system.
Results: Out of 25 cases, 18 were graded based on Ki-67 expression as NET G1 (72%), 5 as NET G2 (20%), and only 2 as NET G3 (8%) tumours. 8 cases presented PTEN negative expression of which 2 were NET G3 (100%), 3 were NET G2 (60%) and 3 were NET G1 tumours (16%) ($p=0.018$). 9 cases were localized in the small intestine, 9 in the large intestine, 3 in the stomach, and 4 in the appendix. All appendix tumours had positive PTEN expression. 3 gastric tumours had negative PTEN (100%), 1 small intestine case was PTEN negative (12%) and 5 cases from the large intestine were PTEN negative (56%) ($p=0.013$).
Conclusion: Neuroendocrine tumours of the digestive tract have a distinct molecular profile that is still troublesome to understand regardless of grade, localization as well as other clinicopathological factors. We propose using PTEN expression as a significant negative prognostic factor for patients with NET of the digestive tract based on tumour grade and localization, but larger studies on more patients from each group are required in order to introduce PTEN expression in the treatment protocols.

PS-07-014

Association between Immunoscore and budding in colorectal carcinoma

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Background & objectives: In colorectal carcinoma, the immunoscore (IS) and tumour cells budding (TCB) score are two emerging parameters that have an independent prognostic value. Our study aimed to research for significant association between IS and TCB score.
Methods: A total of 104 tumour specimens from patients after curative resection were reviewed. For the determination of the IS, we adopted a method described by Galon et al. It was scored into 2 groups through a semi-quantitative method. TCB score was rated according to the ITBCC criteria. Tumour buds were scored manually into 3 groups.
Results: The mean age of the patients was 61.6 years. The IS was low in 60.6%, and high in 39.4%. The TCB score at the invasive front was low, intermediate, and high in 53.8%, 22.1%, and 24% of cases, respectively. We used the Chi-squared test to assess the association between IS and TCB score. A significant association between these two scores was found with $p=0.042$ (<0.05).
Conclusion: Accumulating evidence suggests that adaptive immune response, represented by cytotoxic T cells, plays a crucial role in suppressing tumour invasion and metastasis. A few data have suggested that anti-tumour immune response may restrict tumour buds at invasive margins. Our results are in line with these findings. This significant association may explain the tendency towards a new combined budding-immune cell score.

PS-07-015

Correlation between endoscopic appearance and histology in immune checkpoint inhibitors-induced gastritis

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Background & objectives: Few publications have reported active lesions on gastric biopsies despite a normal endoscopic appearance in patients treated with immune checkpoint inhibitors (ICI). Our objective was to describe the correlation between histology and endoscopy of ICI-induced gastritis.
Methods: All the patients treated with ICI (Ipilimumab, Nivolumab, and/or Pembrolizumab) for metastatic melanoma in Ambroise-Paré Hospital who underwent gastric biopsies were retrieved from pathology laboratory files. Cases correspond to an eleven year-period (2010-2021). Endoscopic results were analysed and correlated with histology. Hematoxylin & eosin

stained slides of gastric and duodenal biopsies were reviewed and immunohistochemistry was performed.
Results: 19/461 patients (4.1%) under treatment with ICIs were histologically confirmed with gastritis. 6/19 (31%) showed severe lesions of active gastritis on biopsies, while 13/19 (69%) showed mild/moderate gastritis. Histologically, all severe cases corresponded to diffuse chronic active gastritis involving the full thickness of the mucosa with different degrees of inflammation between the antrum and fundus. Important neutrophilic infiltrate was present with crypt abscesses, intra-epithelial lymphocytosis CD8+ and massive gland destruction with interstitial CD4+ predominant T lymphocytes. Immunohistochemistry for CMV and Helicobacter Pylori was negative. Among the six cases with severe gastritis, four patients had a normal endoscopic appearance of gastric mucosa/ minor lesions and two patients showed gastric erosions/ulcerations.
Conclusion: Severe damage in ICI-induced gastritis can be associated with a normal endoscopic appearance. It is characterized by a chronic active gastritis pattern with abundant infiltration of mucosa and epithelium by lymphocytes and neutrophils and massive gland destruction. Despite a normal endoscopic appearance, biopsies of both fundus and antrum should be performed, as histology can be contrasting in different gastric regions.

PS-07-016
Diagnostic usefulness of p53 immunostaining in gastric cancer and dysplasia: a real-world clinical experience
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Background & objectives: Stomach cancer are major threat to public health. A subset of gastric cancer harbour mutations of TP53. Gastric cancer with mutant TP53 gene usually accompanies morphologic changes. We have investigated the diagnostic utility of p53 immunostaining in real-world cases.
Methods: We retrospectively searched 50 stomach tumour and tumour-like lesion cases, wherein p53 immunostaining had a pivotal role in the diagnosis. P53 staining pattern was also analysed in association with clinicopathologic parameters.
Results: Mutant pattern p53 staining was significantly correlated with high-grade nuclear atypia ($p<0.001$), high-grade dysplasia and tubular adenocarcinoma ($p<0.001$), and MSS status ($p=0.034$). Furthermore, diagnostic application of p53 immunostaining was useful when 1) biopsy specimen contained only few tumour cells, 2) pathologic resection margin evaluation was difficult to due to the cauterization artifact 3) distinction of low-grade and high-grade gastric dysplasia.
Conclusion: p53 immunostaining can be helpful for the diagnosis of gastric tumour and tumour-like lesions, and accurate pathologic margin evaluation, particularly if the lesion shows intestinal-type differentiation and some degree of nuclear atypia.

PS-07-017
Tumour area infiltration and absolute tumour cell counts in endoscopic biopsies of therapy-naive upper GI tract carcinomas - implications for predictive biomarker testing
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Background & objectives: Guidelines regulate how many biopsies should be taken to obtain reliable results of predictive biomarker tests. Little is known about how well these guidelines are applied, the number of biopsies correlates with the tumour area and the tumour cells counts.
Methods: The study included endoscopic biopsies of untreated carcinomas of the upper gastrointestinal (GI)-tract during the 2015-2020 review period. Archival (H&E)-stained histological sections were digitized, and the tumour areas were manually annotated. The tumour-bearing biopsy area and absolute carcinoma cell count per case were determined by image analysis.
Results: Biopsies from 253 patients were analysed. The following mean values were determined: a) tumour biopsy number: 6.5 (1–25, standard deviation (SD)=3,32, b) number of tumour-bearing biopsies: 4.7 (1–19, SD=2,80), c) tumour infiltrated area: 7.4mm2 (0.19 mm2–59.46 mm2), d) absolute tumour cell count: 13,492 (193–92,834) e) tumour cell count in a primary surgical specimen (tumour size: 6.7 cm): 105,200,176.
The guideline-recommended biopsy count of 10 was not achieved in 208 patients (82.2%), and the required tumour-bearing biopsy count of 5 was not achieved in 133 patients (52.6%).
Conclusion: Biopsies are often used to determine predictive biomarkers, like Her2/neu or PD-L1. Diagnostics standards to ensure representative material have been suggested in guidelines to reduce false-negative predictions. This is the first study describing the relationships between biopsy number, actual infiltrated tumour area, and carcinoma cell number. We advocate, that histopathological reports should indicate on which basis statements on therapy-relevant biomarkers were made. Digital pathology has the potential to objectively capture these parameters for documentation, quality assessment, and future clinical studies.

PS-07-018
Immune microenvironment landscape shows treatment specific differences in rectal cancer patients
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Background & objectives: Neoadjuvant therapy is the backbone of modern rectal cancer treatment. Insight into the biology of tumour response is needed to optimize organ-preserving approaches. The aim of this study is to explore treatment-specific responses of the tumour and tumour microenvironment.
Methods: Locally advanced rectal cancer patients were treated with chemotherapy (CT), radiochemotherapy (RCT), radiotherapy short wait (RTS) or long wait (LRT) or did not receive therapy (NT). 16 patients per group were included. Tumour patterns of response assessed on HE slides. IF-multiplex was performed for Tcyt (CD3+CD8+), Treg (CD3+FOXP3+), Thelper (CD3+CD8-FOXP3-), B cell (CD20+), DC (CD11c+) & Tumour (panCK+).
Results: A fragmented pattern was predominant in CT-and-RCT-treated patients, whereas shrinkage pattern was predominant in LRT-treated patients ($p=0.02$). Thelper cells were the predominant immune cell population across therapies and a higher immune cell density was observed in stroma compared to tumour region. The depletion of Tregs after therapy suggests a long and maybe permanent effect on the tumour microenvironment. Acute RT affects Tcyt infiltrate ($p<0.01$). Brachytherapy-treated patients show the lowest densities of stromal Thelper, Tcyt & Tregs ($p<0.01$). Synergistic effect of RCT induces stromal increase of Tcyt cells and depletion of Thelper cells compared to CT. All patients treated with some form of radiotherapy had a more homogeneous immune response.
Conclusion: We demonstrated treatment-specific differences in the immune microenvironment landscape of RC patients. Local treatment including RT lead to a more homogeneous immune response compared to NT and CT. Understanding the immune

contexture in relation to specific treatments will inform future treatment decisions.
Funding: This work was supported by an Alpe d'HuZes/KWF program grant (KWF UL 2013-6311)].

PS-07-019

H3K27me3 immunohistochemical loss predicts response to neo-adjuvant chemo-radiotherapy (CRT) in patients with locally advanced rectal adenocarcinoma

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Background & objectives: Patients with locally advanced rectal cancer are treated with neo-adjuvant chemo-radiotherapy to improve resectability and decrease the probability of recurrence. This study aims to assess whether H3K27me3 immunostaining in pre-treatment biopsies of rectal adenocarcinoma may predict response to neo-adjuvant CRT.
Methods: We assessed H3K27me3 immunostaining in 43 pre-treatment endoscopic biopsies of locally advanced rectal carcinomas treated with neo-adjuvant CRT and correlated it with Tumour Regression Grade (TRG) measured using Dworak system in the following surgical specimen.
H3K27me3 immunostain was classified: i) retained (≥ 5% stained neoplastic cells); ii) lost (> 95% stained neoplastic cells); iii) inconclusive (unstained normal and neoplastic cells).
Results: H3K27me3 immunostaining was lost in 18 cases, retained in 17 and inconclusive in 8. All tumours with retained H3K27me3 expression had complete tumour regression (TRG 4/5). H3K27me3 loss was significantly associated with absent/partial tumour regression (TRG 0/1/2) in surgical specimen (P=0.0015)
Conclusion: Due to the lower probability to respond to neo-adjuvant CRT, a "watch and wait" approach to avoid side effect of surgery should be used with caution in patients with rectal carcinomas with H3K27me3 loss in the endoscopic pre-treatment biopsy.

PS-07-020

NET G3 of the digestive system: clinico-pathological and molecular features of 7 cases

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Background & objectives: Grade 3 Neuroendocrine Tumour of the digestive system (DS-NET G3) is a recently recognized entity exhibiting well differentiated morphology and high proliferation rate. Our study aimed to analyse the morphophenotypical, molecular and clinical features of 8 DS-NETs G3.
Methods: We collected 8 DS-NETs G3 in our institution between 2015 and 2018. Clinical records and pathological samples were available for further analysis. The histopathological review was performed according to the upcoming WHO classification for Neuroendocrine Neoplasms. Immunohistochemistry for Chromogranin, Synaptophysin, INSM1, p53, Rb, p16, SSTR2A, DAXX/ATRX, Cyclin D1, Ki67 was performed. Next Generation Sequencing (NGS) was executed on 4 cases.
Results: Our cases included 3 pancreatic NETs (PanNETs) and 5 gastrointestinal NETs (1 gastric, 1 ileal, 1 appendicular, 1 caecal, 1 rectal). They were all characterized by a well differentiated morphology and a Ki67 index >20% (mean: 25%, range: 20-40%). General neuroendocrine markers were intensely and diffusely positive in all cells. SSTR2A showed membranous immunoreactivity in 6 of 8 cases. p53, Rb1 and p16 expression weren't altered in any case, whereas Cyclin D1 was frequently overexpressed. Molecular analysis did not reveal any abnormality in key cancer genes, including TP53 and RB1 genes. The mean follow-up of patients was 24 months and no disease-related death was recorded.
Conclusion: Our case series recapitulates the clinicopathological and molecular characteristics of G3 NETs of the digestive system. This analysis highlights common features of these neoplasms, arisen in different sites, useful to distinguish them from neuroendocrine carcinomas occurring in the same locations.

PS-07-021

PINK1 analysis in colorectal adenocarcinoma and their respective hepatic metastasis with clinical relevancy

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Background & objectives: PTEN-induced-kinase-1 (PINK1) is essential for maintaining mitochondria metabolism and survival in colon cancers. Higher PINK1 expressions were correlated with worsened survival. Our aim was to study the immunoexpression of PINK1 in samples from colorectal adenocarcinoma and their respective hepatic metastases.
Methods: Ninety consecutive patients with colon adenocarcinoma and subsequent hepatic metastasis surgically removed between 2005 and 2022 were studied. Tissue arrays were produced using a 2 mm diameter needle. Immunohistochemical studies were conducted and analysed by the H-Score method. Statistical analysis of these findings was carried out using the SPSSv25; p<0.05 program.
Results: Positive immunoexpression was detected in more than 95 percent of both primary tumours and their hepatic metastases with significant median differences (82,27 ± 48,75 vs 91,29 ± 49,59; p= 0,034). A positive correlation was identified for PINK1 immunoexpression between primary and metastatic tumours (r= 0,352; p=0.001). A cut-off of 100 points of PINK1 in primary samples and 110 in metastatic samples segregated patients into groups with a significant different prognosis. For instance, more than 110 points of PINK1 immunoexpression in patients with metastatic samples combined with more than 25 mitotic figures per 10 high-power-fields had a worse global survival (105,25 ± 14,04 vs 54,95 ± 10,47 months; p=0.018).
Conclusion: Overexpression of PINK1 was observed in hepatic metastasis versus primary colon adenocarcinoma with a positive correlation. Defined cut-off with clinical relevance for PINK1 immunoexpression in hepatic metastasis and primary colon adenocarcinomas was identified.
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PS-07-023

The usefulness of Cycline D1 in diagnostics of naive, CD117/DOG1 positive gastrointestinal stromal tumours (GISTs) – correlation with other histological and immunohistochemical factors

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Background & objectives: The aim of the study is to correlate Cycline D1 expression with size and mitotic activity assessment using PHH3 and Ki67 stainings in determining high risk tumours.

Methods: 116 postoperative GISTs were assessed in terms of histology and immunohistochemistry (CD117, DOG1, Ki67 and PHH3). The size of the tumours were based on macroscopic and radiological data. Statistical analysis included non-parametric Wilcoxon test was used to compare continuous variables and chi-square test to compare proportions. Spearman correlation coefficient was used to calculate correlation. All test were two sided.
Results: Cycline D1 was expressed in 72/116 cases (25 LG tumours according to ESMO criteria and 47 HG tumours) – p>0,099. No correlation was found between cycline D1 expression and PHH3 expression (rho=-0,07, p=0,444) mitotic index (rho=-0,12, p=0,216). lThe correlation was found between cycline D1 expression and size of the tumour (mean size of the tumour in cycline D1 positive group = 7,2cm vs cycline D1 negative group = 9,4cm; rho=-0,20, p=0,03)
Conclusion: The immunohistochemical expression of cycline D1 does not correlate with mitotic index and PHH3 and Ki67 immunohistochemical expressions in GISTs. It does not discriminate between LG and HG tumours. Hence it does not influence the risk stratification of GISTs as measured in tissue material.
The correlation between cyclineD1 expression and smaller size of the tumour is observed. It is to be established upon observational studies whether it may represents an independent risk factor as proved in others tumour.

PS-07-024
Granulomatous appendicitis: a diagnostic challenge. Clinicopathological retrospective study of 60 cases
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Background & objectives: Granulomatous appendicitis (GA) is an uncommon finding of appendectomies. The causes can be classified as infections or noninfectious. There is also a group where a cause is never identified (idiopathic). In this study, we report the clinicopathological features of GA.
Methods: We performed a single-centre, retrospective study of appendectomy specimens received by our department over a 26-year period of time (1995-2021). Clinical data were collected retrospectively from the medical records and the histological slides were reviewed. Additional stainings (Ziehl-Neelsen, Gram, PAS and Groccot) and molecular studies were performed.
Results: We identified 60 GA cases: 32 men and 28 women. Ages ranged 1-83 years (median 33.5yrs). 44 cases had transmural acute-subacute inflammation. Granulomas were found scattered throughout all layers of the wall: subserosa only (11.7%), submucosa+mucosa (65%) and transmural (23.3%). 12 GA were necrotizing granulomas. In 27 cases, granulomas were found in the lymphoid follicles with concomitant extrafollicular granulomas in 15. The presence of xanthogranulomatous inflammation was seen in 10 cases. Two cases were Ziehl-Neelsen positive and one case was PCR-TBC positive. The likely clinicopathological cause of GA: idiopathic (55%; 3 cases probably due to Yersinia), Crohn's disease (21.7%), interval appendicitis (8.3%), tuberculosis (6.7%), foreign material (6.7%), and Actinomyces (1.7%).
Conclusion: The incidence of GA was very low: only 60 cases in 26 years. Idiopathic (primary) granulomatous appendicitis is the leading cause of in our series, followed by Crohn's disease. The site of occurrence in the appendix, the morphology of the granulomas and the clinical setting is often paramount in establishing the aetiology. In our series, special stains for infectious organisms in GA are of low diagnostic yield.

PS-07-025
Impact of IL-17-positive lymphocytes and -197A/G SNP in development of gastric cancer
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Background & objectives: An expanding body of evidence implicates the dualistic role of IL-17, a pro-inflammatory cytokine, in both pro- and anti-tumourigenic processes. Elevated IL-17 expression has been observed in a variety of tumour tissues, including gastric cancer (GC).
Methods: We investigated immunohistochemically 45 GC patients with antibodies against IL-17. Genotyping for the -197A/G SNP in the IL-17A gene was performed via PCR-RFLP method. The clinicopathological parameters and survival were analysed retrospectively.
Results: We observed lower infiltration of IL-17-positive lymphocytes (-PL) in the tumour border in patients with low differentiated gastric cancer (Chi-square test, p=0.052). Also, we found a tendency that patients without distant metastasis had lower infiltration in the tumour border with IL-17-PL (Chi-square test, p=0.106), but in the tumour we found that non-metastasis patients had significantly lower infiltration with IL-17-PC (Chi-square test, p=0.024). Our results showed that the carriers of the G-allele for the -197A/G SNP were in advanced clinical stage of the disease (Chi-square test, p=0.072). The G-allele was also associated with the histology type of the tumour- the G-allele carriers had intestinal type tumours (Chi-square test,p=0.105).
Conclusion: Our results suggest that -197A/G SNP and IL-17-positive lymphocytes could be helpful to outline the progression for patients with gastric cancer.
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PS-07-026
Prognostic value of natural killer cells in colorectal carcinoma
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Background & objectives: Natural killer cells are considered to have prognostic impact in several solid tumours. In colorectal carcinoma, their role remains obscure. We aim to determine whether the presence of NK cells in tumour tissue is associated with a better overall survival.
Methods: A total of 104 tumour specimens from patients after curative resection were reviewed. Areas with the highest lymphocyte density in the centre and margins of each specimen were marked. Tissue microarrays regrouping cores extracted from marked areas were formed. Immunohistochemistry was carried out on slides resulting from the section of TMA blocks. Anti-CD56 antibody was used for NK cells identification.
Results: Mean age was 61.6 years. Gender ratio Male/Female was 1.36. 84.6% of tumours were Adenocarcinomas NOS, with a low differentiated grade in 80.7% of cases. 44.2% of patients were pTNM stage III or IV. Average follow-up period was 60 months. 41 deaths occurred. Mean number of NK cells in tumour centre and margins were 2.2 and 1.52 respectively. 31.7% of patients had a total of 4 NK cells or more. There was no significant difference in densities of NK cells between the centre and the margins of the tumour. Mean survival was 55.59 months. There was no correlation between density of NK cells in tumour tissue and overall survival (p=0.272).

Conclusion: In colorectal carcinoma, NK cells are present in very low density in tumour tissue. Their number in situ does not significantly impact overall survival.

PS-07-027

Prognosison the pre-treatment immunological characteristics of neoadjuvant therapy in oesophageal squamous cell carcinoma

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Background & objectives: The expression of PD-L1 and tumour-infiltrating lymphocytes (TILs) in tumour microenvironment can predict the prognosis in oesophageal squamous cell carcinoma (ESCC). This study aims to explore the prognosis of pre-treatment immunological characteristics in ESCC before the neoadjuvant therapy (NAT).
Methods: A total of 205 patients who receive 2-3 cycles of NAT and was surgically resected between 2015 and 2020.The expression levels of PD-L1, CD4+, CD8+, FOXP3+ and CD20+ cells before the NAT were observed. The patients were randomly divided into the training set and the validation set, and then the nomograms were drawn to predict the patient prognosis.
Results: The expression of PD-L1 before the NAT was positively correlation ($P < 0.05$)with different types of TILs, with a positively related trends to the level of histological grade and lymph node metastasis status. The expression levels in TILs are positively correlated with postoperative histological grading, negatively connected to postoperative tumour size($P < 0.05$). We build two prognostic models and further verify it, results show that the predictive lymph node metastasis status model and the predictive depth of tumour infiltration model based on the expression level of PD-L1 and TILs of pre-NAT show a good consistency and have good predictive capabilities compared with ideal models.
Conclusion: The higher of TILs expression in ESCC, the higher of the expression of PD-L1, CD4+, CD8+, FOXP3+ and CD20+ cells. There is a raising trend of histological grade with a high-TILs in the pre-NAT ESCC patients, and the higher the chance of lymph node metastasis. Two predicted models have a moderate to good discrimination and consistency, which can provide the predictive value for the ESCC patients before the NAT, and it also can provide references for clinical precision treatment.

PS-07-028

Adding a zero Buds group (BD0) in the tumour budding scoring system in colorectal carcinomas: is it relevant?

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Background & objectives: The validated Budding scoring system is made up of 3 groups: BD1(0–4 buds), BD2(5–9 buds), BD3(≥10 buds). A recent study suggested adding a fourth group with zero Buds(BD0). We aim to study the accuracy of the onset of BD0 category
Methods: Our study included retrospectively patients who were operated on for CCR during a four-year-period from 2013 to 2016. Patients who received neoadjuvant treatment were excluded. We performed conventional BD scoring for all cases. We divided the BD1 group into two groups BD0 (0 buds/0.785 mm2) and BD1*(1–4 buds/0.785 mm2). We studied the differences between these two groups.
Results: Our sample of 133 patients consisted in 75 men and 58 women. According to the conventional BD scoring system, 67carcinomas were BD1, 33 were BD2 and 33 were BD3. The BD1 group was divided into two groups: 22 BD0 and 45 BD1*. Comparing the two groups, we found no statistically significant difference between BD0 and BD1* groups regarding age(p=0.5), tumour size(p=0.5), tumour grade(p=0.6), T stage, N stage(p=0.5),M stage(p=0.1), AJCC stage (p=0.2), vascular invasion(p=1), perineural invasion(p=0.7) and overall survival(p=0.9). However, when we compared the four groups(BD0, BD1*,BD2,BD3), there was a statistically significant association between BD and perineural invasion(p=0.02) , M stage (p=0.05), AJCC stage (p=0.03) and overall survival(p=0.02).
Conclusion: BD is ever arousing pathologists' interest in the latest years. The onset of a BD0 category has recently been proposed. Our study revealed that there were no statistically significant difference between the two groups BD0 and BD1* regarding the main histoprognostic factors and the overall survival. These findings suggest that adding a fourth group BD0 wouldn't have an additional relevance. However, further and larger studies are needed to assess the accuracy of adding the BD0 group.

PS-07-029

Microsatellite instability (MSI) immunohistochemistry (IHC), colorectal cancer and Lynch syndrome (LS) genetic testing – one year experience at UK District General Hospital

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Background & objectives: BRAFV600E mutation followed by MLH1 promoter hypermethylation to identify LS in colorectal cancer is practised at our centre. This algorithm is followed for cases with loss of MLH1 IHC expression. We audited our practice to identify LS in colorectal cancers.
Methods: 209 colorectal cancers with their MSI IHC results reported during 2021 at our department were retrieved. Cases with loss of MLH1 IHC expression were identified. BRAF status analysed by New Genomic Sequencing (NGS) DNA panel and MLH1 promoter hypermethylation test results were recorded.
Results: 43 cases with loss of MLH1 and PMS2 IHC expression were identified. NGS showed wild-type BRAF in 9 cases. MLH1 promoter hypermethylation was present in 2/9 but absent in 4/9 cases with wild type BRAF. Thus 4/43 cases with loss of MLH1 IHC expression, wild type BRAF and no MLH1 promoter hypermethylation were identified as LS colorectal cancers. The subsequent results following MLH1 IHC testing were not available in time for discussion of treatment options at colorectal Multidisciplinary meeting (MDM) in 7 of these cases. Pathologist did not request MLH1 hypermethylation test in time for 3 cases and negative MLH1 hypermethylation result became available in 4 cases, after MDT discussion.
Conclusion: NICE and Royal College of Pathologists recommend MSI IHC testing in colorectal cancer to detect LS but awareness of its value to guide treatment decisions is lacking. People with LS have colorectal cancers that respond more favourably to immunotherapy and unfavourably to conventional chemotherapy regimens that include 5-Flurouracil. Pathways to facilitate timely MSI testing for district general hospitals which rely on external genomic laboratories for cancer molecular work-up needs to be addressed.

PS-07-031

Morphological spectrum and clinicopathological correlation in appendiceal mucinous neoplasms (AMN) and pseudomyxoma peritonei (PMP): retrospective histopathology review of cases seen at a tertiary care institution between Jan 2012-June 2019

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Background & objectives: We aimed to grade and stage AMN, PMP cases diagnosed between January 2012- June 2019 using AJCC 8th edition and WHO 5thedition criteria; to see if the three-tier system has bearing on prognosis, survival and find individual adverse prognostic factors.
Methods: After obtaining Institutional Review Board approval, slides of 81 patients (74 AMN and PMP; and 7 Goblet cell adenocarcinoma (GCA)) were reviewed and their clinico-radiological details were obtained. For grading and staging, 3-tier system was used. Survival analysis was performed to determine outcome of patients in different AJCC grades and to find individual adverse prognostic factors.
Results: For AMN and PMP, the median age was 56 years and median serum CEA was 14.45 ng/ml. There was a statistically significant difference in the Disease-free survival (DFS) of different grades and different histological entities of AMN (LAMN, HAMN, invasive adenocarcinoma, poorly differentiated mucinous adenocarcinomas) and PMP. Cytological atypia grade in appendix and pathological "M" stage showed statistically significant correlation with the DFS. The DFS of GCA was shorter than that of mucinous adenocarcinomas of appendix (G2 and G3). Tumour heterogeneity, scanty material on biopsy, inability to grade on cell block, discordance between biopsy and resection were some of the challenges faced during review.
Conclusion: Grading AMN in three-tier system is feasible and has bearing on the prognosis. Grade of cytological atypia in appendix and pathological M stage were important variables affecting the prognosis. The prognosis of GCA is worse than mucinous adenocarcinomas.

PS-07-032
Histopathology and surgery in early-onset inflammatory bowel disease: a Colombian-based cohort study
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Background & objectives: Early-Onset Inflammatory Bowel Disease (IBD), both Crohn's Disease (CD), and Ulcerative Colitis (UC) usually presents with greater severity and often need early surgical intervention. We aim to describe histopathological and surgical characteristics of IBD paediatric patients in a Colombian cohort.
Methods: Longitudinal retrospective study including all patients ≤18 years who had an established diagnosis of IBD from 1977 to 2021, at Fundación Santa Fe de Bogotá. Patients were divided in two groups: patients with and without surgical intervention. A Kaplan-Meier curve was performed to estimate the cumulative risk of needing surgery overtime. Variables were analysed as measures of central tendency.
Results: A total of 34 paediatric patients with IBD where found, 17 with CD and 17 with UC. 18 (58.8%) patients presented with severe disease activity confirmed by histopathology. Five (15%) patients developed low grade dysplasia, on average, after 6.7 years (σ: 2.5) and 20 (60%) required surgical intervention within the first 5 years, 75% with CD and 25% UC. Intestinal resection for fistula treatment, was performed in 50% of the cases, and 41.6% required surgical reintervention. A Kaplan Meier Curve estimated a cumulative risk, for the need of surgery, from the time of diagnosis of IBD with severe activity, of 15% at 1 year and 20% at 5 years.
Conclusion: This study shows severe clinical and histopathological presentation of Early-Onset Inflammatory Bowel Disease in our cohort. Surgical intervention requirement was high among this population and tend to increase overtime. Although, as in the literature, CD patients required more surgical procedures, need for surgery for UC was significant. A high percentage of reinterventions within the next years was also noted. Due to the severity of the disease, early suspicion, and diagnosis of paediatric or early-onset IBD could improve its natural course.

PS-07-033
Expression of the ghrelin receptor in GIST
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Background & objectives: Ghrelin is a hormone exerting complex metabolic functions through coupling with its receptor (GHSR). This axis has documented effects in obesity-related neoplasia, with scarce knowledge on gastrointestinal stromal tumour (GIST) tumorigenesis. We describe the expression pattern of GHSR in GISTs.
Methods: The immunohistochemical (IHC) expression of GHSR was evaluated in 124 cases of GIST (78 gastric and 46 small bowel tumours) from adult patients, diagnosed based on histology and a standard panel of markers (CD117, CD34, DOG1). Statistical analysis was performed in order to correlate the tissue expression of the receptor with the classical clinicopathological factors.
Results: The semi-qualitative expression of GHSR revealed diffusely granular, homogenous, cytoplasmic staining and nuclear immunoreactivity that showed differentiated staining, with heterogenous intratumoral distribution in tumour core versus tumour periphery. An IHC score was developed to integrate these findings, differentiating between tumours with absent (score 0), low expression (score 1) and high expression (score 2) of GHSR. The GHSR score correlated with the presence of myxoid degeneration of the stroma ($p<0.001$) and showed a statistically relevant association with patient prognosis, assessed through AFIP and m-NIH criteria ($p<0.03$). Significant correlations with other clinicopathological factors were not confirmed.
Conclusion: Our results demonstrate that GISTs harbour spatial heterogeneity, with tumour cells in the periphery of the proliferation displaying a distinct phenotype when compared to the ones in tumour core. This feature could justify the differences in recurrence rates across tumours with various prognostic staging. The expression of GHSR in GIST is a potential indicator of the involvement of ghrelin axis in tumorigenesis, a promising result which can be further capitalized by molecular analysis of the isoforms GHSR1a and GHSR1b.

PS-07-034
Evaluation of tumour-stroma ratio in gastric adenocarcinomas with semi-automatic digital imaging method and its relation with clinicopathological parameters and prognosis
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Background & objectives: The importance of tumour-stroma ratio (TSR) as a prognostic marker in some cancer types has been demonstrated. The aim of this study is to examine the relationship between TSR and histopathological parameters and survival in gastric adenocarcinomas.
Methods: The study group was formed with 155 cases of gastric resection specimens diagnosed with adenocarcinoma between 2011-2018. Stroma areas were calculated using semi-automatic digital imaging and software (EasyPath, Argenit, Turkey). The

cases were grouped as low stroma (<36%) and high stroma (≥36%) with a threshold value of 36% determined. The clinicopathological findings, recurrence, and survival data were compared with TSR.
Results: According to this threshold value, 63.2% (n=98) of the cases had low stroma and 36.8% (n=57) had high stroma. A statistically significant negative correlation was found between TSR and overall survival, disease-free survival and recurrence rate (p:0.001; p<0.01). Of the clinicopathological parameters, only gender and perineural invasion (PNI) were found to be significantly associated with TSR (p=0.031; p<0.05). In Cox multivariable regression analysis, a significant statistical correlation was shown between overall survival and age, stroma ratio, histopathological subtype, LVI, and T stage (p<0.01). It was determined that tumour stroma ratio ≥36 increased the mortality risk of the cases by 2.253 (95% CI: 1.411-3.597) times.
Conclusion: TSR has a strong, independent prognostic value in gastric adenocarcinomas and would therefore be considered for integration into routine pathology practice after evaluation in validation studies with larger series.

PS-07-035
Mismatch repair status and PDL-1 expression in gastric carcinoma
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Background & objectives: Gastric cancer (GC) is the 4th most common cancer worldwide and the 2nd leading cause of cancer-related death. In our study, the relationship between microsatellite instability and programmed death-ligand 1 (PDL-1) expression in GCs and clinicopathological parameters was investigated.
Methods: Immunohistochemical staining for PD-L1 (22C3 clone) expression was performed on 37 cases. Expression was scored in both the tumour and tumour-infiltrating immune cells. Furthermore, tumoral mismatch repair status (MLH1, MSH2, MSH6, PMS1) was evaluated.
Results: Twenty of our patients were male and 17 were female. The mean age was 62.5 (range 34-87). PD-L1 expression, either tumoral or tumour-infiltrating immune cells, was present in 8,10% (3/37) of GCs. Overall mismatch repair deficiency was seen in 27,02% (10/37) of the cases. PDL1 expression was observed in all mismatch repair-deficient cases (3/3).
Conclusion: We found PDL-1 positive in 30% of our patients with mismatch repair deficiency. Thus, gastric cancer patients with mismatch repair deficiency tend to show PD-L1 expression; this specifically indicated that mismatch repair deficiency could be prime candidates for PD-L1-directed therapy. Further studies in larger series are needed to confirm our findings.

PS-07-036
Assessment of mucosal lymphatic vessels and regional lymph nodes of in-situ colorectal carcinoma
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Background & objectives: Lymph node (LN) metastasis is an important prognostic factor in colorectal carcinoma (CRC). We aimed to demonstrate the presence of lymphatic vessels (LV) in the mucosa of in-situ CRC (pTis), and the analysis of regional LNs using a molecular method.
Methods: This is an observational and retrospective study of surgically resected in-situ CRCs. of LNs were assessed with both the One Step Nucleic Acid Amplification (OSNA) assay and H&E. The OSNA result, or total tumour load (TTL), is the amount of CK19 mRNA copies present in all LNs from a patient. D2-40 immunostaining was performed in both pTis and normal mucosa.
Results: We analysed 39 surgically resected in-situ CRCs. The mean age was 68.6 years-old, 23 (59%) were men, and 22 (56%) were located on the right colon. A median of 16 LNs were freshly dissected per patient. All cases were low-grade, pN0 with H&E and did not receive adjuvant therapy. At follow-up, all patients were alive without disease between 1 and 5 years. All tumours presented LVs in the lamina propria, being negative in normal colon mucosa. We detected 11/39 (28%) patients with positive LNs by OSNA. Positive tumours were more frequent in older men and located in the right colon. The TTL were low, from 400 to 4270 copies/μL.
Conclusion: Despite of pTis is considered to have little or no risk of LN metastasis, this study demonstrates the presence of LVs in the lamina propria of in-situ CRC, and of low amounts of tumour burden in regional LNs, only detected by molecular methods. Nevertheless, this positivity has been demonstrated to confer no clinical significance or risk of recurrence.

PS-07-037
The impact of cancer stem cell markers in distal cholagniocarinoma
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Background & objectives: Distal cholangiocarcinoma (dCCA) has a low incidence but exhibits a poor prognosis even in patients submitted to curative resection. This study sought to evaluate the prognostic value of cancer stem cell (CSC) markers in patients with dCCA, after surgical resection.
Methods: Retrospective cohort study with evaluation of all patients submitted to surgical resection due to dCCA, between 2008 and 2019. The primary endpoint is to assess the value of CSC markers in overall survival (OS) and disease-free survival (DFS). Immunostaining for CD44, ALDH1 and CD56 was performed. The study was approved by the local Ethics Committee (CHUC-123-20).
Results: 37 patients were identified, with 62.2% male and 37.8% female, with an average age of 69.19 (±9.92) years. After a median follow-up of 14±23.7 months, the OS was 16±2.8 months and the DFS was 14±5.2 months. CD44 and ALDH1 expression was observed in 34.8% and 26.1% of the evaluated tumours, respectively. No expression of CD56 was registered. In univariate analysis, CD44 (p=0.032) and ALDH1 (p=0.016) expression had influence in OS. Regarding DFS, no influence was verified. Multivariate analysis confirmed these findings: CD44 (HR=0.089, p=0.033) and ALDH1 (HR=9.24, p=0.037). ALDH1 expression was established as an independent worse prognostic factor concerning OS, with CD44 expression being associated with a better prognosis.
Conclusion: This study supports the role of CSC markers as predictors of OS in dCCA. ALDH1 expression was associated with worse OS, which is related to the more aggressive biological behaviour of these cells. CD44 was unexpectedly associated with a better OS, which may be explained by the fact that in our study the majority of CD44 positive tumours were small and at an initial stage (T1/T2). More studies are needed to clarify this role.

PS-07-038

Agreement in tumour budding and poorly differentiated cluster detection in consecutive digitalized images with focus on mimickers, serial images and expertise

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Background & objectives: Tumour budding (TB) is a recognized adverse prognostic factor in colorectal cancer (CRC) but agreement on its quantification varies significantly. We aim to study interobserver agreement using digitalized slides with an emphasis in mimickers, serial images and observers' experience.
Methods: Three consecutive H&E - CK AE1.3 - H&E digitalized images were obtained from 30 CRC cases, using a "hotspot" study area of 0.785 mm2 for each. Three observers with differing experience reviewed the 90 images, reporting the number of TB and poorly differentiated clusters (PDF) in addition to false positive images. For agreement analysis, the intraclass correlation coefficient was applied.
Results: Analysis showed moderate agreement values for TB and PDC detection in H&E images. Despite the presence of abundant mimickers in CK sections, TB and PDC detection was facilitated, and a higher correlation was observed, especially for cases with moderate or severe inflammation. No significant disparity in slide assessment was evident between the 3 observers.
Consecutive sections have shown a significant evolution of images with variable size and number of small groups of cells in only 10 microns thick. A notable number of cases have shown a significant progression towards a lower or higher TB/PDC number, that is enough to modify the final grade.
Conclusion: Despite reports of moderate to substantial agreement with respect to TB or PDC grade, agreement with respect to individual cell groups is moderate at best. Most studies published to date have selected representative slides but no specific area to be evaluated, leading to intrinsic selection bias. Cell morphology evolution observed in serial images evidence the need of algorithm-based analyses of larger areas to obtain an average value that could be translated into a powerful and reproducible prognostic tool.

PS-07-039

Automated tumour budding quantification in T1 colorectal carcinoma H&E slides: association to lymph node metastasis

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Background & objectives: Tumour budding (BD) is a significant predictor of lymph node metastasis (LNM) in T1 colorectal cancer (CRC). However, the reproducibility of BD-scoring remains suboptimal. This study aimed to automatically quantify BD on H&E slides and assess its association with LNM.
Methods: A deep-learning algorithm was applied on 197 T1 CRC H&E slides to automatically detect BD using HALO® and HALO AI™ image analysis platform. Univariate and multivariate logistic regressions were performed to assess the predictive value of BD and other features currently assessed in the clinic. The Akaike information criterion was used to identify the model with the highest predictive value.
Results: Various automated BD quantification methods were employed including recording the number and density of buds across the entire invasive front (IF) and at a hotspot area. BD number and density assessed on all slides containing the IF (p=0.001 and p=0.001) as well as on a single slide with highest BD (p=0.004 and p=0.013) were shown to be significantly associated with LNM when assessed using univariate logistic regression. The model with highest predictive value for LNM included BD density assessed on all slides, which was also the most significant feature (p<0.001), tumour grade (p<0.001) , lymphovascular invasion (p=0.285) and submucosal involvement depth (p=0.044).
Conclusion: Here, we demonstrate that the use of deep-learning algorithms could prove to be promising for the objective, standardised and reproducible BD quantification in H&E slides as well as for assisting pathologists during treatment decision making.
Funding: This study was funded by the Japan Society for the Promotion of Science. Indica Labs, Inc. provided in-kind resources.

PS-07-040

Inter-observer concordance in the measurement of histological risk factors in pT1 colorectal adenocarcinomas

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Background & objectives: Identification of risk factors associated with lymph node metastasis (LNM) in pT1 colorectal carcinoma (CRC) is performed by histological evaluation. The aim of this study is to assess the inter-observer agreement in the evaluation of histological risk factors for LNM.
Methods: Scanned slides from 10 pT1 CRCs were assessed by 22 pathologists for submucosal infiltration depth (SID), lymphovascular invasion (LVI), histological grade (HG), and tumour budding (TB). The LVI, HG and TB concordance were calculated with percentage of agreement and Krippendorff's alpha; intraclass correlation coefficient (ICC) for SID. An ulterior consensus meeting was held to analyse differences in histologic criteria assessment.
Results: Seven tumours were resected by endoscopy, and three by surgery. Four pT1 arose on pedunculated polyps, and six on sessile polyps. The evaluation of SID had moderate reliability, with an average ICC (two-way random-effects model) of 0.59 (95% confidence interval 0.12-0.88). LVI had the highest agreement rate (83.64%). TB had 71.36% of agreement and Krippendorff's alpha (α) of 0.13. HG had 64.44% of agreement and $\alpha = 0.26$. In the consensus meeting the use of the measuring tool was corrected, as it generated discordances. An agreement on the criteria for assessing SID for pedunculated and sessile polyps was also reached, and the criteria for LVI, TB and HG were reviewed.
Conclusion: This is a pilot ongoing study. Lack of consistency in the evaluation of some prognostic factors by pathologists was mostly due to differences in measurement criteria, as well as the small number of cases evaluated by many pathologists.

PS-07-041

Diagnostic utility of CK20, SATB2, CDH17, and Villin for the identification of gastrointestinal tumour origin: a tissue microarray study on 7,711 tumours of 117 tumour entities

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Background & objectives: Adenocarcinomas of the gastrointestinal tract (GIT) represent a common source of liver and lung metastasis. Markers used to distinguish metastases from GIT tumours include CK20, SATB2, CDH17, and villin.

Methods: To comparatively assess the staining patterns of these markers across a broad range of different tumour entities, tissue microarrays containing 7711 neoplasms from 117 different tumour types and subtypes was analysed by immunohistochemistry.
Results: Positivity for CK20, SATB2, CDH17, and villin was seen in 94.4%, 88.1%, 98.3%, and 96.7% of colorectal, 36.4%, 22.4%, 52.8%, and 72.4% of gastric, 38.3%, 15%, 51.7%, and 65% of oesophageal adenocarcinomas, 49.1%, 20.8%, 69.8%, and 66% of adenocarcinomas of the ampulla of Vater, 19.4%, 1.4%, 40.3%, and 54.9% of pancreatic ductal adenocarcinomas, 8.7%, 2.2%, 2.2%, and 23.9% of hepatocellular carcinomas, and in 5.5%, 10.1%, 12.8%, and 12.8% of pulmonary adenocarcinomas. A positivity of ≥3 (or all 4) markers occurred in 96.2% (83.2%) of colorectal, 33.2% (13.3%) of gastric, 23.2% (11.7%) of oesophageal, 8.3% (0%) of ductal pancreatic, 0.9% (0%) of pulmonary adenocarcinomas, and in 0% (0%) of hepatocellular carcinomas.
Conclusion: All individual markers support the distinction of GIT adenocarcinomas from liver and lung cancer while a combined analysis of multiple markers may increase diagnostic accuracy. Characteristic staining patterns also occur in other entities. For example, Villin expression is linked to neuroendocrine neoplasms and yolk sac tumours. CDH17 is often positive in in neuroendocrine neoplasms. CK20 is linked to urothelial neoplasms and Merkel cell carcinomas. SATB2 occurs in Merkel cell carcinomas, renal cell carcinomas, and several mesenchymal tumour entities.

PS-07-043

Nonconventional dysplasia in inflammatory bowel disease associated colorectal adenocarcinoma: a clinicopathologic study of twenty-four cases

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Background & objectives: Several types of nonconventional dysplasia have been recently described in inflammatory bowel disease (IBD). However, strict morphologic criteria are lacking, and their clinicopathologic features including potential association with conventional dysplasia and/or colorectal cancer are poorly understood.
Methods: A total of 24 IBD-associated CRC (IBD-CRC) colectomy specimens of 22 patients were reviewed. Seven morphologic patterns were recognized: hypermucinous dysplasia, traditional serrated adenoma-like, sessile serrated lesion-like and serrated lesion, not otherwise specified, Paneth cell differentiation and goblet cell deficient dysplasia. Lesions were classified according to the WHO 2019 criteria and literature review.
Results: We identified 149 dysplastic lesions and occurred with similar frequency in men and women (n=17 and n=5, respectively), with a mean age of 57 years (range: 34-82) with long history (mean: 9,6 years, range: 2-27) of ulcerative colitis (n=11, 42%) and Crohn's disease (n=13, 58%). All nonconventional dysplasia types were common (55% of the cases), present as focal or extended, pure or mixed, in peritumoral and remote mucosa. Tumours were more likely to be well-differentiated (43%), left-sited (58%), with mucinous features (33%) and signet-ring cell (12.5%). Many cases were deeply invasive (62% were pT3 or pT4) and 54% had lymph node metastasis.
Conclusion: Clinicopathological characteristics of IBD-associated CRC were significantly different from sporadic colorectal adenocarcinoma. Histopathological findings of nonconventional patterns of dysplasia were common in IBD-CRCs. Most cases had mixed and focal or extended features of all nonconventional dysplasia types. Nonconventional dysplasia occurred with similar frequency in ulcerative colitis and Crohn's disease. We did not find association between nonconventional dysplasia type and characteristics of IBD-CRC.

PS-07-044

Clinicopathological study of retroperitoneal margin invasion in right radical hemicolectomy with colon cancer

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Background & objectives: There is high variability in relapse rate among series (3-14%) after right radical hemicolectomy. Retroperitoneal margin is a well-recognized parameter, frequently forgotten. The objective is to assess the invasion of retroperitoneal margin in pathologic specimens after radical right hemicolectomy.
Methods: Prospective histopathologic and clinical analysis of 79 patients who underwent right hemicolectomy (2017-2019). Retroperitoneal margin was inked and measured macro- and microscopically and was defined as affected when tumour distance was less or equal to 1mm. Association between retroperitoneal margin invasion and other histological and oncological results was analysed.
Results: Involvement of retroperitoneal margin was found in 15 cases (18.98%) and was significantly associated with more advanced degrees of dedifferentiation (G2: p=0,017; G3: p=0,037) tumour budding (intermediate grade: p=0.028; high grade: p=0.005), presence of poorly differentiated groups (p=0,039) and perineural invasion signs (p=0,044). The involvement of the retroperitoneal margin was associated with a worse overall survival (p=<0.01) and worse overall recurrence (p=<0.01).
Conclusion: Retroperitoneal surgical margin resection involvement could be considered an anatomopathological marker of poor prognosis and greater incidence of relapse after oncological right colectomy. Tumours involving this circumferential margin show features of aggressive behaviour such as increased degrees of dedifferentiation, tumour budding, presence of poorly differentiated groups and perineural invasion. A greater number of cases and longer follow-up term are needed to confirm the clinical significance of this parameter.

PS-07-045

Haemorrhoidectomy specimens: incidental malignant lesions. An eight-year retrospective study with eleven case reports

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Background & objectives: The prevalence of haemorrhoids is estimated at 4.4% (up-to 13-20%). Findings of malignant lesions in haemorrhoidectomy specimens are infrequent. The objective of this study is to be aware of the incidence of malignant lesions found in haemorrhoidectomy-specimens, not clinically suspected.
Methods: We carried out an eight-years retrospective study of haemorrhoidectomy specimens collected of the Mateu Orfila Hospital (Menorca), Spain. All samples coded as "haemorrhoidectomy" and/or "haemorrhoid" between 2013 and 2021, were selected from the Pathology Department database. Clinicopathological and demographic variables were collected from the electronic clinical records.
Results: 444 specimens from 246 men and 198 women, were analysed. The mean age was 45 years (range 20-84 years).

Incidental findings were identified in 11 specimens (6 men, 5 women): 1.-Squamous Cell Carcinoma (SCC) and Anal Intraepithelial Neoplasia (AIN) III;2.-SCC-in-situ;3.-AIN II-III;4.-Neuroendocrine Tumour (NET) poorly-differentiated;5.-Adenocarcinoma well-differentiated and AIN-II;6.-AIN-II;7.-AIN I-II;8.-Malignant Melanoma (MM);9.-Squamous Cell Carcinoma (SCC) and AIN-III;10.-AIN-II;11.-AIN-I. The resection-margins were positive in three cases, negative in three and could not be determined in five cases. Cases 1 and 2 had HIV. Cases with only AIN and cases 1 and 3 had clinical follow-up. The SCC-in-situ, margin expansion was performed. Case 9 received QT-RDT. NET and MM cases were treated at another centre.
Conclusion: In our study the incidence of malignant lesions found incidentally in haemorrhoidectomy specimens was 2.47%. We consider that the surgical margins should be stained whenever possible and include a good representation of the material sent from the haemorrhoidectomy specimens, because although it is not frequent, we can find malignant lesions in these samples; and if so, we should try to provide as much histological information as possible.

PS-07-046
Prognostic value of Decorin expression at the invasive front of colorectal adenocarcinomas
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Background & objectives: Tumour budding (TB) and tumour-stroma ratio (TSR) are independent prognostic factors in colorectal carcinomas. Our aim was to assess the expression of small leucine-rich protein (SLRP) Decorin qualitatively and semi-quantitatively and to correlate this with TB, TSR and stromal desmoplasia.
Methods: Eighty-six cases of colorectal adenocarcinoma were used to generate tissue microarrays that were stained with Masson trichrome, reticulin, orcein, and immunostained with pankeratin, decorin, CD8, and PDL1. Information about mismatch repair proteins (MMR) and Eosinophil leucocyte density were known. Decorin mRNA was assessed with rtPCR.
Results: Cases were subdivided into 4 groups: Group A 18% TB-HIGH/TSR-HIGH, Group B 14% TB-HIGH/TSR-LOW, Group C 21% TB-LOW/TSR-HIGH, Group D 40% TB-LOW/TSR-LOW. Decorin mRNA and protein expression were decreased in TB regions ($p<0.003$) and TSR regions ($p<0.001$). Decorin expression was also decreased in desmoplastic characterized areas. Decorin was a more sensitive indicator of stromal changes at the invasive front when compared with the morphologic assessment of collagen deposition and desmoplasia ($p<0.001$). There was no correlation between decorin expression and clinicopathologic parameters, MMR and Eosinophil density. Survival analysis showed no prognostic significance of Decorin protein and mRNA expression.
Conclusion: Decorin expression is decreased at the tumour front and in both the TB and TSR annotated regions. Decorin is a more sensitive indicator of the initial stromal changes that take place at the tumour-stroma borders compared to morphological assessment of desmoplasia. Decorin expression appears of no prognostic value in colorectal adenocarcinomas in our cohort.

PS-07-047
Simulated digital gastric cancer endoscopic biopsies and surgical resections stained with PD-L1 IHC 22C3 pharmDx present similar PD-L1 expression when scored using combined positive score
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Background & objectives: The dynamic range of PD-L1 expression in endoscopic biopsies of gastric cancer (GC) is not as well-documented as that of surgical resections. This abstract aims to demonstrate the range of PD-L1 expression in simulated digital endoscopic biopsies (SBs) of GC.
Methods: PD-L1 expression in GC SBs (simulated via ImageScope software from surgical resections stained with PD-L1 IHC 22C3 pharmDx) was evaluated in whole-slide images using combined positive score. Scores are determined by dividing the number of viable PD-L1-stained tumour cells and tumour-infiltrating immune cells by the total number of viable tumour cells. Totals are multiplied by 100 and displayed as integers.
Results: Of the 231 GC (including both gastric and gastroesophageal junction adenocarcinoma) SB samples, the average denominator, determined using QuPath, was found to be 11,742 tumour cells. In contrast, the average denominator of the 20 resection samples was 231,623 cells. Despite this greater than 19-fold difference in number of tumour cells, the distribution of combined positive score (CPS) scores remained similar in both sample types. SBs and surgical resections demonstrated similar distributions of CPS scores in terms of minimum, maximum, 25th, 50th, and 75th percentiles. In addition, the average CPS scores for SBs and surgical resections were approximately CPS 24 and CPS 25, respectively.
Conclusion: These results suggest that, although the tumour cell counts of SBs are substantially lower than for resection samples, both present a dynamic range of PD-L1 expression. This suggests that GC SBs demonstrate a PD-L1 expression range similar to that of surgical resections, improving confidence in the evaluation of both small and large samples using CPS.

PS-07-048
Impact of the Covid-19 crisis on digestive cancers operated on in a Tunisian hospital centre
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Background & objectives: Several studies have assessed the impact of the Covid-19 crisis on cancers around the world. However, no similar study has been conducted in Tunisia. We aim to Study the impact of Covid-19 crisis on the anatomopathological characteristics of different digestive cancers.
Methods: We present a retrospective study conducted on cases of digestive carcinomas: colorectal (CRC), gastric (GC), pancreatic (PC) and gastrointestinal stromal tumours (GIST) operated on at Habib Thameur Hospital in between the first December 2016 and June 30, 2021.We subdivided these cases into two groups according to the date of their operation (before/during and after the lockdown) and we compared their histoprognostic characteristics.
Results: These were 270 cases, including 83 diagnosed during and after confinement (30.7%). These were 219 cases of CRC, 22 cases of GC, 13 cases of PC and 16 GIST. Among the 83 cases operated starting from the lockdown, 12 were grade 3, 72 stage T3 or T4, 37 had lymph node metastases, one had visceral metastases, 27 presented vascular emboli and 31 had perineural invasion. Carcinomas operated on starting from the lockdown were statistically significantly correlated with visceral metastasis ($p=0.01$) and a more pejorative histological grade ($p<10-3$).

However we did not find any statistically significant difference concerning the stage T, Nstatus, vascular emboli, perineural invasion and stage.
Conclusion: From the onset of the Covid-19 crisis, the political and the health institutional policies were to avoid delaying management of cancerous pathologies. Our study showed that Covid-19 pandemic clearly affected the prognosis of cancer with significantly increased risk of high grade cases and metastases. This could be explained by the fact that patients avoided seeking for medical assistance for fear to be exposed toCovid-19 in health structures. Further studies are needed to assess the impact of this crisis on the survival of cancer patients.

PS-07-049
Prognostic relevance of tumour budding and poorly differentiated clusters in gastric adenocarcinoma
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Background & objectives: Tumour budding (TBing) is a prognostic factor in colorectal cancer and recent studies indicated similar role of poorly differentiated clusters (PDC). However, their prognostic value is still controversial in gastric adenocarcinoma (GAC), thus our aim was to determine it.
Methods: HE slides of 290 GAC patients was investigated. TB was defined as an isolated tumour cell or a tumour cell cluster of up to four cells, while PDC as a tumour cell cluster of five or more cells. TBs and PDCs were evaluated according to the International Tumour Budding Consensus Conference and divided into low- (Grade1+2) and high (Grade3) groups.
Results: Univariable (Kaplan-Meier) analysis revealed significant negative correlation of both TBing (p=0,0001) and PDCs (p=0,02) with overall survival (OS) in the total cohort and TBing in the intestinal GACs. No significant correlation was found regarding the diffuse and mixed Lauren type GACs. Significant negative correlation with OS was also found by multivariable (Cox) analysis of PDCs in the total cohort, moreover in case of both TBing and PDCs in the intestinal type GACs. Logistic regression analysis with backward selection showed a significant positive correlation of TBing with the presence of regional lymph node metastasis (p=0.009).
Conclusion: Both tumour budding and PDCs are promising prognostic markers of gastric adenocarcinomas. High tumour budding is associated with increased risk of nodal metastasis.
Funding: This study was partly supported by the New National Excellence Program (ÚNKP-21-4-I-SE-32) of the Ministry for Innovation and Technology, Hungary.

PS-07-050
Microsatellite instability status and tumour regression grading on gastric and gastroesophageal junction adenocarcinoma – the first portrait of a Portuguese reality
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Background & objectives: Locally advanced gastroesophageal junction and gastric adenocarcinoma (GEJGA) usually carry a poor prognosis; a molecular subgroup is associated with microsatellite instability (MSI), whose chemotherapy response has not been well characterized yet. Our aim was to evaluate tumour regression (TR), stratified by MSI status.
Methods: A retrospective and unicentric cohort study was assembled, encompassing patients submitted to surgery and perioperative chemotherapy (pQT) in 2015-2020. Clinical data regarding pre and post-treatment features, surgical approach, pQT schemes and follow-up was collected. All histological samples were reviewed by two observers; TR grading was reassessed, and mismatch repair proteins (MMRp) expression was evaluated through immunohistochemistry on tissue micro-arrays.
Results: Out of a total of 64 patients with available tissue samples, only 42 displayed residual tumour. Patients were mostly male (64%), ranging from 60 to 72-years-old (median:67). The series comprised 38,1%(n=16) were moderately differentiated adenocarcinomas and 42.9%(n=18) were poorly differentiated adenocarcinomas (G3) with 14,3%(n=6) were poorly cohesive, the majority of were located in the antrum (n=19); most tumours (57,1%) revealed less than 50% of TR (grade 3). From our sample, 40.5%(n=17) have anomalous MMRp expression and compared with tumours with preserved MMRp expression, the former group showed a statistically significant (p=0.024) worse tumour regression after pQT. However, there was no statistical difference between overall survival (p=0.603) and progression-free survival (p=0.823).
Conclusion: In our sample, defective MMRp neoplasms showed worse response to pQT, whereas anomalous and preserved MMRp groups did not seem to differ on prognosis. These new findings in the portuguese context, even if stemming from a limited series, are in line with emerging evidence suggesting the negative role of pQT on MSI tumours and might aid in prompting routine evaluation of MSI on GEJGA for therapy selection in the future.

PS-07-051
Duodenal adenoma in familial adenomatous polyposis (FAP), a case series
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Background & objectives: Duodenal adenomas are rare tumours which mostly occur in individuals with familial adenomatous polyposis (FAP) and they can reveal abundant neuroendocrine or Paneth cells' differentiation. Our goal is to describe clinical and pathological differences between sporadic and FAP-associated duodenal adenomas.
Methods: Twenty-eight cases of duodenal adenomas diagnosed at our institution (from 2010 to 2022) have been collected. Nine patients (pts) were in FAP (group 1), whilst in the other 19 cases FAP was not clinically suspected (group 2). We revised the histology and performed additional immunohistochemical stains for synaptophysin, chromogranin, CDX2, MUC2, MUC5 and MUC6.
Results: The mean age was 44.3 years in group1 and 71.5 years in group2(p=0.001). In group1, 67% of patients were women while in group2 73.7% were men. In both groups, duodenal adenomas were found more frequently in locations other than ampullary (67% and 73.7%, respectively), being multifocal in 56% of group1 and mostly unifocal in group2 (89,5%)(p=0,020). A moderate/high number of Paneth cells was found in 67% of group1, while the vast majority (84.2%) of group2-adenomas had an absence/few Paneth cells(p 0,013). 68.4% of group1-adenomas had moderate/high chromogranin expression compared to 31.6% of group2. Another finding was the presence of neuroendocrine hyperplasia in four cases, one of which was in FAP-group.
Conclusion: Duodenal adenomas associated with FAP usually occur in younger patients and are frequently multifocal. Histologically, they show a significantly higher number of Paneth cells and

an increased chromogranin expression was found in our series. Occasionally, neuroendocrine hyperplasia within the adenomas can be observed. Nevertheless, data does not suggest a higher probability of existence of neuroendocrine tumours in adenomas associated with FAP.

PS-07-052

Spasmolytic polypeptide-expressing metaplasia as a marker for gastric cancer risk prediction

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Background & objectives: Assessment of chronic atrophic gastritis is the key factor in gastric cancer preventing strategy. Spasmolytic polypeptide-expressing metaplasia (SPEM) can be indicated as possible marker of extensive gastric atrophy with following association of gastric cancer development.
Methods: Resection specimens (n=30) from patients who had gastrectomy due to invasive gastric adenocarcinoma were obtained, processed routinely, stained with H&E. Pseudopyloric metaplasia (PPM) was recognised as antral-type glands in oxyntic mucosa. Microarray method was used to prepare specimens for IHC. Tissue specimens were stained with MUC6, TFF2 and pepsinogen-1 (PG-1) antibodies to reveal either PPM or SPEM accordingly.
Results: Widespread (involving 4-5 glands) PPM was detected in 14 cases. In 9 cases single (3-4 glands) areas were determined, in 7 cases pseudopyloric metaplasia wasn't detected. Foci of metaplastic changes were distributed as follows: PMM sites were found at distance of 4-7 cm from the border of invasive tumour. In 3 cases, a combination of epithelial dysplasia, intestinal metaplasia, and PPM was determined. Expression of PG-1 was found in 12 cases, in 1 case expression was artificial. TFF2+ glands were determined in 21 cases, including sites nearest to dysplasia foci. SPEM foci were designated as a part of true pyloric metaplasia (PPG-1 -) and pseudopyloric metaplasia (PPG-1 +) .
Conclusion: Distribution of PPM wasn't perifocal as expected, but found mostly at the distant zone of adenocarcinoma, although in some cases was nearby dysplasia foci. The expression of TFF2 and PG-1 didn't always overlap and not all PPM glands could be considered a SPEM. The significance of these findings is yet to be understood, but recognising pseudopyloric/SPEM metaplasia in biopsy specimens could potentially help clinicians to reveal patients with considerably higher risk for gastric cancer.

PS-07-053

Concurrent loss of MLH1, PMS2 and MSH6 immunoexpression in gastrointestinal cancer indicating a widespread dysregulation in DNA reparation processes

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Background & objectives: DNA mismatch repair proteins function as heterodimers (MLH1/PMS2; MSH2/MSH6), usually resulting in deficiency in one subsystem in microsatellite instable cancers. As the involvement of both subsystems is unusual, we aim to shed light on the molecular basis of this phenomenon.
Methods: We retrospectively analysed gastrointestinal cancers that underwent immunohistochemical testing for deficient DNA mismatch repair proteins during the last four years in our hospital to identify cases with a simultaneous deficiency in MLH1/PMS2 and MSH2/MSH6. To understand this unusual phenomenon, we performed further molecular testing (MSI-PCR, MLH1 promotor and/or BRAF status) and next-generation sequencing focusing on genes related to DNA reparation.
Results: In the cohort, we could identify 103 cases with deficient DNA mismatch repair proteins. In nearly all cases only one mismatch repair heterodimer - either MLH1/PMS2 or MSH2/MSH6 - was affected. However, five cases showed a concurrent loss of MLH1/PMS2 and MSH6. Whereas some cases seem to be sporadic with a MLH1 promotor hypermethylation and/or BRAF V600E mutation, we also could detect potential germ line mutations. Importantly, next-generation sequencing indicates that the concurrent loss of MLH1/PMS2 and MSH6 expression is associated with a dysregulation in DNA reparation as all of these cases showed additional mutations in genes coding for proteins like ATM, BRCA2, BARD1, CHEK1, FANCA, PALB2, RAD54L and RAD51D.
Conclusion: Our study suggests that the simultaneous loss of MLH1, PMS2 and MSH6 immunoexpression among different gastrointestinal cancers is associated with and potentially even based on more widespread alterations in DNA repair processes. Next-generation sequencing could reveal further mutations in additional DNA repair-related genes in the present cases. With the advent of drugs targeting DNA repair in clinical practice, especially PARP-inhibitors, and their potential indication extension for mutations other than BRCA1/2 such as PALB2 our results are of immediate clinical significance.

PS-07-054

Intestinal spirochetosis: clinicopathological features of 22 year experience in a single institution

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Background & objectives: Intestinal spirochetosis (IS) is an infrequent infection and its clinical significance in individual cases has remained unclear as their association with other diseases. We report the clinicopathological features of the patients diagnosed in our hospital in a 22 years experience.
Methods: Retrospective and descriptive study from the patients with a diagnosis of intestinal spirochetosis from 2000-2021 in We histologically reviewed paraffin-embedded section slides made from 2000 to 2021at Navarras University Hospital.
Clinical records were reviewed for each one of the patients for epidemiological features, treatment and follow up.
Results: We identified 29 cases of IS. Median age was 48 years old (25 - 76 years old). 79% were males. In 69% of the patients an endoscopic ultrasound was performed due to gastrointestinal symptoms.
The most common symptom was diarrhoea (44, 8%). 27, 6% of the patients were asymptomatic. 17,2% were in the colorectal cancer screening program.
48,3% of the patients were treated with antibiotic (metronidazole). 24,1% of the patients were HIV positive.
Transverse colon was the most common localisation (37,9%), 24,7% of the patients had more than one affected colonic segment. Six patients (20,7%) had an associated polyp (3 tubular adenomas, 2 hyperplastic polyps and one juvenile polyp).
Conclusion: Intestinal spirochetosis is more frequent in young population and in male homosexuals. It presents as a symptomatic disease in immunosupresed patients and is very rare symptomatic in other the population except in children. The most common symptom is diarrhoea. Patients treated with antibiotics had a favourable outcome. The most common localisation was the transverse colon, but it can affect other colonic segments even in a discontinuous

manner. Immunosuppressed patients have a highest risk of multi colonic segment affection.

PS-07-056

Crypt epithelial apoptosis: sounds like IBD is on the horizon...

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Background & objectives: In inflammatory bowel disease(IBD), inflammatory crypt damage leads to shedding of epithelium, manifesting as increased crypt epithelial apoptosis which is usually overlooked. Here, we focused on crypt epithelial apoptosis and other histopathologic features of colitis in paediatric and adult IBD.
Methods: Initial diagnostic biopsies containing at least five different sites taken from adult(n=38) and paediatric(n=29) IBD cases were evaluated retrospectively. Histopathologic features of colitis, cryptitis in terms of extent and location (basal/midzonal/full-thickness), crypt abscesses (neutrophilic, mixed, apoptotic) and crypt epithelial apoptosis graded as (0:none,1:scattered, 2:countable, 3:uncountable) were evaluated in each biopsy. Statistical analysis was performed using Chi-square test and Spearman's rank correlation.
Results: There were 29 paediatric cases(PC) comprising 20(69%) ulcerative colitis (UC), 9(31%) Crohn's disease (CD) while there were 26 (68.4%) UC, 12 (31.6%) CD in 38 adults. Apoptosis (97%) was the most frequent feature present throughout the colon in all cases in both UC and CD followed by cryptitis (93%) and crypt abscesses (60%) the majority of which were apoptotic or mixed. Apoptosis was significantly more common and more severe in UC compared to CD in left colon (p=0.017). There was positive correlation between grade of apoptosis and full-thickness cryptitis for left colon in PC (r=0.538,p=0.014), for right colon in adults (r=0.447,p=0.042) and for right colon in all cases (r=0.410,p=0,004).
Conclusion: Crypt epithelial apoptosis seems to be more common in UC compared to CD and is correlated with the extent of cryptitis in all age groups. These findings suggest that inflammatory damage to the crypt epithelium leads to apoptotic cell death in the active phase of the disease, since no correlation was found between the features of chronicity and apoptosis in our cohort. We believe that apoptosis may be an early sign of IBD, particularly when drugs are ruled out.

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PS-08-001

Heat artifact simulating serous tubal intraepithelial carcinoma: systemic histological analysis of prophylactic fallopian tube resection specimens

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Background & objectives: Prophylactic fallopian tube resection has been prevailing. Among pathological changes in tubular specimens, serous tubal intraepithelial carcinoma (STIC) is most important for patient management, and heat artifacts simulating STIC should be acknowledged in order to avoid misdiagnosis.
Methods: One thousand consecutive cases of prophylactic fallopian tube resection by laparoscopic excision using an electronic knife our hospital between 2015-2020 were examined, and the characteristic morphology and incidence of heat artifacts were analysed. Two blocks of the distal fallopian tube were prepared for examination in each case. The cases were benign uterine and ovarian disorders.
Results: Heat artifacts were observed in 530 of 1000 cases (53%). Marked changes were found in 118 cases (11.8%), moderate changes in 102(10.2%) and minor changes in 250 cases (25%). Eight cases were initially diagnosed as STIC. No patient had STIC. Histological findings of heat artifacts included cellular pseudostratification, a pronounced papillary arrangement and detachment of the epithelium from the connective tissue, mainly in the fimbria. Cytological changes included marked nuclear elongation and smudging, eosinophilic cytoplasm and obliteration of cell boundaries and lack of mitotic figures in the epithelial lining. These findings mimicked STIC. Immunostaining of p53, WT1 and Ki67 performed on 33 representative cases did not indicate STIC.
Conclusion: Heat artifacts from electronic knife usage are not uncommon. The marked papillary pattern of the epithelium was the principal histological characteristic leading to confusion with STIC, likely resulting from the structural characteristics of the tubal fimbria. Heat applied to tissue can produce nuclear elongation, hyperchromatism, smudging of nuclei, eosinophilic cytoplasm, and obliteration of cell boundaries. Awareness of this potential source of diagnostic error leads to its complete avoidance.

PS-08-002

Intravenous leiomyomatosis of the uterus: a clinicopathological analysis of nine cases

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Background & objectives: Intravenous leiomyomatosis (IVL) is a rare and benign smooth muscle neoplasm. It grows intravenously in the uterus and may invades cardiovascular and pulmonary system. The purpose of this study was to analyse clinicopathological data of 9 cases of IVL.
Methods: We retrospectively reviewed 9 patients treated for IVL and diagnosed at Pathology Department from 2008 to 2020. All patients underwent surgical treatment.
Results: Mean age of patients was 41.8 years (22-49 years). The 9 patients presented with no specific symptoms including menorrhagia (n=4), uterine mass (n=2), hypogastralgia (n=2) and dysuria (n=1). The diagnosis was made on myomectomy (n=5) and hysterectomy specimens (n=4). The diagnosis of IVL was suspected macroscopically in 4 cases by the presence of peripheral digitiform tabs or peripheral buds appearing to be endovascular. No intravenous leiomyomas were detected. Microscopically, all the cases showed a proliferation of benign smooth muscle within the vessels. Rare mitoses were noticed. Three patients were lost to follow-up. Six patients who were followed up are still alive and experienced no recurrence after a follow-up of 60months.
Conclusion: IVL can be easily misdiagnosed as symptoms are not suggestive clinically and it can mimic uterine leiomyoma. Radiologists should make an early detection of IVL when there is venous blood flow signals in fissure-like echoe. Hysterectomy is the treatment and myomectomy could be considered when there is fertility needs. Pathologists should perform careful sampling insisting in the surrounding uterine smooth muscle. IVL is yet a benign disease but is considered malignant due to its recurrency. Long-term follow-ups are crucial.

PS-08-004

Immunohistochemical expression of neuroendocrine markers in a large cohort of primary ovarian tumours

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Background & objectives: Expression of neuroendocrine markers in primary ovarian tumours without neuroendocrine morphology has only rarely been evaluated and data on its extent is limited. We have analysed neuroendocrine markers expression in tumours lacking neuroendocrine features and assessed its prognostic meaning.
Methods: The cohort consisted of 556 primary ovarian tumours, including serous borderline tumours (mSBT; 42), low grade serous carcinomas (LGSC; 100), high grade serous carcinomas (HGSC; 114), clear cell carcinomas (OCCC; 124), endometroid carcinomas (EOC; 52), mucinous borderline tumours (MBT; 80) and mucinous carcinomas (MC; 44). Immunohistochemical analysis was performed using TMA approach with antibodies against synaptophysin, chromogranin, CD56, and INSM1.
Results: The highest number of positive cases was observed in mucinous tumours and INSM1 marker (60/124; 48%), where the MBT and MC subgroups had similar proportions of positivity (MBT - 42/80; 53% vs. MC – 18/44; 41%). Mucinous tumours also showed the highest expression of synaptophysin (32/124; 26%) and chromogranin (51/124; 41%). In other tumour types, only weak or no expression of neuroendocrine markers was detected, except for HGSC, which showed the highest expression of CD56 (30/114; 26%). The data was statistically processed concerning the extent of neuroendocrine marker expression, and its association with clinicopathologic data was also investigated. Survival analyses showed that neuroendocrine markers have no prognostic significance.
Conclusion: This study examines the expression of neuroendocrine markers in primary ovarian tumours of non-neuroendocrine morphology, with a special focus on providing a comprehensive overview of the staining characteristics of individual tumour types, and the possible significance the expression of these markers could have for differential diagnosis. In terms of patient survival outcomes, the immunohistochemical expression of neuroendocrine markers seems to be of no clinical significance.
This work was supported by Ministry of Health of the Czech Republic (projects NV19-03-00007, RVO64165).

PS-08-005
Immunohistochemical expression of NLRP3 inflammasome in endometrial carcinoma
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Background & objectives: NLRP3 belongs to the inflammasome family, an innate immune system complex. Recent studies have shown its role in the development of different malignancies. We aimed to investigate the NLRP3 expression in endometrial carcinoma and to correlate it with clinicohistopathological parameters.
Methods: Formalin-fixed, paraffin-embedded endometrial tissues from 46 samples were studied. 36 of them diagnosed with endometrial cancer (study group) and the other 10 (control group) came from total hysterectomies due to uterine prolapse. NLRP3's expression was investigated immunohistochemically using a monoclonal anti-NLRP3 antibody and was also correlated with clinicohistopathological parameters.
Results: NLRP3 has been found to be expressed in endometrial tumour samples more frequently compared to control group. There was a statistically significant correlation between NLRP3 expression and patient's age (p=0,009), degree of differentiation (p<0,001), stage of cancer (p<0,001), histological type and tumour depth (p<0,001). At the same time a decreased probability of survival (p=0,0003) and an increased mortality rate were clearly observed in samples with high NLRP3 expression (p<0,001).
Conclusion: Our research demonstrated that an overexpression of NLRP3 in endometrial malignancy can accelerate to advanced stage and tumour depth, resulting in poor prognosis and short survival. Although, more studies need to be performed to establish these results, as NLRP3 may be a useful diagnostic -prognostic factor or a therapeutic target in endometrial carcinoma.

PS-08-006
Malignant struma ovarii with peritoneal implants: a report of 4 cases with molecular analysis on each site
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Background & objectives: This study investigates genomic alterations in a series of 4 malignant struma ovarii (SO), including 2 Highly Differenciated Follicular Carcinoma of the Ovary(HDFCO) with their corresponding peritoneal implants, using nucleic acid sequencing to assess possible molecular profiles predicting clinical behaviour.
Methods: For each case, one representative block from ovarian tumour and one from peritoneal spread were selected. Genomic DNA was sequenced using high throughput sequencing on Illumina sequencer. RNA library preparation was performed following the Archer Fusion-Plex Protocol for Illumina. An in-house panel was used for NGS and RNA-Seq, targeting respectively 87 and 171 major oncogenes and deregulated tumour suppressor genes.
Results: In two cases, ovarian tumour was follicular variant of papillary carcinoma (FV-PTC) with BRAF G469A for one case and NRAS Q61K mutation for the second case. Peritoneal implants were histologically benign-looking and showed respectively BRAF G469A and no mutation.
The third case was composed of a histologically benign struma ovarii in the ovary. Recurrences included a benign struma ovarii on the contralateral ovary, with a TERT promoter deletion, and a benign-looking peritoneal implant without any mutation.
Last case was a histologically benign struma ovarii in the ovary with a peritoneal implant classified as follicular carcinoma and carrying NRAS Q61R mutation. Molecular analysis failed on the ovary.
Conclusion: This study shows that despite being benign-looking, peritoneal implants of struma ovarii can carry classical mutations of thyroid-type cancer: similar mutation to the initial histologically malignant struma ovarii or a novel one. Still, 2 out of 4 peritoneal implants of our series are not mutated.

PS-08-007
Expression of programmed death ligand-1 and mismatch repair status in epithelial ovarian carcinomas
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Background & objectives: Programmed death ligand -1 (PD-L1) is a co-regulatory molecule which suppresses the local immunity. Mismatch repair (MMR) deficiency has been implicated in the

pathogenesis of many malignancies and has been reported to influence response to anti PD-L1 targeted therapy.
Methods: Expression of PD-L1 and MLH1, MSH2, MSH6 and PMS2 was assessed by immunohistochemistry (IHC) on 50 resected cases of epithelial ovarian carcinomas (EOCs).
Results: Mismatch repair deficiency was noted in 15 cases (30% of the cases). PD-L1 expression was noted in 20% of the cases (10 cases) in tumour cells and in 14% of the cases (7 cases) in the tumour infiltrating lymphocytes (TILs). A statistically significant inverse correlation was noted between PD-L1 expression in TILs and PD-L1 expression in tumour cells with extra-ovarian spread of tumour, and between TILs and lymphovascular invasion. There was no statistically significant association between MMR deficiency and PD-L1 expression in tumour cells or PD-L1 expression in TILs.
Conclusion: Approximately one third cases of EOCs showed MMR deficiency and PD-L1 expression was noted in only one sixth to one fifth of the cases. There was no statistically significant association between MMR deficiency and PD-L1 expression in the current study. However, more studies on a larger sample size are required to study relation between MMR status and PD-L1 expression in EOCs.

PS-08-008
Oct-4 expression as a pluripotency factor and changes of apoptosis in the uterus during spontaneous and immune-dependent abortions in mice
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Background & objectives: The balance of apoptosis and proliferation plays an important role in maintaining pregnancy. The aim: to study Oct-4, Bax and Bcl-2 expression in the uterus during spontaneous and immune-dependent abortions in mice.
Methods: 18 mice formed three identical groups. Control-♀CBA/Lacx♂BALB/c, spontaneous abortions(SA)-♀CBA/Lacx♂DBA/2J; immune-dependent abortions(IDA)-♀CBA/Lacx♂BALB/c with intraperitoneal administration of β-heptyl glycoside muramyl dipeptide in dose of ≈1 mg/kg on days 5 and 7 of gestation (DG). Mice were taken out of the experiment on the 8 DG. The uterus were excised and immunohistochemically stained with antibodies to Bax(Δ21), Bcl-2, Oct-4.
Results: The level of embryos resorption in control was 12.5%, in SA- 34.8%, in IDA- 46.7%. Bax(Δ21) expression was detected in the decidua. Staining intensity varied from weak to moderate in control and from moderate to strong in SA and IDA. Bcl-2 was localized in the stromal part of the endometrium in control (intensity staining) and in IDA group (very weak staining), but no staining in SA. Oct4+ cells with nuclear or cytoplasmic staining are localized in the myometrium and perimetrium. The percentage of Oct-4+ nuclei in SA and IDA groups was less than in the control, with negative correlation between Oct-4+ nuclear staining and the level of embryo resorption (r=-0.99,95CI(-0.99;-0.88);p=0.0003)
Conclusion: Thus, the negative correlation between the level of embryo resorption and the percentage of Oct-4+ cells in the myometrium and perimetrium in SA and IDA is probably due to an insufficient increase in the volume of the fetoplacental unit under conditions of enhanced apoptosis.
Funding: The study was carried out within the framework of State Assignment No. 122030200534-4

PS-08-009
The effect of a mesenchymal stem cell conditioned medium fraction on uterine healing after full-thickness surgical incision
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Background & objectives: The mechanism of cesarean scar defect development is unclarified. Treatment of that complication is an important obstetric task. We assessed the effect of the conditioned medium obtained by culturing mesenchymal stem cells with low oxygen content (10%) on uterine healing.
Methods: Component from MSCs was used to treat uterine wound of Sprague Dawley rats (treated group=15, without treatment=11). Histologic examination was performed 5 and 15 days after surgical operation with Mallory staining and monoclonal antibodies to aSMA and CD34. The healing area between damage myometrium and the area of the blood vessels in the healing zone were calculated.
Results: By the 5th day, there was a complete closure of the uterine wall. The area between the separated muscle layers in the treated group was ($p<0.05$) smaller compared to the control in 5 ($p<0.05$) and 15 ($p<0.05$) days. In the control group, the healing area from the 5th to the 15th day increased unreliable ($p>0.05$). The area of the vessels in the healing zone of treated group was significantly lower compared to control in 5 ($p<0.05$) and 15 days ($p<0.05$). Blood vessel area of treated group decreased to 15th day in damage myometrium zone ($p<0.05$) but not damage perimetrium.
Conclusion: Protein composition obtained by culturing the cells under a reduced content of O2 (10%), significantly influences on size and vascularization of healing area between damage myometrium and perimetrium in uterine wall after full-thickness surgical incision. Area of connective tissue and fibrosis in healing uterine wall after treating the composition decreased that seems to improve uterine wall healing.

PS-08-010
Morphological features of the placenta in women with confirmed SARS-CoV-2 infection
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Background & objectives: It`s known that angiogenesis with vascular branching failure is characteristic of chronic intrauterine hypoxia. The aim was to assess the morphological features of the placenta in women with SARS-CoV-2+ infection, children whom have suffered from acute hypoxia in labour.
Methods: The main group of the study was women with positive test of SARS-CoV-2 gave birth to a live born children (n=42), and control group (n=40) with negative test to SARS-CoV-2. We performed histological(H&E staining) and immunohistochemical study on the placenta with antibodies to CD34.
Results: It was revealed that in 8.3% there was acute foetal hypoxia in second stage of the labour, which required operative delivery. We observed a higher percentage of infarctions, the presence of thrombosis of the chorionic vessels, intervillous and subamniotic hematomas in the main study group as compared to the control group ($p<0,05$). Histological examination revealed angiogenesis with a predominance of vascular branching (more than 10 blood vessels in one terminal villus, comparison 3-7 as normally) ($p<0,05$). Intrauterine hypoxia and depletion of compensation mechanisms, even with even week exposure (uterine contractile activity, umbilical

cord compression, and others), there is a breakdown of adaptation mechanisms and the development of acute foetal hypoxia.
Conclusion: Thus, in physiological conditions, the compensatory capabilities of the placenta provide a high degree of resistance of the mother-placenta-foetus system to acute oxygen deficiency. The development of clinically foetal hypoxia during labour in most cases is due to morpho-functional disorders of the placenta that formed in the antenatal period.

PS-08-011
PD-L1 IHC 22C3 pharmDx: Analytical validation on cervical cancer specimens
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Background & objectives: PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay being developed to detect PD-L1 expression in formalin-fixed, paraffin embedded (FFPE) cervical cancer tissue. We report analytical studies using PD-L1 IHC 22C3 pharmDx in cervical cancer specimens.
Methods: Blinded and randomized studies were performed on FFPE cervical specimens, including adenocarcinoma and squamous cell carcinoma. Studies included Sensitivity of PD-L1 IHC 22C3 pharmDx, Inter and Intra-Observer Scoring Precision and Combined Testing Precision (Inter-instrument/Inter-operator/Inter-day) using PD-L1 IHC 22C3 pharmDx. Positive/negative status was applied to scores using the Combined Positive Score (CPS) and binary diagnostic cutoff of CPS ≥1.
Results: A statistical analysis was performed to calculate Negative Percent Agreement (NPA), Positive Percent Agreement (PPA) and Overall Agreement (OA) with corresponding confidence intervals (CI). The acceptance criteria (AC) for precision studies were set such that the lower bound of the two-sided 95% CI computed on percent agreement must meet or exceed 85%.
Sensitivity of the assay was 68.5% in 130 specimens scored as CPS ≥1. Inter and Intra-Observer Precision on 50 specimens met AC for NPA (98.6%/97.7%), PPA (96.2%/97.8%) and OA (97.6%/98.2%), respectively. Combined Precision results for 36 specimens met AC for NPA (93.2%), PPA (90.2%) and OA (95.2%)
Conclusion: These studies demonstrated consistent and highly reproducible results using PD-L1 IHC 22C3 pharmDx in analytical studies for sensitivity and precision in cervical cancer specimens.
Funding: Merck & Co., Inc.

PS-08-012
Number of FoxP3+ regulatory T-cells are associated with recurrence in vulvar squamous cell carcinoma
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Background & objectives: FoxP3+ Tregs suppress anti-tumour immune responses and contribute to the escape of tumour cells from the immune system. We evaluated FoxP3+ lymphocyte infiltration in tumour stroma and tumour cell islands separately in vulvar squamous cell carcinoma.
Methods: Cases diagnosed with vulvar SCC in our department between 2005 and 2021 were retrospectively reviewed. The paraffin blocks were selected, and immunohistochemical studies were performed in accordance with the manufacturer's instructions. Cell counts were made in areas with the highest concentration of FoxP3 positive lymphocytes. Positive cells detected in tumour stroma and within tumoral cell groups were counted separately
Results: We found a positive correlation between high FoxP3+ lymphocyte count and good prognostic parameters. There was less recurrence in the group with high FoxP3+ lymphocyte counts in tumoral cell islands. Overall survival was not statistically different between these groups. Less lymphovascular invasion was observed in the group with high lymphocyte count in the tumour stroma.
Conclusion: Tumour-infiltrating FoxP3+ Tregs not only influence tumour progression and clinical course of disease, but may also determine immunotherapy response. In vulvar SCC, FoxP3+ Treg infiltration into the tumour stroma and into tumoral cell islands is associated with good prognostic features. In these tumours, stage appeared as the only independent prognostic parameter. Studies to be conducted in larger series may reveal whether Tregs can be targeted in cancer treatment.

PS-08-013
Diagnostic value of immunohistochemical staining in fumarate hydratase-deficient leiomyoma
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Background & objectives: Fumarate hydratase-deficient (dFH) leiomyoma is a subtype of leiomyoma, that can be misclassified as atypical one due to a similar morphology. Consequently, we aimed to identify dFH leiomyoma, previously diagnosed as atypical leiomyoma with the help of immunohistochemical (IHC) staining.
Methods: Samples of 24 patients with atypical leiomyoma, who had been provided operation at the Research Center for Obstetrics, Gynaecology and Perinatology (Moscow, Russia) during the years 2016-2021, were recruited. Slides were analysed for special features suggesting dFH leiomyomas, as well as fumarase IHC staining was performed with controls. Statistical significance was analysed using Fisher's test and Kruskal Wallis test.
Results: From the obtained data, it is apparent that of these 24 tumours, 42% were found to be deficient for FH. There were significant differences between patients' age (Me=31 years in dFH leiomyoma and Me=40 years in atypical leiomyoma, $p < 0,05$). There was also a significant positive correlation between hyaline globules and FH deficiency ($p < 0,05$), as well as severe nuclear atypia and FH deficiency ($p < 0,05$). At the same time, statistical tests did not show any significant differences of prominent nucleoli, perinuclear halo, staghorn vessels, and alveolar-part oedema between dFH leiomyomas and atypical ones.
Conclusion: This study has shown that diagnosis of dFH leiomyoma has potentially low reproducibility among pathologists due to the low correlation between histologic features and IHC results. Our findings suggest that the most representative morphologic appearance is only hyaline globules. Consequently, similar histologic features of two leiomyoma subtypes suggest to provide a differential diagnosis with the help of IHC staining. Besides, fumarate hydratase-deficient staining is of clinical importance in revealing a group of young patients for genetic counselling to exclude HLRCC.
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PS-08-014
Endometriosis cases of a tertiary centre. Retrospective evaluation of patients detected in a year
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Background & objectives: Although endometriosis is a benign condition, its high prevalence, recurrence risk and association with malignancies make it an important health problem. In this study,

we compiled the clinicopathologic features of cases diagnosed with endometriosis within a year in our department.
Methods: The biopsy materials evaluated in our clinic in 2021 were retrospectively analysed. Clinicopathologic data, in terms of age, localization, recurrence, operation type, comorbidity, parity were gathered. Gynaecological and non-gynaecological materials were classified. Type of the comorbidity were listed.
Results: There were 78 materials of 70 cases. The mean age of the patients was 39 years. Recurrence was seen in 4 patients. The most common pelvic location was ovary. Vaginal cuff involvement was observed in only 1 case. Eight cases were located in the extrapelvic region. 13 patients had multifocal disease and 4 patients had atypical endometriosis. There were ovarian neoplastic lesions accompanying ovarian endometriosis in eight cases. Endometrioid carcinoma of the uterine cavity was present in 3 cases. Benign uterine lesions such as adenomyosis, adenomyotic nodule and leiomyoma uteri were present in 34 cases.
Conclusion: As a result, 5,7% of the cases were recurrent. Endometriosis associated carcinomas accompanied 2,9% of the cases, and 5,7% of the cases were diagnosed with atypical endometriosis, which is accepted as precursor of the endometriosis associated carcinomas. 92,8% of the cases presented in pelvic location, and multifocal disease at diagnosis occurred in 18,5% of the patients. Careful microscopic examination, detection of multifocal disease, and identification of accompanying neoplastic lesions will enable endometriosis cases to be correctly diagnosed and treated appropriately.

PS-08-015
Trend analysis as a quality measurement for biomarkers - mismatch repair application
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Background & objectives: Universal screening of endometrial cancer (EC) for Lynch syndrome using mismatch repair (MMR) immunohistochemistry is becoming standard of care in many countries. We defined MMR-deficiency (MMRd) rates in EC and examined steadiness over time to identify trends and benchmark measurements.
Methods: Pathology reports of EC biopsy and curettage (2018-2021) and MMR immunohistochemical biomarker reports from Life Labs, Canada were audited. Two-sided logistic regression was used for sample size analysis and generalized linear models were used for trend analysis. 60 patients quarterly were identified as minimum case volume by sample size calculations required to establish benchmarks for testing proficiency ($P \leq 0.05$, 80% power).
Results: Our cohort reached case volume ≥60 cases starting from the fourth quarter of 2019, thus meeting this requirement. The 1181 ECs included in the study were classified into MMR-d (n=313, 26.5%) or proficient (n=868, 73.5%). MMRd was highest in high-grade and mixed EC that included endometrioid EC (EEC, n=34/63, 54%) compared to low-grade EEC (n=256/919, 28%) and high-grade non-EEC (n=23/209, 11%), $P<0.001$. Proportion of MLH1/PMS2 loss was 22.1% (95% CI: 19.8-24.6%), MSH2/MSH6 1.8% (95% CI: 1.1-2.7%), MSH6 2.2% (95% CI: 1.4-3.2%) and PMS2 0.8% (95% CI: 0.3-1.4%). For each protein, the proportion of MMRd cases was quarterly steady over the entire time period ($P>0.05$).
Conclusion: Large laboratories may have the minimum volume to establish benchmarks for internal MMR immunohistochemistry quality control, and follow up trends over time, but this volume is not attainable for smaller laboratories. This study underscores the importance of trend analysis and the need to ensure that pathologists have sufficient expertise in biomarkers reporting.

PS-08-017
Expression patterns of the gonadotropin and sex hormone receptors in various cell types of human endometrium during the menstrual cycle
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Background & objectives: Expression alterations of oestrogen and progesterone receptors as well as follicle-stimulating and luteinizing hormone receptors lead to a number of reproductive issues. Therefore, understanding the physiological features of their expression and topical distribution is important for a endometrium comprehensive assessment.
Methods: Endometrial tissue samples of 7 healthy females, who participated in IVF programs at the Research Center for Obstetrics, Gynaecology and Perinatology (Moscow, Russia) due to male infertility were recruited. Fluorescent immunohistochemistry was used for Q-score evaluation of ER, PR, FSHR, and LHR expression levels during menstrual cycle in endometrial glands, stoma, endotheliocytes, and macrophages.
Results: The increased immunoreactivity of ER, PR, FSHR, and LGHR in the endometrial glands and stroma was initiated at the stage of early proliferation and reached its maximum level at the stage of late proliferation. Then, the expression of ER in the glands and stroma decreased during the early and middle stages of secretion, the immunoreactivity of PR in the stroma persists throughout the all stage of secretion, increased immunoreactivity of FSHR and LGHR in each component of the endometrium was observed in all secretion stages.
Conclusion: It was shown that there is a connection between studied receptors immunoreactivity and endometrial structural features during menstrual cycle. Increased ER, PR, FSHR and LGHR expression in proliferative phase occurs according to endometrial growth, while increased PR, FSHR and LGHR expression in secretory phase is associated with endometrial decidual transformation and optimal condition for embrio implantation in case of pregnancy.
Funding: State Assignment number 122020900122-7 The research was funded by RFBR and Moscow city Government, project number 16-29-07434

PS-08-018
An EMT-based score model identifies poor prognosis endometrial cancer (EC) patients and highlights COL11A1 as an independent risk factor of adverse events
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Background & objectives: Increasing evidence points to COL11A1 as a poor prognosis biomarker in several malignancies but not yet in EC. We aim to investigate the role of COL11A1 as a biomarker in EC and to study their relationship with epithelial-to-mesenchymal transition-related genes.
Methods: We included 82 tissue biopsies from patients with a histological diagnosis of EC who underwent surgery at our institution (2014-2017). For normalization purposes, a control group consisted of endometrial tissues from 16 non-cancer hysterectomized

patients. Tissue specimens were obtained at surgery. Expression of genes of interest was assessed by RT-qPCR. Statistical analyses were performed with R (v.4.0.3) software.
Results: Results from the TCGA cohort (n=232) demonstrated that COL11A1 expression significantly associates ($p<0.05$) with that of cancer-related extracellular proteoglycans (VCAN), EMT triggers (POSTN), EMT-inducing transcription factors, (SNAI1, SNAI2, ZEB1) and mesenchymal markers (FN1). One step further, we developed an EMT-based prognostic algorithm:
(SNAI1x0.0984) + (COL11A1x0.5535) + (CDH2x0.0297) + (FN1x0.0008) + (VIMx-0.0014)
COLL11A1 predominantly contributes to the EMT-score model. Further analyses by RT-qPCR on a validation cohort (n=82) determined that COL11A1 expression is significantly elevated in Type 2 vs Type 1 EC (p=0.006), G2-G3 vs G1 EC (p=0.011 and p=0.025), metastasis (p=0.043), progression (p=0.017), relapse (p=0.034) and EC-related exitus (p=0.007). Additionally, we obtained the same results with the EMT-score.
Conclusion: In light of these results and in agreement with the literature, it seems that diverse EMT biomarkers have prognostic connotations in different types of tumours. We have found that, in EC, COLL11A1 is related to EMT markers and tumours expressing COLL11A1 are usually more aggressive. Currently, these results are being validated by immunohistochemical staining.
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PS-08-019

Mesonephric-like adenocarcinomas of the ovary: pathological and molecular characterisation of a case series

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Background & objectives: Mesonephric-like adenocarcinoma (MLA) of the ovary is a rare malignant tumour of the female genital tract. In this study, we investigated the clinicopathological, immunohistochemical, and molecular features of 9 ovarian MLAs.
Methods: Clinical data and history were extracted from the patient's medical records (from January 2019 to December 2021). Immunohistochemistry (IHC) and targeted Next-Generation sequencing analysis were performed.
Results: MLA accounted for 1.9% of cases (9/269). In 6 cases, MLA was associated with coexisting ovarian lesions: seromucinous borderline tumour (3), polypoid endometriosis (1), endometrioid carcinoma (2). Synchronous endometrial MLA was found in 2 cases. Diffuse endometriosis was present in all cases. Microscopically, tumours showed varying proportions of architectural patterns: glandular 9/9; papillary 7/9; glomeruloid 8/9; sex cord-like 7/9; solid 5/9; and spindle cell 6/9. All cases were positive for PAX8 and GATA3 with heterogeneous expression of CD10 and TTF1. MMR proteins were preserved in all cases. NGS analysis revealed pathogenic variants of KRAS in 8 cases and BRAF in 1 case. Mutations in TP53, POLE, BRCA1/2 were not identified.
Conclusion: In our study, 8 patients presented with advanced disease, and in 2 cases early disease recurrence was observed after chemotherapy treatment. MLA represents a rare and novel histotype of ovarian carcinoma with distinct pathologic, immunohistochemical and molecular features and it can be added to the list of endometriosis-associated ovarian neoplasms. In consideration of the propensity for recurrence/metastasis MLA may be considered a potentially aggressive histotype despite its apparent low-grade morphology.

PS-08-020

Neuroendocrine neoplasms of the female genital tract: correlation of molecular, immunohistochemical and clinical features in 24 cases

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Background & objectives: Neuroendocrine neoplasms (NENs) are uncommon in the female genital tract. Due to their rarity, little is known about them. Aim of this study is to correlate their molecular and immunohistochemical features with clinical data and to investigate their prognostic value.
Methods: The electronic medical record of our Pathology Institute was utilized to identify women diagnosed with gynaecological NENs from 1983 to 2019. All cases underwent histological and immunohistochemical review. Patients' clinical, demographic and treatment characteristics were searched. Molecular analyses were performed (including Next-generation Sequencing, real-time PCR, microsatellite instability evaluation). The association between tumour histology and survival was examined using Kaplan-Meier analyses.
Results: A total of 24 cases were identified. 42% of the NENs were cervical, 25% endometrial and 33% ovarian. Median age was 62 years (range 39–78 years), with site-specific differences. Only high-grade NENs were retrieved on cervix and endometrium: 1 Neuroendocrine-tumour (NET) G3, 8 Neuroendocrine-carcinomas (NECs) and 7 Mixed-Neuroendocrine-non-neuroendocrine-neoplasms (MiNENs), whereas the most common histological subtype in ovary was NET. 20/22 cases (91%) expressed Chromogranin-A and/or Synaptophysin and 17/23 cases (74%) expressed INSM1. Most of the cases didn't show immunoreactivity for site-specific antibodies. HPV-infection and concomitant p16 overexpression was found in 8 cervical and 2 endometrial cases. 4 cases had altered immunohistochemical expression of DNA-mismatch-repair-proteins and associated microsatellite instability (MSI).
Conclusion: Gynaecological NENs represent a rare tumour entity and constitute a diagnostic challenge. They usually show immunoreactivity for traditional neuroendocrine markers (Chromogranin-A and Synaptophysin), but we recommend caution in INSM1 reliability, since it showed a minor sensitivity in our study; NENs resulted mainly negative for site-specific markers, therefore they cannot be used to rule out metastases. Limited data regarding gynaecological NENs pathogenesis are available; our study highlighted NENs might follow site-specific molecular pathways, like HPV-related infection, or NEN-specific pathways, like MSI.

PS-08-021

Contribution of β-catenin in endometrial cancer progression

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Background & objectives: This study aims to investigate the influence of β-catenin on endometrial cancer progression. Currently the molecular subgrouping of EC proposed by the TCGA is a milestone. Furthermore, the driving mechanisms are vital to identify correlations between genes and their regulators.
Methods: A total of 103 White female patients with confirmed EC were enrolled. For the analysis, we used next-generation sequencing with Hot Spot Cancer Panel provided by Illumina Inc, San Diego, California, USA, and immunohistochemical analysis FOXA-1, FOXP1, oestrogen receptor, and β-catenin.
Results: Beta-catenin showed a correlation with AKT1 mutation (R = 0,2508 p = 0,04058 and surprisingly not with CTNNB1 mutation R = 0.5176 p = 0,000007). Moreover, beta-catenin expression was observed in TNM R = 0.2209, p = 0.0263, with prognostic impact RFS (R = 0,2049 p = 0,0388). Indirectly, the worse clinical outcome was observed in obese patients with beta-catenin expression (BMI R = 0.1931 p = 0.0510).
Conclusion: The study suggests a prognostic value of B-catenin in EC. Our study confirmed that beta-catenin is a reliable biomarker in the prognosis of EC outcomes. It indicates that β-catenin can be used as a biomarker for the prognosis of patients with malignant cancers. Furthermore, there is no implementation of classification by molecular basis. Based on this medical research it is necessary to use biomarkers such as beta catenin in the prognosis of endometrial cancer.

PS-08-022
Histopathological features of placentas of mothers who have had COVID19 infection during pregnancy
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Background & objectives: The COVID19 pandemic has been affecting the worldwide since 2020.The SarsCov2 can cause changes in many tissues. The aim is to investigate changes that occur in the placentas of women who have had COVID19 infection during any period of their pregnancy.
Methods: The study was performed prospectively with 24 women who had COVID19 infection at any period of their pregnancy and gave birth by cesarean section or vaginal. The data of the patients were evaluated for clinical, the pregnancy period of COVID19 infection and placental histopathological features.
Results: In 24 cases, the mean age was 28 years and the mean birth week of cases was 38th week.10 cases were vaccinated with two doses, others were unvaccinated. 3 cases were in the period of active covid infection and the mean week of COVID19 infection of other cases was 22th week. In histopathological examinations, calcifications, congestive chorionic villis, intervillous haemorrhages and increase in focal syncytial knots were common findings. Focal distal villous hypoplasia, hofbauer cells and focal hydropic villis were observed less. There are fibromuscular stenosis in 3 cases and marked distal villous hypoplasia in 2 cases.
Conclusion: It is believed that the SarsCov2 virus can cause pregnancy complications such as foetal malformations, foetal growth retardation and stillbirth. Placental abnormalities including foetal and maternal vascular malperfusion have been reported despite negative SarsCov2 tests of infants of mothers who had COVID19 infection during pregnancy. According to this study, COVID19 infection caused significant maternal vascular malperfusion findings in a few cases, although it did not cause significant histopathological changes of the placenta in many cases.

PS-08-023
Expression of Caspase-8 and Bcl-2 in eutopic endometrium of women with chronic endometritis and endometriosis
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Background & objectives: Apoptosis is characterized by a series of perturbations to the cellular architecture that contribute to cell death. This process involved in the pathogenesis of gynaecological diseases associated with chronic inflammation such as chronic endometritis and endometriosis.
Methods: The immunohistochemical expression of apoptotic markers Caspase-8 and Bcl-2 was evaluated in 50 patients divided into 3 groups: group 1 (normal endometrium, n=7), group 2 (chronic endometritis, n=20), group 3 (endometriosis, n=23). QuPath software was used to assess the level immunohistochemical staining intensity (optical density (OD) of staining). We used Kruskal-Walli's test for statistical analysis.
Results: Expression of Caspase-8 in stromal and glandular cells of eutopic endometrium samples was significantly different across the three groups (p=0,016 and p=0,004 respectively). OD of gland cells in the first group: Me=0.113 (Q1-Q3: 0.086-0.119), second: Me=0.314 (Q1-Q3: 0.106-0.445), third: Me=0.101 (Q1-Q3: 0.09-0.142). OD of stromal cells in the first group: Me=0.057 (Q1-Q3: 0.05-0.06), second: 0.133 (Q1-Q3: 0.07-0.218), third: Me=0.056 (Q1-Q3: 0.05-0.06). Bcl-2expression in glandular cells of eutopic endometrium samples was significantly different across the three groups (p=0,004). OD of gland cells in the first group: Me=0.113 (Q1-Q3: 0.086-0.119), second: Me=0.314 (Q1-Q3: 0.106-0.445), third: Me=0.101 (Q1-Q3: 0.09-0.142).
Conclusion: Our findings suggest that there is an increase the activity of caspases-8 in stromal and glandular endometrial cells as well as an activity bcl-2 in glandular cells in chronic endometritis to compare with endometriosis and normal samples. These results might help to shed more light on the role of apoptosis in gynaecological disease associated with chronic inflammation.
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PS-08-024
Mesonephric-like adenocarcinoma of the endometrium frequently associated with KRAS mutation and adenomyosis
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Background & objectives: Mesonephric-like adenocarcinoma (MLA), a rare subtype of endometrial carcinomas with aggressive behaviours, is histologically similar to the cervical mesonephric adenocarcinoma, but not associated with mesonephric remnants. It remains unclear whether the MLAs represent mesonephric origin or Müllerian neoplasm.
Methods: We studied the clinicopathologic, immunohistochemical and molecular features of 6 endometrial MLAs and 1 endometrial carcinoma with mixed mesonephric-like and endometrioid patterns.
Results: Four cases had initially been diagnosed as low-grade endometrioid endometrial adenocarcinomas. Histologically, MLAs showed a variety of morphologies including tubular, ductal, papillary, retiform, and solid. Five cases (71%) were associated with adenomyosis. All tumours showed negativity for ER and PR, p53 wild type and retained staining for the mismatch repair proteins. Most cases revealed positivity for GATA-3 (5/6), CD10 (6/7) and TTF-1 (5/6). Next generation sequencing documented mutations in KRAS (4/4), PIK3CA (1/4), ARID1A (1/4) and ERBB3 (1/4). One case showed copy number variations in MDM4 and AKT3. Two patients were in FIGO stage lll, 1 in stage IV and 4 in stage I-II. Three patients developed lung metastasis.

Conclusion: As MLAs demonstrate varied architectural patterns, it often could lead to misdiagnosis, especially on a small biopsy specimen. Endometrial MLA represents a distinct subtype of endometrial carcinomas associated with KRAS-mutations and characteristic immunohistochemical findings. Clinically, MLAs show an aggressive behaviour with a substantial risk for lung metastasis. Frequent association with adenomyosis, no mesonephric remnant, and mutations in PIK3CA and ARID1A suggest a Müllerian origin of the endometrial MLAs.

PS-08-026

HPV-positive status and p53 alterations are associated with improved disease-free survival in patients with vulvar squamous cell carcinoma

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Background & objectives: Three clinically distinct subtypes of vulvar squamous cell carcinomas (VSCC) have been described on the basis of human papillomavirus (HPV) status and p53 alterations. HPV-positive and p53 wild-type status have been reported to confer better disease-free survival and overall survival.
Methods: 193 surgically treated from 1975 to 2021 in a single institution in Spain were included. Median follow-up was 69 months (range 1–285). p53 was determined by immunohistochemistry (IHC) and HPV by p16 IHC. We assessed the survival of the patients stratified in three groups (HPV-positive, HPV-negative/p53 mutant and HPV-negative/p53 wild-type). Correlations with outcome were analysed using Kaplan-Meier survival curves.
Results: 35 patients (18.1%) had HPV-positive VSCC, 137 (70.9%) HPV-negative/p53 IHC abnormal and 21 (10.8%) HPV-negative/p53 wild-type carcinomas. Age at diagnosis of women with HPV-positive tumours was lower than those with HPV-negative/p53 abnormal and HPV-negative/p53 wild-type VSCC (median 62 years vs. 76 and 77 years, respectively, p=0.06). Patients with HPV-positive tumours showed lower rates of relapse than those with HPV-negative carcinomas (p<0.01). Remarkably, among women with HPV-negative VSCCs, patients with p53 abnormal IHC staining showed lower rates of relapse than those with p53 wild-type IHC (p=0.01). However, no differences in disease-specific survival or in FIGO stage (initial vs advanced) were identified among the three groups (p=0.40 and 0.37, respectively).
Conclusion: Our findings indicate that patients with HPV-positive VSCC, as well as patients with HPV-negative carcinomas with p53 abnormal IHC staining show improved disease-free survival, but these factors seem not to influence disease-specific survival. Patients with HPV-negative carcinomas, particularly those with p53 wild-type neoplasms may warrant wider margins and more strict surveillance after surgery due to their high risk of relapse.

PS-08-027

Intraoperative pathologic evaluation of the ovary: a 21-year institutional practice review

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Background & objectives: Intraoperative pathologic evaluation may assist in therapy management of ovary pathology by confirming diagnosis and cancer type and providing information about the extent of the disease. Herein, we reviewed our institution's practice regarding this examination.
Methods: We analysed all reports of ovarian intraoperative pathology evaluations from a tertiary healthcare institution spanning a 21-year period [2001-2021], totalling 329 cases. Intra- and postoperative diagnosis, gross pathology features, lesion size, bilaterality and number of frozen blocs analysed were recorded. Of these, only 254 had intra- and postoperative responses available and were selected as our study cohort.
Results: Most patients were ≥45-years old (74.0%) and suspected of having an adnexal/ovarian neoplasm (n=205; 80.7%), an indeterminate cystic lesion (n=24; 9.4%) or another infrequent reason (n=25; 10.4%); 14 patients (5.5%) underwent examination for bilateral lesions. Frozen sections were done in 75.2%, averaging 1.9 sections/exam, with the remainder being only evaluated macroscopically. A concordant intra- and postoperative result occurred in 239 cases (96.5%), with discordant results arising from: overvaluing malignant potential (n=2; 0.8%), tumour misclassification (n=2; 0.8%), misinterpretation of artefactual tissue as carcinoma (n=1; 0.4%) and inadequate sampling (n=1; 0.4%). Three cases were deferred (1.2%). As higher-grade components cannot be consistently excluded, intraoperative results undervaluing malignant potential were considered concordant.
Conclusion: Ovarian intraoperative examination remains a reliable and useful tool for deciding therapeutic management. A systematic approach to grossing, sampling and clear communication between clinician and pathologist are encouraged to avoid misdiagnosis and wrongful treatment. When a precise diagnosis is not feasible, either the most probable diagnosis can be reported with an indication of other differential diagnosis which cannot be excluded, or the examination can be deferred when doubt remains after careful examination and consideration.

PS-08-028

A new homologous recombination deficiency (HRD) test in ovarian cancer provides a high diagnostic yield

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Background & objectives: Homologous recombination repair (HRR) pathway deficiency (HRD) is involved in the carcinogenesis of ovarian cancer (OC) and poly(ADP-ribose) polymerase (PARP) inhibitors can be effective for patients with HRD. We investigated the HRD status and its clinical significance in OC.
Methods: We used a new HRD solution combining information from germline and somatic HRR mutations including BRCA1 and BRCA2 with a measure of genomic scarring. On next-generation sequencing in 39 OCs, BRCA mutations and amplification of associated genes were detected. Genomic integrity (GI) index was calculated and a GI status was concluded. By combining the results, HRD status was subsequently determined.
Results: HRD status in 34 (87.2%) OCs was successfully analysed. Five cases (12.8%) were undetermined due to inconclusive or rejected GI index. Twenty three (67.6%) out of 34 case were HRD positive and 11 (32.4%) cases were HRD negative. Tumours with BRCA1/2 mutation were 9 (26.5%) and tumours with positive GI index were 21 (61.8%). HRD was associated with high-grade serous carcinoma and high FIGO stage (≥IIIB) (p=0.032 and 0.028, respectively). Patients with high GI index (>9.7) displayed better disease-free survival compared to those with low GI index (p=0.012).

Conclusion: A new HRD solution beyond BRCA1/2 mutation detection provides expanded clinical information and improves the diagnostic yield of HRD in OC. This could be useful for personalized OC treatment.

PS-08-029

Influence of histological and immunohistochemical features of endometrioid adenocarcinoma on the microvascular tumour density

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Background & objectives: Endometrioid adenocarcinomas of the uterine body account for about 70-80% of all endometrial carcinomas. The most proven prognostic markers are age, stage of the disease, histological grade, microvascular density (MVD), and expression of prognostically important receptors.
Methods: The investigation was conducted on 30 samples of endometrioid adenocarcinomas. The presence of E-cadherin, VEGF, ER, PR, Ki-67, and p53 was detected by immunohistochemistry.
Results: The pronounced predominance of MVD in moderately and low-differentiated tumours over highly differentiated endometrioid adenocarcinomas was found ($F=6.34$, $p=0.0055$). A positive correlation was found between MVD and the expression of VEGF ($r=0.47$, $p=0.0086$) and Ki-67 ($r=0.54$, $p=0.0023$) in tumour cells; a negative – between MVD and PR ($r=-0.45$, $p=0.012$). Expression of ER, E-cadherin, and p53 had no effect on the MVD of neoplastic tissues ($p>0.05$).
Conclusion: The neovascularization degree and microvascular density of endometrioid endometrial adenocarcinoma tissues are enhanced by tumour dedifferentiation and VEGF overexpression. There is a positive correlation between the proliferative activity level of tumour cells and MVD; a negative – between the expression of PR and MVD.

PS-08-030

Germline and somatic BRCA1 and BRCA2 mutational analysis in non-mucinous ovarian carcinomas. A retrospective and descriptive study of 80 cases

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Background & objectives: BRCA1 and BRCA2 somatic or germline mutations in ovarian cancer (OC) have familial, prognostic and predictive significance. We analysed the mutational status of these genes in our cohort of patients and its correlation with several clinical and pathological parameters.
Methods: Next-generation sequencing of BRCA1 and BRCA2 was performed in 80 patients with non-mucinous OC, in tumour and peripheral blood, from January 2019: 62 high-grade serous (HGSC), 8 low-grade endometrioid, 3 high-grade endometrioid (HGECC), 4 clear cell (CCC), 1 low-grade serous carcinomas, 1 carcinosarcoma and 1 borderline serous tumour. Age, FIGO stage, histological type, clinical behaviour and molecular features were collected.
Results: Twenty-five pathogenic variants(PV) in 23/79 tumour-samples (30%) were detected: 16 BRCA1/ 9 BRCA2; 15 germinal(g) (60%) and 5 (20%) somatic(s) (5 blood pending); 16 "frameshift", 5 "nonsense", 3 "missense" and 1 "splicing" (identical results in germinal confirmed cases). Somatic medium allelic frequencies(AF) were 28% versus 68% in germinal cases. One additional germinal (no tumour analysis available) was detected. 22 were HGSC (15 BRCA1/7 BRCA2), one CCC (gBRCA1/sBRCA2), and one HGECC (BRCA1/ BRCA2, blood pending, tumourAF 54%/70%). BRCA mutated-patients were 55.7yo-medium and 20% stage I-II, at diagnosis; non-mutated were 65.5yo and 25% I-II. All BRCA mutated-patients are alive, 40% with no disease(AWND); 12% of non-mutated-patients are exitus and 20% are AWND.
Conclusion: The mutational study of BRCA1/BRCA2 in tumour-tissue is cost-effective, sensitive and specific for germinal and somatic line PV detection. Germinal, "frameshift" type and HGSC are the prevalent mutation-line, PV and histologic type, respectively. PV in tumour and blood in germinal confirmed cases were identical. Mutated cases are associated with younger onset age patients and better clinical behaviour, compared to non-mutated cases. This analysis is essential for an optimal management and for individual and family counselling.

PS-08-033

Uterine smooth muscle tumours of uncertain malignant potential (STUMPs) with fumarate hydratase deficiency: report of 2 cases

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Background & objectives: Fumarate hydratase (FH) deficiency accounts for characteristic architectural and cytological features, which may result in erroneous classification of uterine neoplasms if not recognised. We report 2 cases of FH-deficient smooth muscle tumours of uncertain malignant potential (STUMPs), diagnosed after myomectomy.
Methods: Case 1 refers to a 42-year-old woman presenting with a solitary uterine transmural nodule with 95 mm, without relevant personal or family history. Case 2 refers to a 27-year-old woman, with multiple uterine nodules since the age of 21 and family history of "leiomyomas", the largest with 111 mm, refractory to ulipristal acetate therapy.
Results: Microscopically, both tumours were composed of a spindle cell proliferation with focal areas of alveolar-type oedema and frequent vessels, sometimes with hemangiopericytoma-like pattern. Moderate to severe atypia was observed, including bizarre nuclei or prominent nucleoli with perinucleolar halo. Cytoplasm was eosinophilic, with rhabdoid inclusions focally. Immunoreactivity for FH was lost. Mitotic index was lower than 4/mm2. Necrosis of indeterminate nature was present in the first case, and both tumour cell necrosis and ischemic-type necrosis were detected in the second. The diagnosis of FH-deficient STUMP was made. Patients were referred to the Genetics consultation to exclude FH germline mutations, associated to hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.
Conclusion: It is essential to recognize the prototypical morphology of FH-deficient neoplasms, in order to avoid overdiagnosis of malignancy in uterine smooth muscle tumours, with special impact on young women who desire to preserve fertility. Although close follow-up is recommended, the majority of STUMPs have benign behaviour. FH-deficient neoplasms may occur sporadically or associated to HLRCC syndrome, hence the importance of its prompt recognition to enable the early detection of aggressive forms of renal cell carcinoma.

PS-08-034

High-risk HPV screening - A retrospective study of a Portuguese cervical cancer screening program

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Background & objectives: Cervical cancer is the fourth most common female malignancy. High-risk HPV molecular testing has been considered a useful screening option to identify women with cervical cancer. Herein, we aimed to correlate our institutional molecular results with the histological follow-up.
Methods: A retrospective and unicentric study was conducted, regarding the cervical cancer screening program of the Lisbon and Tejo Valley region, between October 2017 and December 2019. Women with HPV16 and/or HPV18 infection were considered; patients infected with the former strains and by other high-risk strains were also included; their clinical data and biopsy diagnosis were collected.
Results: From a total of 33567 high-risk HPV detection tests (cobas®), 3%(n=1138) were HPV16, and/or HPV18 positive, with/without co-infection with other strains: HPV16 positive–43,32%(n=493), HPV18 positive–13,26%(n=151), HPV16&18 positive–0,96%(n=11), HPV16&18 and other high-risk strains–1,76%(n=20). About 78,6%(n=895) were evaluated by colposcopy with posterior biopsy. From these, HPV16 group(n=399) was associated in 34,01%(n=136) with high-grade lesions [high-grade squamous intraepithelial lesion(HSIL)–95,59%(n=130); squamous cell carcinoma(SCC)–0,73%(n=1); adenocarcinoma(ADC) in situ-2,94%(n=4); ADC-0,73%(n=1)]; in HPV18 group(n=115), 6,56%(n=8) cases were associated with high-grade lesion (all HSIL). In HPV16/18 group(n=9), 77,78%(n=7) patients were associated with high-grade lesion (all HSIL). In the HPV16/18 with other high-risk strains group(n=13), 46,15%(n=6) cases were associated with high-grade lesions [HSIL-80%(n=5); ADC-20%(n=1)].
Conclusion: High-risk HPV molecular testing of our population has given us the opportunity to screen cervical cancer and to get the real incidence of HPV infection genotype 16 and 18. Despite the necessity of further studies to appreciate the specificity/sensibility of this test, namely considering patients infected with other high-risk strains besides 16 and 18, we conclude that patients with co-infection with various high-risk strains and HPV16 infection have the greatest association of high-grade lesions; HPV18 group is the least associated.

PS-08-035

Disagreement in anatomopathological review reports in gynaecological pathology and its impact on treatment: the importance of the subspecialist pathologist in a cancer centre

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Background & objectives: The anatomopathological report is crucial for clinical decisions. In this context, reference cancer centres often review external reports to reduce errors and inappropriate therapies. This study aimed to assess the degree of disagreement in reviews of external reports in gynaecology.
Methods: This is a single-centre, retrospective study, in which 219 cases of gynaecological pathology were reviewed between January 1, 2021 to December 31, 2021. The degree of disagreement was separated into “major” (when the discrepancy between the reports generated a change in the patient’s therapy), "minor" (when there was no impact on patient management) and "no change" (when there was agreement).
Results: 219 cases were analysed. The median age of the population was 48 years. 201 cases were oncological and 18 cases were not related to cancer. Most of the cases represented primary gynaecological neoplasms (only 6 cases were from metastases or tissues outside the female genital tract). There was agreement (“no change”) in 70 cases (31.9%), "minor" disagreement in 107 cases (47.4%) and "major" disagreement in 42 cases (19.1%). When together, the major and minor disagreements correspond to 66.5% of the sample. The results were tabulated in tables and graphs.
Conclusion: The data presented, although showing a reality of only one year, are consistent with the perspective that in pathology, and especially in gynaecological pathology, the analysis of cases by a subspecialist is essential for the proper management of the patient. That is fundamental not only to ensure the provision of adequate treatment for patients, but also to reduce the risk of morbidities associated with aggressive cancer therapies.

PS-08-036

Ovary intraoperative consultation – are we doing the best we can? – A ten-year retrospective analysis of our experience

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Background & objectives: Ovarian tumours are frequently subjected to intra-operative consultation (IOC). These can be challenging cases and misdiagnoses are frequent[DGP1]. Our aim is to evaluate how our intraoperative diagnoses affected patient management in our institution to improve future performance.
Methods: We identified all the ovarian tumours subjected to IOC over a period of 10 years (2012-2022), which required intraoperative examination, in our institution. We analysed the concordance between intraoperative and definitive diagnosis by means to evaluate how our intraoperative diagnosis affected patient management. The dataset was based on the patients’ pathology reports and clinical files.
Results: In this period, we performed 81 IOCs for ovarian tumours. The average age of patients was 56 years. Sixty-one IOCs (76,3%) were concordant with the final diagnosis and twenty were discordant (23,7%). Four discordant cases changed from benign to borderline; five from benign/borderline to malignant and five from borderline to benign tumour. Histological type of six of the malignant tumours was changed. Discordant cases were more frequent in serous tumours (n=7; p=1, not significative) and six were of the mucinous type.
Conclusion: Intraoperative examination of ovarian masses is known to have a high accuracy and therefore provides some guidance to the surgeon’s conduct. It is also known to have many pitfalls posing a challenge to the pathologist. At our institution, the concordance between intraoperative diagnosis and definitive diagnosis is in line with the literature. Mucinous neoplasms pose a higher challenge compared to other histological types, although in our series we didn’t find significant differences between IOC diagnoses of serous and mucinous tumours.

PS-08-037

Intra-operative consultation of endometrial cancer – are frozen sections better than gross inspection alone? – A single-centre retrospective series over seven years

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Background & objectives: Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries. By analysing intraoperative consultation (IOC) of EC cases, we want to assess our performance so far, aiming at determining the best approach for these cases.
Methods: We identified all cases of EC that underwent IOC, over the last 7 years at out institution. Data were gathered from pathology reports and patients' clinical files. We focused on analysing the purpose of the IOC (diagnosis vs. staging), if frozen sections were performed, concordance of intra-operative with definitive diagnosis and how this result influenced the surgical procedure.
Results: Seventy-eight IOC in endometrial lesions were performed, 75 for staging and 3 for diagnosis. The average age of the patients was 67 years. Sixty-four (82,05%) cases were concordant, eleven (14,1%) were discordant and three (1,85%) were deferred. Twenty-seven IOC had frozen sections performed. Four discordant cases were upstaged in the surgical specimen due to myometrium invasion, two due to cervical stromal invasion and four due to serosa and/or adnexal involvement. No frozen sections were performed in the latter. There were no statistically significant differences between cases with and without frozen section (p=0,7362) in terms of concordance.
Conclusion: At our institution, concordance between IOC and definitive diagnosis is high, with only seven discordant cases (8,97%) with impact on the patient. Out results show that gross evaluation is mostly adequate for staging EC, but frozen sections might be of particular use on grossly borderline cases for myometrial and cervical stromal invasion. Serosal or adnexal nodules should be detected grossly, and frozen sections performed. IOC is useful in cases of EC, eliminating the need for reintervention in many patients.

PS-08-038
PD-L1 and mismatch repair (MMR) protein expression in small cell carcinomas of the uterine cervix
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Background & objectives: Cervical neuroendocrine carcinoma(NEC) is rare with limited therapeutic options. Recent studies described abnormal p53, MMR deficient and PD-L1 expression in cervical NECs. Our aim was to evaluate p53, PD-L1 and MMR protein expression in NECs and its correlation to prognosis.
Methods: We selected 5 cases of NECs with known clinicopathological and prognosis data diagnosed over 22 years(2000 to 2022). Immunohistochemistry for p53, p16, PAX8, chromogranin, synaptophysin, TTF-1, PD-L1(22C3 clone) and MMR proteins was performed. PD-L1 was assessed using the combined positive score(CPS) with a threshold of ≥1 required for positivity and aberrant p53 (overexpression or null) was considered positive.
Results: Mean patient age was 58 years (range 33-71), all cases were diagnosed in FIGO stage IV and 2 died of disease. Three cases were pure small-cell NEC and 2 were mixed carcinomas, associated with adenocarcinoma (n=1) and squamous cell carcinoma (n=1), each. All cases demonstrated p16 positive staining, synaptophysin focally positive staining, chromogranin negative staining and PD-L1 negative. PAX8 was positive in 4 cases, TTF-1 in 3 cases, p53 mutant pattern was observed in 3 cases and no MMR deficiency was observed.
Conclusion: Our study showed strong nuclear staining for p16 in all cases, demonstrating the influence of high-risk HPV infection on its carcinogenesis. The variability of p53 expression demonstrate the diversity of genomic landscape of this tumour, being in accordance with the most common genetic alterations usually found. No expression of PD-L1, as well as no MMR deficient was found, suggesting a lower expression of PD-L1 in tumours with microsatellite stability.

PS-08-039
Polymerase-ε exonuclease domain mutations predict excellent outcome among SWI/SNF-deficient undifferentiated and dedifferentiated endometrial carcinomas
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Background & objectives: SWI/SNF-deficient undifferentiated (UDEC) and dedifferentiated (DDEC) endometrial carcinomas are aggressive malignancies with poor treatment response. The prognostic role of the molecular classification is unknown in those malignancies. Here we review a molecularly and clinically annotated series of SWI/SNF-deficient UDEC/DDEC.
Methods: We collected a series of UDEC/DDEC with loss of expression of a core SWI/SNF protein (SMARCA4, SMARCB1, or ARID1B). The molecular subtype was assigned according to the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), including hotspot *POLE* mutation testing and immunohistochemistry for mismatch repair proteins and p53. Kaplan Meier survival analysis was performed across all different molecular subgroups.
Results: We included 60 UDEC/DDEC, the median age of the cohort was 59 years (range: 37-82 years) and most cases were high stage at presentation (19/36). Of the 60 cases, 36 were MMR-deficient (MMR-d), 6 were *POLE* mutated (*POLE*mut), 4 p53 abnormal (p53abn) and 14 with no specific molecular profile (NSMP). The median overall survival of *POLE*mut cases was 26.1 months without any death, compared to 11.8 months in the rest of the cases (p=0.034). The cases classified as MMR-D, p53abn or NSMP had similar outcome (p=0.319).
Conclusion: All *POLE*mut cases had an excellent prognosis while the other three molecular subgroups (MMR-D, p53abn and NSMP) had poor outcomes. Molecular classification among the non-*POLE*mut cases was not informative of clinical behaviour in our study. These results highlight the importance of hotspot *POLE* mutation testing in SWI/SNF-deficient UDEC/DDEC to help guide management.

PS-08-040
Contribution of Forkhead box A1 to endometrial cancer progression
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Background & objectives: Investigate the influence of Forkhead-box on endometrial cancer progression. The molecular subgrouping of EC proposed by the Cancer Genome Atlas is vital in precise molecular-based patient triage. The driving mechanisms are necessary to identify correlations between genes and their regulators.
Methods: A total of 103 White female patients with confirmed EC were enrolled. For analysis, we used next-generation sequencing

with Hot Spot Cancer Panel provided by Illumina Inc, San Diego, California, USA, and immunohistochemical analysis FOXA-1, FOXP1, Oestrogen receptor. Participants underwent surgical treatment without previous radio-chemotherapy to conduct a credible comparative analysis of tumour characteristics, the treatment, and unchanged molecular profiling.
Results: we observed a negative correlation with FOXA-1 revealing that FOXA-1 silencing led to worse outcome based on the negative correlation with FOXA-1(test log-rank for FOXA1 2,031559, p = 0.04220 and HR 2.66, p = 0.06), The estimation of targeted protein frequency was conducted revealing that FOXA-1 occurred in 24 cases, especially in the FIGO IA stage . Furthermore, a correlation was found for FOXP-1 (R = 0,2872 p = 0.0041). This depicts Kaplan-Meier curves for FOXA-1 (p = 0.042). FOX proteins were closely correlated with TP53 and KRAS mutation. Oestrogen receptor expression was detected in all FOXP-1 positive cases and more than 90% of FOXA-1 positive ones.
Conclusion: Our study confirmed that FOXA-1 is a reliable biomarker in the prognosis of Endometrial cancer outcomes. The changes of FoxA downstream profiles in different cancers would provide more valuable clues for FoxA's biological function and could be considered as efficient biomarkers for cancer diagnosis or prognosis. The FOX transcription factor family is closely correlated to hormone-dependent carcinogenesis by interacting with steroid receptors. Thus, FOX binds the promoters of more than 100 genes, in turn, regulating many cellular functions.

PS-09 | Poster Session Haematopathology

PS-09-003
Flow cytometric characterisation of adult T-cell leukaemia/lymphoma (ATLL) and the associated cytogenetics and next generation sequencing (NGS) Findings

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Background & objectives: ATLL, a rare aggressive mature T cell neoplasm is frequently positive for CD4/CD25 and shows loss of CD7 expression. Rarely, they present with unusual immunophenotypes therefore diagnostically challenging. We summarized the immunophenotypes of ATLL and analysed their associated cytogenetics/NGS findings.
Methods: In this study, we summarized the immunophenotypes of ATLL by flow cytometry and analysed the associated cytogenetics/next generation sequencing (NGS) findings. We retrospectively identified 117 patients with ATLL in a single institution in USA during a 19-year period (2003-2021). Of these 117 patients, 100 patients had flow cytometry tests, 70 patients had cytogenetics tests, and 43 patients had NGS tests.
Results: Out of the 100 patients with flow cytometry tests, 87 patients (87%) showed CD4+/CD7- immunophenotype, 7 (7%) patients showed CD4+/CD8+ immunophenotype, 2 (2%) patients showed CD4-/CD8- immunophenotype, 3 (3%) patients showed CD5- immunophenotype, 1 (1%) patient showed CD4-/CD7+ immunophenotype. The cases with unusual immunophenotypes frequently show complex cytogenetics/NGS findings with TP53, TBL1XR1 and NOTCH 1 being the most frequently mutated genes.
Conclusion: ATLL is associated with human T lymphotropic virus (HTLV-1) infection, usually in endemic areas such as Japan and Caribbean countries. CD4+/CD7- is the most common immunophenotypic findings of ATLL. ATLL can rarely show unusual immunophenotypes and frequently accompanied by complex cytogenetics/NGS findings. These cases can be incredibly challenging diagnostically. However, by combining the demographic features of the patients and typical clinical presentations, the possibility of ATLL should be raised and confirmed by HTLV-1 testing.

PS-09-004
Primary thyroid lymphoma: a retrospective-observational study of 11 cases

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Background & objectives: Primary thyroid lymphoma (PTL) is an uncommon heterogeneous neoplasm diagnosed more frequent in women, commonly associated with autoimmune thyroiditis and account for less than 5% of primary thyroid malignancies. This study aimed to assess the clinico-pathological profile of PTL.
Methods: A retrospective observational study was conducted by analysing the medical records and examining the histopathological features of thyroidectomy and lobectomy specimens, from 11 patients diagnosed with PTL at the Emergency County Hospital from Timisoara. Clinical, pathological and immunohistochemical data (antibodies anti Ki67, CD20, CD10, CD30, CD5, Bcl-2, Bcl-6, cyclin-D1, ALK-1, kappa, lambda) were assessed.
Results: The mean age at the time of diagnosis was 69 years old. Eight women and three men were diagnosed with PTL resulting a female to male ratio of 2.7:1. Nine (81.81%) patients accused a painless and progressive growing tumour mass in the anterior cervical region, accompanied by local compression symptoms: dyspnea, dysphagia and dysphonia. All cases were diagnosed as non-Hodgkin, B-cell lymphomas (CD20 positive). The histological type consisted of six diffuse large B cell lymphoma, three MALT lymphoma, one follicular lymphoma and one case with follicular and diffuse lymphoma features. In 10 cases, PTL associated autoimmune lymphocytic thyroiditis. Seven cases (63,63%) were staged IE, two cases-IIE and two cases-IIIE.
Conclusion: This study reaffirms the clinico-pathological features of primary thyroid lymphoma, with a slight variation in female to male ratio. PTL are rare tumours and should be considered in the differential diagnosis of patients complaining of painless, progressive growing goiter or neck masses, and have a history of Hashimoto autoimmune thyroiditis. The prognosis of these patients is excellent and the overall survival is improved due to the advances in both diagnosis and treatment in recent years.

PS-09-005
Molecular profiling of MYD88 and PIM1 genes in tissue samples from diffuse large B-cell non-Hodgkin's lymphomas - defining element of their evolution and prognosis

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Background & objectives: Entire exome sequencing studies of DLBCL tissues have identified MYD88 and PIM-1 genes as involved in the development and signalling of this pathology. We aim to genotype profiles of MYD88 and PIM-1 genes and their implications on the prognosis.
Methods: We have conducted a retrospective study that included 50 paraffin-embedded tissues of DLBCL diagnosed at the Pathology Department of the Emergency County Clinical Hospital, Constanta, Romania, and Sacele Municipal Hospital, Brasov, Romania, between 2012 and 2021. The genotyping was analysed by RT-PCR using TaqMan® genotyping master mix and readymade TaqMan® genotyping assays for MYD88 (p.L252P) and PIM1 (p.G28A, p.L184V, p.V197F)
Results: Twenty-two patients were female and twenty-eight were male with ages ranging from 26 to 91 (mean:60,32 years).Twenty-four tumour samples were located in the lymph nodes and spleen, sixteen were located in the gastrointestinal tract (GI), four were located in the central nervous system and six tumours were located in the skin, testis, head and neck. Four cases (8%) were found to have mutation p.Leu252Pro in the MYD88 gene which occurs due to the transition of T>C at c.755 and only one case (2%) was found to have a mutation p.Gly28Asp in the PIM1 gene, as a transition of G>A at c.83.
Conclusion: In conclusion, our preliminary data suggests that the oncogenic mutations of PIM1 and MYD88 in our diffuse large B-cell lymphoma (DLBCL) cohort may improve diagnosis and prognosis of the patients with this pathology.
Funding: This study was funded by "Grants competition in the bio-medical field 2021", Contract no. 5/21.10.2021, registered at "Ovidius" University of Constanta with no. 14453/21.10.2021. This research was performed in the Center for Research and Development of the Morphological and Genetic Studies of Malignant Pathology from "Ovidius" University of Constanta.

PS-09-006
T-cell lymphoma in bone marrow: morphologic and immunophenotypic study
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Background & objectives: T-cell lymphomas (TCL) account for 10-15% of all lymphoproliferative disorders. Although commonly present, bone marrow involvement by TCL can be diagnostically challenging. Our aim was to establish a diagnostic approach to reliably identify bone marrow infiltration of TCL.
Methods: Retrospective study of 58 cases of bone marrow involvement by TCL collected in the pathology department over a period of 20 years (January 2001-December 2021). We analysed the morphological particularities of bone marrow infiltration by TCL.
Results: Our series included 41 males and 17 females with a median age of 45 years. The major subtype was TCL NOS in 58% followed by the angioimmunoblastic TCL in 18%. The anaplastic, the hepatosplenic and the NK subtype were diagnosed in 8% of cases for each one.
The infiltration pattern was interstitial in 72%, nodular in 15%, focal para trabecular in 10% and intrasinusoidal in 3% of cases highlighted with immunochemistry markers.
The infiltration percentage was less than 20% of cell population in 10 cases and more than 50% in 15 cases.
Conclusion: Bone marrow involvement in TCL is prognostically important for appropriate management. Morphology with immunochemistry can be reliably used to diagnose the bone marrow infiltration and to rule out the differential diagnosis.

PS-09-007
Prevalence of Epstein Barr virus in de novo diffuse large B-cell lymphoma NOS in Algeria
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Background & objectives: The prevalence of EBV in DLBCL accounts for <5-15% of DLBCL among Asian and Latin American patients and <5% among western patients. Our aim was to define the prevalence and clinicopathological features of EBV (+) DLBCL in Algeria.
Methods: A total of 162 cases of de novo DLBCL treated with R-CHOP were evaluated from January 2015 to August 2019. LMP1 and EBNA2 were performed for latency. The presence of EBV determined by EBER-ISH assay with 20% of cut-off. Clinical and pathological data were analysed.
Results: Of these 162 cases with DLBCL,13 (8%) showed EBV positivity. The median age of EBV(+)-DLBCL patients was 59, range from 22-87. 77% EBV(+)-DLBCL present in the nodal site . The ABC phenotype was found in 100% of our cases. 53.8% showed type III EBV latency. Clinically, EBV(+)-DLBCL presented an advanced clinical stage (84.6%), a high IPI (46.2%), and a low rate of response to treatment and survival (69.2%). Our results showed a significant difference between the two groups EBV(+)-DLBCL and EBV(-)-DLBCL on the response to R-CHOP treatment (p=0.01) and survival rate between the two groups. Log Rank (Mantel-Cox) p=0.0001
Conclusion: The prevalence of EBV in DLBCL is estimated at 8% in our series, joining the Asian series. This is still considerable compared to Western countries. Survival was significantly associated with EBV in our study.

PS-09-008
The molecular spectrum of anaplastic large cell lymphoma (ALCL) - the wide next-generation sequencing profiling
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Background & objectives: ALK-negative anaplastic large cell lymphoma (ALCL)) is a malignant CD30-positive T cell neoplasm and clinically/molecularly three different subgroups have been outlined: *DUSP22*-rearranged, *TP63*-rearranged, and triple-negative cases (lacking *DUSP22,TP63,ALK*) with 5-year overall survival 90%, 17%, and 42%, respectively.
Methods: We investigated 26 ALCL cases: 17 ALK-negative and 9 ALK-positive (as a control group). The histopathological confirmation of the diagnosis (morphology and immunoprofile) with a consecutive 125-gene panel assay dedicated to lymphomas was performed. Samples and genes were clustered according to the Kendall rank correlation coefficient calculated on the percentage of reads value.
Results: The subgrouping of ALCL revealed: no(0) *DUSP22*-rearranged, three(3) *TP63*-rearranged, and sixteen(16) triple-negative cases. The prevalence of genes fusions (PGF) in the ALCL ALK-positive and ALK-negative groups included *CCND1* and *CCND3* (100%); the most frequently presented gene isoforms (PGI) in these two ALCL groups were *BATF3* (70%) and *ETV6* (60%). The profile of PGI in ALK-positive and triple-negative cases differed in *LMO2, MUM1/IRF*, *MUC1* and were respectively 15%, <1%, 57% *vs.* 44%,

13%, 19%. The PGF including *MYC* was 14% in ALK-positive and 19% in triple-negative cases. Additionally, the *TP63*-rearranged cases showed a strong gene fusion connection between *FOXP1* and *EIF4E3*.
Conclusion: The ALK-negative ALCL is a rare lymphoma, which is now classified as a separate entity that should be differentiated from primary cutaneous ALCL, and other T-cell/B-cell lymphomas with CD30 expression and anaplastic morphology. Comprehensive molecular studies under a larger cohort of ALK- ALCL are limited due to the low number of cases. Further investigation is needed not only to give more insight into the clinical significance of genetic alterations but also in search of new molecular targets for personalized therapy.

PS-10 | Poster Session Soft Tissue and Bone Pathology

PS-10-001
Diagnostic utility of h3.3k36m immunostaining in chondroblastomas: a study of 16 cases from a tertiary cancer referral centre in India

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Background & objectives: Chondroblastoma is a relatively uncommon benign bone tumour. At times, there is a challenge in differentiating it from its diagnostic mimics, especially on limited biopsies, with treatment-related implications.
To evaluate H3.3K36M immunostaining in chondroblastomas.
Methods: Ten cases were in the form of biopsy specimens and six were referred cases in form of paraffin blocks. Immunohistochemical staining for H3.3K36M (monoclonal, RM193, 1:100 dilution) was graded in terms of staining intensity(1+to 3+) and the percentage of tumour cells showing unequivocal nuclear staining.
Proximal tibia (5/16, 31.25%) was the commonest site, followed by the proximal humerus (4/16, 25%).
Results: We observed positive immunohistochemical staining for H3.3K36M in 15/16(93.75%) chondroblastomas, including all the tumour components, such as tumour cells and pink cartilage, but sparing the osteoclast-like giant cells. The percentage of tumour cells showing positivity ranged from 30% to 95%. We observed 3+ staining in 13/15((86.6%) cases and 2+ staining pattern in 2/15(13.3%) cases. A single case, which showed nuclear atypia displayed positive immunostaining for H3.3K36M in 80% of tumour cells with 3+ staining. None of the other 12 giant cell-rich lesions, including giant cell tumour of bone, displayed positive immunostaining for H3.3K36M.
Conclusion: Overall diagnostic sensitivity of H3.3K36M for chondroblastoma was 93.7% and specificity was 100%. This study, which is one of the first from our country, supports the diagnostic value of H3.3K36M for diagnosing chondroblastoma, including its distinction from its various diagnostic mimics on limited biopsy specimens.

PS-10-003
Metalic-alloy wear debris after total hip arthroplasty is inducing periprosthetic tissue inflammation on subcellular level

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Background & objectives: The metallic-associated adverse local tissue reactions (ALTR) and events accompanying worn implant materials are poorly understood on the subcellular level. Current immunohistochemical techniques lack chemical sensitivity to investigate causal relations between material and biological response on submicron scale.
Methods: A combination of photon, electron and ion beam microscopy-spectroscopy techniques including hybrid optical fluorescence and reflectance micro-spectroscopy, scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDS), helium ion microscopy (HIM) and micro-particle-induced X-ray emission (micro-PIXE) were applied on periprosthetic tissue obtained at revision surgery of a patient with osteoarthritis, who was treated earlier with a titanium-alloy total hip arthroplasty.
Results: Micron sized wear debris was found as the main cause of the tissue oxidative stress exhibited through lipopigments accumulation in the nearby lysosomes. This may explain the signs of chronic inflammation from prior histologic investigation. Furthermore, insights on extensive fretting and corrosion of the debris on nm scale and a quantitative measure of significant Al and V release into the tissue together with hydroxyapatite-like layer formation particularly bound to the regions with the highest Al content were revealed. Finally, by micro-PIXE we observed a wide spread of Ti- alloy debris throughout the whole tissue sample and confirmed selective metal leaching that corresponds to elevated concentrations in the patient's serum.
Conclusion: The functional and structural information obtained at the subcellular level contributes to a better understanding of the macroscopic inflammatory processes observed on the tissue level. The established label-free correlative microscopy approach can efficiently be adopted to study any other clinical cases related to ALTR, as it can reveal more insights into implant rejection processes compared to the conventional histological examination further down on a submicron to single molecular scale.
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PS-10-004
Extraadrenal soft-tissues Myelolipomas: clinicopathological study of 10 cases

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Background & objectives: Myelolipoma is an uncommon benign tumour. It is most often found in the adrenal glands, although lesions in other unusual sites have also been described. The aim of our study is to describe the clinicopathological features of extraadrenal myelolipomas.
Methods: The pathology departmental archives of two University Hospitals were searched from 2005-2021 for patients originally diagnosed as extraadrenal myelolipoma. The cases were reviewed by the authors. Clinical parameters such as age, gender, tumour sites, and follow up were obtained from the existing medical records.
Results: Ten patients were identified: 7 males and 3 females, age ranged from 55 to 48 years. None of the patients had a previous history of malignancy or haematological diseases. All patients were diagnosed incidentally. The tumours involved posterior mediastinum (1), retroperitoneum (2), pelvic soft tissues (1), and paravertebral presacral (6). CT scan showed in all patients a well-demarcated tumour with fat density showing heterogeneous enhancement. So liposarcoma was suspected and surgical resection was performed. The tumours were well-circumscribed, encapsulated, with yellow to grey cut surfaces. Histologically, the tumours showed mature adipose tissue and hematopoietic elements, with concordant inmunohistochemistry. All patients went follow-up with no recurrence at the time of evaluation.

Conclusion: Myelolipoma is an uncommon benign tumour composed of adipose tissue and normal hematopoietic elements, which incidence is 0,08-0,2%. We present 10 cases of extraadrenal myelolipomas. Extraadrenal myelolipoma is a rare benign and asymptomatic tumour that may be misdiagnosed as a malignant lipomatous tumour on radiological studies. Most of them are incidentally detected during radiological investigation of unrelated symptoms. Surgery is the recommended treatment. The final diagnosis relies on pathologic findings.

PS-10-006

Anastomosing haemangioma with unusual location and mimicking malignancy: a case series and literature review

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Background & objectives: Anastomosing haemangioma (AH) is a relatively newly defined entity seen mostly in the kidney. Extrarenal localizations have also been reported. Herein, we report two non-renal cases, one of which is the second case in English literature involving anterior mediastinum.
Methods: Excisional biopsies were obtained from a 68-year-old woman with an anterior mediastinal mass (8 mm), and a 41-year-old man with a mass of 12.5 mm located between left adrenal gland and tail of pancreas. The latter had a pre-diagnosis of a malignancy. Both of them was incidentally found. Radiological examinations including CT, MRI and PET scans were also evaluated.
Results: Both lesions were un-encapsulated, well-circumscribed tumours consisting of predominantly small, anastomosing, splenic-like sinusoidal vascular structures which were lined by single layer of flat endothelial cells with occasional hobnail cells. Small fibrin thrombi was present in some vascular channels. No multilayering of endothelial cells, cytological atypia, necrosis, mitotic activity, extramedullary haematopoiesis or invasion into surrounding tissues was found. Immunohistochemically, tumour cells were diffusely positive with CD31, ERG and CD34 but negative for GLUT1, D2-40, Desmin or Cytokeratin. Ki67 proliferation index was lower than 5% in tumour cells. Cases were diagnosed as AH. Anterior mediastinal AH had positive surgical margins, the patient has been following for 2 years without any local recurrence.
Conclusion: Anastomosing haemangioma is a relatively newly described benign vascular tumour. It is a rare neoplasm which can have some overlapping histologic features with well-differentiated angiosarcoma. It was originally described in kidney and perinephric adipose tissue in 2009, but extrarenal sites including testis, spermatic cord, ovary, adrenal glands, gastrointestinal tract, mesentery, soft tissues and bone had also been reported. Recognition of this entity and knowing that it may occur in unexpected localisations may help it's differential diagnosis from more aggressive lesions.

PS-10-007

Three cases of Kaposi sarcoma as initial manifestation of HIV infection and AIDS

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Background & objectives: Epidemic Kaposi sarcoma (KS), the most common subtype, is seen in the setting of HIV infection and related acquired immunodeficiency. We report three cases of KS as initial manifestation of AIDS.
Methods: We analysed medical records from Register of bone and soft tissue lesions biopsies in the Institute of pathology, Medical Faculty, University of Belgrade from 2006 to 2022.
Results: Only three patients had KS associated with HIV infection as initial manifestation of AIDS. All of them were males. One patient was 40-year-old with KS localized in tonsil, and two of them were 43-year-old with KS localized in cervical lymph nodes. All patients were presented with bulky masses and all of them underwent excisional biopsy. Histological analysis showed spindle cell tumour, without pleomorphism, mixed with inflammatory cells. Aforementioned spindle cells were immunohistochemically positive for vascular markers. Positivity for HHV-8 indicated diagnosis of KS and further clinical examinations in order to confirm/exclude AIDS were performed. All patients were found to be HIV positive, with developed AIDS.
Conclusion: Even though rare, KS could be initial manifestation of AIDS. In order to confirm/exclude the diagnosis of KS, when there are any histological suspicion, HHV-8 should be applied. Early diagnosis of KS and AIDS prevents complications and ensures better prognosis.

PS-10-008

Pediatric chordomas: report of five cases with emphasis on poorly differentiated subtype and SMARCB1/INI1 deficiency

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Background & objectives: Chordoma is a rare primary malignant bone tumour showing notochordal differentiation. They usually affect adults, and extremely rarely seen in paediatric age group. For children, such tumours present a different biology with aggressive histological features, and worse prognosis.
Methods: All chordomas diagnosed between January 2016-January 2022 in one institution were reviewed for the study (total number of 41). Five patients belonging to paediatric age group were found and included in the study.
Results: Patients ages ranged between 2 to 18 years(median:9 years); 3 females, 2 males. Tumour localizations were as follows: two cervical vertebrea, two clivus and one intracranial(cerebellopontin angle). On histomorphologic examination, three cases showed conventional chordoma features, one of them was compatible with chondroid chordoma and two of the cases had poorly differentiated morphology. On immunohistochemical analysis all tumours showed cytokeratin and EMA positivity. Four tumours showed S100 positivity with one of the poorly differentiated tumours being negative. Four of the tumours were brachyury positive (wasn't applied to one of the conventional chordoma). SMARCB1(INI1) immunohistochemistry was applied to all and both of the poorly differentiated tumours showed loss of expression.
Conclusion: Currently, WHO classifies chordomas into three subtypes: conventional, poorly differentiated, dedifferentiated. Features in paediatric population are different from the corresponding adult tumours. Majority of "poorly differentiated" tumours are found in children and diagnostic feature of this subtype is loss of SMARCB1(INI1) expression. Demonstration of bracyury positivity with loss of SMARCB1(INI1) expession are easily applicable diagnostic tests. Although the limited data on poorly differentiated chordomas show that they have poor prognosis, proving SMARCB1(INI1) loss provides an opportunity for possible targeted therapies.

PS-10-009

Does MYC-amplification help distinguishing primary from radiation-induced angiosarcomas?

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Background & objectives: Angiosarcomas (AS) can be primary (PAS) or secondary (SAS) to radiation therapy or chronic lymphedema. Both share histological findings, but genetic and molecular differences have been reported. We compared these features in 8 cases of AS.
Methods: We retrospectively reviewed 8 cases of AS (4 males and 4 females) diagnosed at our hospital between 1996 and 2022. Clinicopathological, immunohistochemical (IHC) and molecular studies were performed in 5 cases of PAS and 3 of SAS.
Results: Eight patients with an age range of 18-79.
Three had SAS 3-30 years after irradiation for breast carcinoma (2 cases) or brain astroblastoma. Five PAS were from the skin, breast, pleura, popliteal artery and penis. Histopathological study revealed a high-grade malignant mesenchymal tumour with proliferating endothelial cells and varying degrees of atypia and growth patterns (epithelioid, spindled, or vasoformative) in all cases, not distinguishing PAS from SAS.
p53 overexpression was seen in all 5 PAS, but it was absent in the 3 SAS cases.
While c-myc overexpression was demonstrated by IHC in all but the penile AS, only 3 PAS and 1 SAS showed low-level MYC amplification (3-5 copies).
Conclusion: In our study, c-myc immunohistochemical overexpression did not correlate with MYC gene amplification in all the cases. Low-level MYC amplification was found in 50% of our cases. Interestingly we couldn't demonstrate high-level MYC amplification (>10 copies) in any case. In our series, MYC and/or p53 alterations may play an important role to induce oncogenesis in AS, independently of prior radiation therapy, by increasing genomic instability.

PS-10-010

Usefulness of novel SS18-SSX and SSX c-terminus antibodies for identification of specific fusion oncoprotein in sarcomas

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Background & objectives: Chromosomal rearrangement can be identified by direct methods or immunohistochemical staining for a component of the fusion oncoprotein as a surrogate marker. We aim to gain insights into the staining profile of sarcomas using novel SS18-SSX and SSX c-terminus antibodies.
Methods: Retrospective analysis of 303 soft tissue sarcomas diagnosed at our Institution between 1999 and 2019 was performed, and tissue microarrays were constructed. Immunohistochemistry was conducted on the Benchmark Ultra platform with iVIEW DAB Detection Kit. Two different antibodies for SSX locus were used: SS18-SSX and SSX c-terminus. Ten whole-tissue sections of genetically confirmed synovial sarcomas were used as a control.
Results: In total, 19/303 (6.3%) and 23/303 (7.6%) sarcomas showed in most of the cases strong nuclear staining with SS18-SSX and SSX, respectively. In detail, from 21 synovial sarcomas, 19 (90.5%) stained positive for both antibodies. In 5 cases, nuclear staining for SSX antibody was weak. 9/10 (90%) control cases showed strong nuclear staining for SS18-SSX, and 3/10 (70%) were negative for SSX. Furthermore, SSX nuclear expression was also found in 4/56 (7.1%) myxofibrosarcomas. All other sarcomas, including various liposarcomas, angiosarcomas, undifferentiated pleomorphic sarcomas, leiomyosarcomas, and epithelioid sarcomas, were negative for both antibodies.
Conclusion: Novel SS18-SSX and SSX c-terminus antibodies are reliable diagnostic markers and can be used as surrogate markers to identify a specific fusion. The former antibody is more specific and shows strong nuclear staining in synovial sarcomas, whereas SSX can present with weak staining and is less specific. RNA-based NGS analysis should be performed in equivocal cases to confirm the specific rearrangement.

PS-10-011

Chordoma: significance and correlation of the localisation, vascular density and Ki67 for the occurrence of chordoma recurrence

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Background & objectives: Chordomas are malignant slow-growing, locally invasive tumours, usually localized in sacrum, vertebra and scull base, characterized by frequent relapses. The aim of the study is to examine the correlation between localization, blood vessels density and Ki67 value and disease recurrence.
Methods: All chordoma biopsies, taken in Institute for Orthopaedic Surgery Banjica in the period of five years (2017-2021), were analysed at the Institute of Pathology, in Belgrade. A total number of 21 cases were divided into two groups: patients with and without relapses. Ki67 value was counted on 100 cells in hot spot. Vascular density was estimated using CD34 immunostaining in 1mm2.
Results: Out of total 21 patients with chordoma only 9 had a relapse. The most affected bone was sacral bone, but without a statistically significant difference in the frequency of recurrence at different chordoma localizations. The average number of blood vessels in 1mm2 and value of Ki67 was statistically significantly higher in group of tumours with recurrence (p=0,015, p=0.033 respectively). Ki67 proliferative index values greater than 10% show a statistically significant difference in the frequency of relapses. The value of the proliferative index higher than 15% has a moderately high correlation with the occurrence of relapse.
Conclusion: Chordoma is a rare, but locally aggressive tumour, with high recurrence rate (35-40%). Based on our results, determination of the immunohistochemical expression of CD34 antigen in evaluation of vascular density, together with proliferative index Ki67 can be helpful to predict tumour recurrence.

PS-11 | Poster Session Cytopathology

PS-11-001

Pancreatobiliary cytopathology: the use of the Papanicolaou Society system in the transition towards a new era of standardised reporting

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Background & objectives: Modern diagnostic techniques have allowed for a less invasive approach to pancreatic cytopathology

sampling in combination with routine staining and immunohistochemistry. Our study aimed to compare the emerging Papanicolaou System with the C1-C5 grading system in a single UK institution.
Methods: We retrospectively assessed 723 cases of pancreatobiliary cytology with 142 cases demonstrating corroborative histology. The reported C1-C5 grade was reviewed by 2 independent pathologists and assigned a grade within the Papanicolaou Society of Cytopathology Guidelines for pancreaticobiliary cytology. We were then able to compare the 2 grading systems for diagnostic accuracy, sensitivity, specificity, false positive and false negative rates.
Results: All cases which were originally assigned to C1, C2, C4 and C5 categories maintained the diagnostic category assignment when comparing to the Papanicolaou Society system. The number of cases reported as atypical was reduced from 93 to 73 when using the Papanicolaou Society system; 5 cases were subsequently reported as IVA and 15 cases IVB.
Sensitivity was 98.3%, specificity 75%, false positive rate 2.5% and false negative rate 11.8% with a diagnostic accuracy of 91.5% with the C1-C5 system. The Papanicolaou Society guidelines showed a sensitivity of 99.1%, specificity of 79.1%, false positive rate of 2.5% and a false negative rate of 5% with a diagnostic accuracy of 94.3%.
Conclusion: The increasingly international approach to pathology highlights the need for a standardised reporting system to facilitate safe but effective communication whilst enabling national and international data comparisons. Our data supports the adoption of the Papanicolaou system recommended by the Royal College of Pathologists (UK); comparable results are achieved compared to C1-C5 whilst reducing the number of cases reported as atypical allowing for more informed diagnostic decisions to maximise patient benefit as we embark on the next generation of pathology.

PS-11-003
Pancreatic neuroendocrine tumours: the shifting scales of lesion classification
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Background & objectives: Pancreatic neoplasms are classified using C1-C5 or Papanicolaou Society of Cytopathology; the latter groups lesions of variable malignant potential into a single category. The World Health Organisation proposes a new classification with pancreatic neuroendocrine tumours as malignant entities alongside adenocarcinomas.
Methods: We analysed 68 cases of pancreatic neuroendocrine tumours with corroborative cytology available in 47 cases over a 12 year period. We classified each case using C1-C5 Grading, Papanicolaou Society of Cytopathology and the proposed World Health Organisation classification for pancreatic lesions. We assessed the Ki-67 grading and presence of poor prognostic factors including vascular or perineural invasion and resection status.
Results: Cytological assessment reported 80.4% of lesions as IVB on Papanicolaou grading and 76% as C5 lesions. 73.1% of resected tumours were grade 1, 19.4% grade 2 and 7.5% grade 3. Overall staging using TNM8 showed 44.8% of lesions were T1, 31.3% T2, 19.4% T3 and 4.5% T4. 10 cases (14.9%) showed lymph node involvement. Complete resection was achieved in 83.6% of cases. Vascular invasion was seen in 29.9% of cases and perineural invasion in 9%. 32 biopsies had both cytology grade and histological grade reported and this was concordant in 87.5% of cases. 1 multifocal tumour was reported which was non-concordant highlighting the importance of clinicopathological correlation following biopsy sampling.
Conclusion: Standardised reporting systems are an important tool facilitating effective communication on a national and international level. The Papanicolaou system uses a pragmatic approach to distinguish these lesions from more aggressive entities to offer flexibility in management however the updated WHO system removes this distinction. It may be beneficial to use the new WHO low risk and high risk pancreatic neoplasm categories to promote discussion on the risk to benefit ratio of surgery for these lesions whilst effectively risk stratifying patients.

PS-11-004
What is the risk of malignancy associated with diagnostic categories of proposed World Health Organization international system for reporting pancreaticobiliary cytopathology?
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Background & objectives: The Papanicolaou Society of Cytopathology(PSC) reporting system for pancreaticobiliary cytology has 6 categories(I-VI) providing risk assessment and guidance for patient management. World Health Organization(WHO) proposed an updated reporting system. Risk of malignancy(ROM) of new categories of WHO system needs defining.
Methods: 420 pancreatic ESU-FNA materials from 410 patient from our archive from the last 12 years have been reviewed and categorized both according to the PSC and proposed WHO reporting systems. Histological diagnosis and/or clinical follow-up of patients were searched from hospital's database and risk of malignancy for both systems respectively were evaluated through statistical analysis.
Results: The absolute risk of malignancy for each diagnostic category of the proposed WHO system were as follows: 35% for insufficient/inadequate nondiagnostic category, 1.0% for benign/negative for malignancy, 69.0% for atypical, 11% for PaN-Low, 100% for PaN-High, 91% for suspicious for malignancy, and 100% for malignant. Comparatively, the absolute risk of malignancy for the same cohort with the diagnostic categories of the PSC system was as follows: 34% for nondiagnostic category, 1.0% negative (for malignancy), 50.0% for atypical, 0.0% for neoplastic: benign, 16% for neoplastic: other, 5% for neoplastic: other with LGA, 100% for neoplastic:other with HGA, 88% for suspicious (for malignancy), and 100% for positive or malignant.
Conclusion: -This study has shown that, with its high ROM(100%), the PaN-HGA group could be included at least in the "suspicious for malignancy" category because these patients will already be managed by surgery because of risk of having invasive component. In our cohort, a separate group for these cases seems to be unnecessary.
-Inclusion of SPN and NETs in the ''positive for malignancy'' group is a justifiable decision.
-There is no need for a separate "Neoplastic:benign" category for SCA and lymphangioma cases.

PS-11-005
Fine needle aspiration biopsy and cytomorphologic spectrum of Hashimoto's thyroiditis

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Background & objectives: To determine the cytologic interpretation as well as various differential diagnostic problems of Hashimoto's thyroiditis that is the most common form of thyroiditis.
Methods: We analysed data on 93 patients with nodular or diffuse palpable enlargement of the gland, who underwent fine needle aspiration and were diagnosed with Hashimoto's thyroiditis. Thyroid hormonal assay and antithyroid antibody levels were evaluated.
Results: Hurthle cells mostly in tissue fragments were present in all cases and the cellularity was variable. Histiocytes with phagocytic debris were present in 9 cases(9,6%), whereas follicular cells without follicular pattern in 22(23,6%). All cases showed lymphocytes and occasional plasma cell and immunoblasts. Colloid was absent. Coexistence with papillary carcinoma confirmed by histology was found in6 (6,66%) female patients Laboratory examination revealed high levels of TSH and anti-peroxidase antibodies in all malignant cases. In 4(4,3%) patients a differential diagnosis with non Hodgkin lymphoma was taken into account but immunocytology confirmed the reactive nature of the lymphocytes.
Conclusion: Hashimoto's thyroiditis diagnosis can be achieved in the majority of cases. Careful interpretation of fine needle aspiration material and correct evaluation of all cytomorphological findings are required in order to minimize potential pitfalls. Papillary carcinoma and non Hodgkin lymphoma have to be ruled out in some cases. The differential diagnosis includes also follicular and Hurthle cell neoplasms.

PS-11-007
Mediastinal metastases diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration. Beyond lung cancer metastases
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Background & objectives: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is increasingly used in the diagnostic and staging of mediastinal lymph node metastases. The cytological diagnosis of metastases from extrapulmonary primaries can be challenging if we only consider a pulmonary origin.
Methods: A retrospective review of EBUS-TBNA specimens with clinical and radiological diagnosis of mediastinal lymph node metastases (PET-CT SUV max >2,5) from the Pathology Department files of our institution between 2018-2021 was performed. In total, 179 patients were included. In all cases, an immunocytochemical study was done in order to determine the origin of the neoplasm.
Results: A lung origin was confirmed in 146 of the studied cases (81.5%). The diagnosis of the cases with an extrathoracic primary tumour was confirmed in 19 cases (10.6%). Metastases of mammary (n=6); prostate (n=2); colorectal (n=2); urothelial (n=3) and mesenquimal(n=2) origin were observed. Despite the complementary studies, a definitive origin could not be reached in 14 cases. Enteroid pattern adenocarcinomas (n=1) and squamous adenocarcinomas in patients with a previous history of primary urothelial (n= 3) and cervical neoplasia (n=2) supposed a difficult differential diagnosis. Also mucinous neoplasms mimicking a gastro-biliary-pancreatic origin (n=3), acinar patterns (n=2) resembling prostate adenocarcinomas and neuroendocrine neoplasm without known primary (n=3) implied a diagnostic challenge.
Conclusion: Advanced target therapies in lung cancer force pathologists to optimize the material obtained in EBUS-TBNA procedures for molecular study. A comprehensive review of the cytological features may help recognising the origin of the neoplasm. However, an holistic view of the patient clinical history and immunocytochemical or even molecular techniques are also needed, specially if extrathoracic metastatic cases are suspected.

PS-11-008
Programmed Death Ligand 1 (PD-L1) expression in fine needle aspiration cell blocks of head and neck squamous cell carcinoma and its cytohistological concordance
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Background & objectives: PD-L1 immunoexpression in head and neck squamous cell carcinoma (HNSCC) determines immunotherapy eligibility. Patients are often diagnosed using fine needle aspiration (FNA) of metastatic lymph nodes, however, the cytohistologic correlation of the combined positive score (CPS) is largely unknown.
Methods: This study retrospectively identified 43 patients, between 2016 and 2020, with HNSCC diagnosed on surgical (SpS) and cytologic specimen (CyS). Slides were reviewed and cases with <100 tumour cells or if the block was missing, were excluded. This resulted in 36 cytology cell blocks and 39 surgical tissue blocks for PD-L1 immunohistochemistry (22C3 clone). All cases were scored with CPS.
Results: The CPS (<1%/≤20%><!--1-->20%) for the SpS and CyS were as follows: 2(5.9%) /17(50.0%) /15(44.1%) and 10(29.4%) /11(32.4%) /13(38.2%), respectively. There was a total of 34 case pairs, composed of 13 pairs with matched site (neck lymph nodes) and 21 pairs with the primary site of SCC (biopsy/resection) and corresponding FNA of lymph node metastasis. There was fair overall agreement (OA) of 76.5% (k=0.261) at a CPS cut-off of 1%. The OA did not differ significantly between the case pairs with matched and unmatched sites (p=0.4653). CyS has a specificity and positive predictive value (PPV) of 100%, but only a sensitivity of 75% and negative predictive value of 20%.
Conclusion: PD-L1 immunohistochemistry assessment on CyS only shows fair agreement with its surgical counterpart. However, CyS demonstrates high PPV with no false positive results based on our limited study. This needs further evaluation as our study are low in case with negative CPS (<1%). In the event of a negative CPS on CyS, a reassessment of PD-L1 on a surgical/histological specimen should be attempted due to the chance of a false negative result.

PS-11-009
Association of high-risk HPV strains other than 16 and 18 with progression from atypical squamous cells of undetermined significance to worse abnormal cervicovaginal cytology over a 5-year period: results from a single academic institution
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Background & objectives: Cervical cancer is the fourth most common cause of cancer in women. We aimed to assess association of high-risk HPV strains (other than 16 and 18) with progression from atypical cells of undetermined significance (ASCUS) to worse cervicovaginal cytology.

Methods: A retrospective review of 417 consecutive patients from 2014-2021 identified 65 patients with ASCUS cytology and high-risk HPV strains (other than 16 and 18). Progression from ASCUS to low grade squamous intraepithelial lesion (LSIL), atypical squamous cell cannot rule out high grade (ASC-H), high grade intraepithelial lesion (HSIL) or cancer in cytology was assessed and stratified by HPV vaccination status.
Results: A total of 65 female patients (age range = 22-71 years, mean age = 37.2 years) who were infected with high-risk HPV strains (other than 16 and 18) and had ASCUS cytology were included. In a follow up period ranging from 6 months to 5 years, 50 out of the 65 patients had no progression, 12 progressed to LSIL, 1 had ASC-H and 2 had HSIL on Papanicolaou smears. 17 patients received bivalent, trivalent or quadrivalent HPV vaccines whereas only 4 patients received the nonavalent HPV vaccine. The rate of progression was 25% in unvaccinated patients, 19% in vaccinated patients and 0% amongst patients who were administered the nonavalent vaccine.
Conclusion: Our preliminary findings indicate a high association of high-risk HPV strains other than 16 and 18 and progression from ASCUS to worse abnormal cervicovaginal cytology, especially in the patients who did not receive the nonavalent vaccine. Of note, ASC-H and HSIL progression was observed only in unvaccinated patients. We will explore these associations in larger population datasets to confirm our findings and potentially encourage utilization of the more comprehensive nonavalent HPV vaccine.

PS-11-010
Atypical urothelial cells: two-year-experience with the Paris system for reporting urinary cytology in tertiary care centre pathology
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Background & objectives: The implementation of The Paris System for Reporting Urinary Cytology (TPS) emphasizes detection of high-grade urothelial carcinomas in urine. “Atypical urothelial cells” is a TPS category reserved for cytological samples with mildly or moderately atypical urothelial cells.
Methods: Urinary cytological specimens from the first two-year-period (January 2017-December 2018) after TPS introduction were retrospectively analysed with cyto-histological correlations. The timeframe for histological follow up was at least 6 months.
Results: Total of 3741 urinary specimens were analysed during the study period with the following categorization: 49 (1.31%) insufficient samples, 3334 (89.12%) negative samples, 205 (5.48%) “atypical urothelial cells” samples, 89 (2.38%) “suspicious for high-grade urothelial carcinoma” samples, 62 (1.66%) cytological “high-grade urothelial carcinoma” samples and only two (0.05%) “low-grade urothelial neoplasm” samples. Out of 205 “atypical urothelial cells” samples, histological follow up was available in 97 (47.32%) cases: 27 (27.84%) were low-grade urothelial carcinomas, 34 (35.05%) high-grade urothelial carcinomas and 36 (37.11%) non-tumorous lesions in final histology.
Conclusion: The risk of malignancy was 29.8% in all “atypical urothelial cells” samples and 62.9% in histologically verified specimens. Urinary cytology is a rapid, non-invasive and cost-effective method both in diagnosing and follow up of urothelial malignancies with TPS increasing its clinical value.
Funding: VTR grant from Pirkanmaa Hospital District

PS-11-011
Fine needle aspiration biopsy of pilomatrixoma (Cytological features of 6 cases histologically approved)
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Background & objectives: Pilomatrixoma is a rare, benign skin adnexal tumour of hair matrix, commonly presents as a slow growing firm to hard intradermal or subcutaneous solitary nodule. We present our experience with fine-needle aspiration biopsy (FNAB) of 6 histologically confirmed pilomatrixoma cases.
Methods: Our series includes FNAB slides of 6 cases of pilomatrixoma, which were histologically approved. The slides were prepared by conventional method and liquid-based cytology techniques. Conventional method was used to prepare the cell blocks.
Results: The ages of patients ranged from 8-63 years old. The male-to-female ratio was 2/1. All cases occurred in the head and neck area. The aspirates were cellular. The smears contained moderate to high numbers of basaloid cells, anucleated squamous cells and debris. Basaloid cells were small and uniform. They were arranged in crowded groups. The chromatin was finely granular and consistently even in distribution. Most of the smears were rich in giant cells and cell debris in the background. Mitotic figures and sheets of ghost cells were identified as well. Five cases were diagnosed as pilomatrixoma and one as epidermoid/dermoid cyst.
Conclusion: Excisional biopsy is often the preferred method of diagnosis for the cutaneous masses. There are very few reports on the cytologic features of pilomatrixoma in FNAB smears. The combination of basaloid cells, ghost cells, squamous and giant cells are the key features that will allow a conclusive diagnosis of pilomatrixoma by FNAB.

PS-11-012
Metastases of extrapulmonary malignancies in mediastinal lymph nodes sampled by Endobronchial ultrasound-guided transbronchial needle aspiration
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Background & objectives: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is also useful method for detecting metastases of extrapulmonary malignancies (EPM) as well as metastases of lung cancer. We aimed to analyse the cytomorphological and immunohistochemical features of EPM metastases in mediastinal lymph nodes.
Methods: The 375 EBUS-TBNA samples were analysed retrospectively that reported by a cytopathologist in an 18-month period. Demographic data and clinical information were obtained from pathology reports. The slides were prepared by conventional method and liquid-based cytology techniques. Conventional method was used to prepare the cell blocks.
Results: Of the 375 EBUS-TBNAs, 147 (39.2%) were mediastinal LN metastases from lung cancer, 10 (2.7%) were metastases from EPM, two (0.5%) were lymphoma, and 199 (53.1%) were benign. The mean age metastasis of EPM was 67.2 (range: 52-86) with a male-to-female ratio 3:2.
The distribution of metastases from EPM as follows: adenocarcinoma of gastrointestinal tract: 3, breast carcinoma: 2, prostatic adenocarcinoma: 2, renal cell carcinoma: 2, and papillary thyroid carcinoma: 1. Immunohistochemical study was performed in 9 of 10 cases. Cell block was not formed in one case. Most used immunohistochemical marker was TTF-1 (n:9).

Conclusion: EBUS-TBNA is an effective and useful procedure in detecting EPM metastases as well as lung cancer metastases in mediastinal lymph nodes. It should be kept in mind that there may be EPM metastases to this region even in cases with unknown primary, and additional studies will be useful when necessary.

PS-11-013

Standardization of p16/ki-67 immunocytochemistry in conventional cervical cytology for detection of high-grade cervical squamous intraepithelial lesion

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Background & objectives: Detection of p16/Ki-67 expression increases the cervical liquid based cytology performance to diagnose high-grade squamous intraepithelial lesion (HISL). Scarce studies have evaluated its use in conventional cytology, the screening test used in women <30 years in many Latin American countries.
Methods: The implementation of p16/Ki-67 dual staining was evaluated in conventional cervical cytology smears with HSIL, with a corresponding confirmatory biopsy study. Xylene pretreatment of the smears was carried out to remove the coverslip, before discoloration, rehydration and antigen retrieval. The dual-staining protocol was followed with different incubation times of the primary antibodies, in areas with morphologically altered cells, previously demarcated.
Results: Were included 40 smears with median storage of 233 days. Most of the slides (80%) required a previous time in xylene of two days. There were no statistically significant differences in p16/Ki-67 dual staining in relation to results of conventional cytology, nor with the histopathological diagnosis. Also not in comparison with the slides storage time, the time previously required in xylene, or the incubation time of the primary antibodies. Comparing p16/Ki-67 dual staining with cytological results, it was positive in 75% of the cytologies reported as HSIL; regarding histopathology, it was observed in 61.5% of the cases with diagnosis of HSIL/CIN2, and in 81.2% of the cases diagnosed as HSIL/CIN3.
Conclusion: The p16/Ki-67 dual staining can be performed on archival conventional cervical cytologies with good results. The techniques for the pretreatment of these smears are varied but effective, and for an optimal result the staining protocol should be followed according to the manufacturer recommendations. Considering the wide use of conventional cytology in Latin America, and the scarcity of studies on the usefulness of p16/Ki-67 dual staining in this type of smears, it is necessary to continue research in this field.
Funding: Universidad de Cartagena, Cartagena, Colombia.

PS-11-014

Secondary thyroid tumours in fine needle aspiration cytology: Finding the black cat in a coal cellar!

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Background & objectives: Despite the rarity, secondary thyroid tumours(STT) can mimic the commoner primary thyroid tumours challenging the cytopathologist who serves as primary diagnostician in the initial workup of thyroid disease. We aim to review our experience and analyse STT with cytopathologic correlates.
Methods: Retrospective study between a 13 year period(2009-2021). Secondary thyroid tumours were defined as non thyroid-epithelial origin tumours which included either metastasis or direct extension from adjacent organ into thyroid parenchyma. Thirty-three cases of STT were found from archives. Clinical history, age, gender, radiologic and cytologic features were noted. Validation of cytologic diagnosis was made by immunocytochemistry(cell blocks) or on biopsy.
Results: The most common site of origin was head and neck(15/33). Age ranged between 4–80 years(median 55) with slight male predilection(M:F ratio 1.6:1). Most presented as a solitary nodule within the thyroid(23/33) with a concomitant primary in the vicinity or distant area. Metastatic disease elsewhere at presentation was seen in majority(17/33). Exclusive presentation as carcinoma of unknown primary in thyroid was seen in one-fourth(8/33). None of the cases underwent thyroidectomy. Chemotherapy was used to treat hematopoietic neoplasms(8/33). The interval from primary diagnosis to thyroid metastasis varied between 0-6 years. Diagnostic challenges surfaced when distinguishing squamous cell carcinoma from high grade/anaplastic thyroid carcinoma and metastatic adenocarcinoma from follicular thyroid lesions.
Conclusion: New findings from our research include predominance of head and neck squamous cell carcinoma attributable to geographic variation and STT presenting substantially as solitary thyroid mass. Few unusual tumours like langerhans cell histiocytosis, thymic carcinoma and large cell carcinoma were encountered. FNAC is indispensable in diagnostic workup of STT. Distinction between primary versus secondary thyroid tumour has divergent clinical implications, mandating high precision diagnosis. Thorough clinicoradiologic correlation with cytomorphologic subtleties, use of ancillary techniques(cell block, immunocytochemistry) ensures optimal patient management.

PS-11-015

Pathologist-performed palpation-guided fine needle aspiration cytology of head and neck masses including oral lesions: impact on sample adequacy and the importance of obtaining cell blocks for diagnostic accuracy

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Background & objectives: Fine-needle aspiration cytology (FNAC) is a simple, feasible, safe, inexpensive method in diagnostic, surgical, therapeutic approaches to superficial head and neck masses. Here, we share the data from our practice and point at the role of pathologists during FNAC procedure.
Methods: A total of 124 FNAC (on 121 patients), were performed without ultrasound guidance in our pathology department by an experienced (25+ years) fine-needle aspiration (FNA) pathologist (*) for palpable masses from January 2015 to March 2022, and were reviewed according to the anatomic location (oral cavity, soft tissues, lymph nodes and salivary glands).
Results: Three out of 124 FNACs (2.4%) were non-diagnostic (acellular). 12 (9.7%), 19 (15.3%), 48 (38.7%) and 45 (36.3%) were from the oral cavity, salivary glands, lymph nodes and soft tissue; respectively. A total of 106 cell blocks (85.4%) were obtained. Of these 106 cases; immunohistochemistry was studied in 37 (34.9%), histochemistry in 9 (8.5%) and in situ hybridization in 13 (12.2%). Histological data (follow-up resection specimens and/or cell blocks obtained from FNACs) were obtained in 114 cases (91.9%).

Conclusion: In conclusion, our data supports that pathologist-performed FNAC is an important part of the initial evaluation in patients presenting with a head and neck mass, and helps in avoiding unnecessary surgical procedures with high diagnostic accuracy. During the FNAC session, the pathologist examines the patient, takes a good clinical history, performs the aspiration procedure, prepares the slides with rapid on-site assessment, checks the adequacy, and then continues the process until sufficient material is obtained to ultimately make a diagnosis.

PS-11-016

Evaluation of a cytomorphology-molecular co-test of urine in bladder cancer patients

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Background & objectives: Urine cytology used for monitoring of Non-Muscle Invasive Bladder Cancer (NMIBC) has low sensitivity for low-grade tumours, which present FGFR3 mutations. These activating mutations were examined in urine processed with THIN PREP, as potential biomarker to improve cytology performance.
Methods: We examined 38 urine specimens in THIN PREP. A slide for cytology was prepared and the remaining sample was used for DNA isolation. Exons 7 and 10 of FGFR3 gene harbouring hot spot mutations were amplified by PCR and analysed by direct sequencing. Molecular results were compared with cytology reported according to Paris system and were correlated to histology.
Results: Cytology was performed in urine samples of 38 patients; 26 cases were classified as high-grade urothelial carcinoma (HGUC), 6 as atypical urothelial cells (AUC) and 6 as suspicious for high-grade urothelial carcinoma (SHGUC). Sequence analysis of both exons 7, 10 of the FGFR3 gene was performed. Exon 10 analysis revealed no mutations. However, 4 patients had a c.746C>G substitution leading to p.S249C mutation at exon 7 of FGFR3 gene. Cytology report was AUC in two of them and SHGUC in the remaining two. The corresponding histology showed low- and high-grade carcinomas in three and one cases, respectively. None of the patients classified as HGUC had FGFR3 mutations.
Conclusion: Urine cytology is useful for detecting HGUC, whereas AUC does not provide specific information and may include low-grade tumours. We found that FGFR3 activating mutation p.S249C in exon 7 is present mostly in low-grade carcinomas and exceptionally in high-grade carcinomas. This preliminary study shows that a cytomorphology-molecular co-test in the same urine sample could contribute to define the atypical and suspicious categories of cytology by depicting low-grade tumours. Thus, a more precise stratification of patients can be achieved.

PS-11-017

Cytological rapid on-site evaluation in pulmonary biopsies: optimizing material and accelerating diagnosis

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Background & objectives: The in situ cytological assessment of pulmonary biopsies obtained by different techniques allows evaluating the quality and quantity of the material obtained, avoiding reintervention especially in hard-to-reach lesions and speeding up the definitive diagnosis.
Methods: We present a prospective study of 23 cases comparing the in situ assessment of the imprint of the biopsy with the final delayed diagnosis. The rapid on site evaluation (ROSE) technique was performed by fixing the imprint in alcohol and staining for 1 minute with haematoxylin. A cytotechnician and a cytologist evaluated the sample (65% of them through telecytopathology).
Results: Cases were classified as positive, negative, insufficient, suspicious of neoplasia and undetermined. A concordance of 82.6% was reached between both methods (19/23 cases). There was only one case with disagreement between ROSE and the definitive diagnosis: the former classified as negative and the latter positive (squamous cell carcinoma). ROSE was not conclusive in 13% cases (3/23): one of them suspicious for carcinoma with a final diagnosis of infiltrating adenocarcinoma, a second one undetermined with a diagnosis of metastatic adenocarcinoma and the last one with insufficient material in the imprint to reach a proper orientation that resulted in a negative diagnosis for neoplasia.
Conclusion: Carrying out an in situ cytological assessment of lung biopsies is a practical approach that is usually concordant with the definitive diagnosis and could facilitate and optimize the obtention of an adequate sample to avoid extra intervention by evaluating the adequacy of the sample. Thus, an adequate and representative sample of the lesion facilitates a more accurate morphological, immunohistochemical and molecular study, leading to an important impact in prognosis and targeted treatment of patients in the era of personalized medicine.

PS-11-018

Clinical trial: a new method for preparing cell blocks from paucicellular aspirates

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Background & objectives: Multiple methods have been historically utilized for obtaining cell blocks with significant variation and lack of reproducibility. Complex, time-consuming steps generate high losses of cellular material whilst the low yield of sections precludes evaluating coordinate immunoreactivity patterns on serial sections.
Methods: The CytoPod™ method for cell blocks employs a concave nitrocellulose filter affixed to a perforated sectionable matrix and vacuum filtration for capturing cellular material. Clinical samples such as: EBUS-TBNA, BAL, bronchial and pleural aspirates and ascites fluid were processed in duplicate into cell blocks using both the Thermo Scientific Shandon Cytoblock and the CytoPod™ systems.
Results: After the preliminary steps of washing/concentrating the aspirates (if needed) both methods allowed the preparation of cell blocks. Remarkably, the CytoPod™ method performed with low- to substantially zero-cell losses, was compatible with all usual fixatives and from each paraffin block over 150 serial sections were obtained. Even with very low volume samples (<1 mL) and cellularity (<100,000 cells) the diagnostic material was distributed uniformly on both the bottom and along sidewalls of the filter. Serial sectioning was undemanding while reading the slides proved expeditious due to predictable cellularity and layout of the diagnostic material within the sectionable matrix. No interference with IHC and ISH was observed.
Conclusion: Cell blocks from paucicellular aspirates are a cost-effective option in cytopathology and can be comparable in diagnostic value to FFPE from biopsy. Such a practice in a universal fashion would result in reproducible results with interinstitutional

comparability and would yield valuable results of ancillary studies (IHC and molecular tests) as well as an excellent archival material. This is highly significant due to the increasing number of tests with direct impact on targeted therapy, in the personalized medicine.

PS-11-019

Cervical atrophy as a pitfall for cytological diagnosis: a 5-year study from a tertiary centre in Lisbon

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Background & objectives: Atrophy is a well-documented diagnostic pitfall for squamous cell lesions in cervical cancer screening in peri- and post-menopausal women. This study aims to evaluate the screening accuracy in women aged 45-years or older to determine whether aging affects cytological interpretation.
Methods: We reviewed all cervical cytology reports, spanning through 2017-2021 and pertaining to women ≥45 years. A correlation of Bethesda categories of "Negative for Intraepithelial Lesion/Malignancy'' (NILM) with reported atrophy, "Atypical Squamous Cells cannot exclude high-grade" (ASC-H) and "High-grade Squamous Intraepithelial Lesion" (HSIL) with subsequent histological studies were performed. High-risk HPV co-testing results (Cobas®) were additionally recorded.
Results: A total of 226 cytological diagnoses and matched histological evaluations (taken simultaneously or up to 24 months prior) were assessed. In instances with multiple tissue specimens, the higher-grade diagnosis was recorded; samples insufficient for diagnosis were excluded. The risk of malignancy (ROM) ranged from 13.1% to 80.6% in negative and positive categories, respectively; the performance analysis revealed a sensitivity of 93.0%, a specificity of 62.4%, a positive predictive value of 80.6% and a negative predictive value of 86,9%. When intraepithelial lesion was present, HPV-16 was detected in 29.5% and HPV-18 in 3.6% of cases.
Conclusion: Overall, as a cervical cancer screening, cytology shows a good sensitivity with a lower specificity, as expected. Although Bethesda criteria accurately define atrophy, it is important to be aware that these benign changes can lead both to overdiagnosis, mostly by overvaluing slight changes, and underdiagnosis, by dismissing cytological atypia.

PS-11-020

Added value of cell block over liquid-based cytology alone in the diagnosis of non-necrotizing lymphadenopathy on endoscopic ultrasound–guided-transbronchial needle aspiration of mediastinal lymph nodes for sarcoidosis investigation

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Background & objectives: Endoscopic ultrasound–guided-transbronchial needle aspiration (EBUS-TBNA) for sarcoidosis investigation can be evaluated by conventional cytology, liquid-based cytology (LBC) and cell block (CB), with few data published about their performance. We reviewed our case history for discordant results between CB and LBC.
Methods: We reviewed all of the cases addressed over the last year for investigation of mediastinal lymphadenopathy with suspicion of sarcoidosis, for which patients had signed the general consent for research in our institution. We identified four patients who had undergone EBUS-TBNA. All of them were also investigated by bronchoalveolar lavage (BAL). Flow cytometry was performed on BAL with lymphocytosis.
Results: We recovered 4 patients (4 males; mean age: 50 years) with a total of 9 TBNAs of mediastinal lymph nodes. For all of the TBNAs, no granuloma was observed on LBC slides (in two cases, only histiocytes were present). CB was done for 8/9 TBNA (89%); in 7/8 cases (88%), granulomas were seen on the CB in the absence of necrosis, thus leading to the diagnosis of non-necrotizing lymphadenopathy in 4/4 patients. On BAL, two patients showed lymphocytosis with mildly increased CD4+/CD8+ (3.9 and 3.08; reference range: 1.3–3).
Conclusion: The addition of CB in the processing of EBUS-TBNA performed in the context of sarcoidosis investigation in patients with mediastinal lymphadenopathy can help to detect the presence of granulomas, which may otherwise not be present on LBC slides. As not all laboratories routinely perform CB in tandem with LBC preparations, this may represent a diagnostic pitfall. We therefore recommend that a CB be performed on EBUS-TBNA in this particular context.

PS-11-021

Random rescreening 10% of negative cervicovaginal smears: method for quality assurance

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Background & objectives: Laboratories use different methods of quality assurance for cervicovaginal smears. Random rescreening of %10 of negative gynaecologic smears is one of the effective methods for decreasing false negativity. In this study, we presented our single-institution data.
Methods: All negative gynaecologic smears diagnosed over 29 months are included in this study. We plan the review of the smears weekly. We randomly select 10% of negative smears and distribute them crosswise among pathologists. If any discrepancy occurs between primary and secondary screeners, we try to reach a consensus on the diagnosis by including tertiary or quaternary assessments.
Results: Twenty-eight thousand five hundred twelve smears were negative, and 10% were rescreened between November 1, 2019, and March 31, 2022. Of these rescreened ones, sixteen of them were evaluated as false negatives. Eleven were reported as atypical squamous cells of undetermined significance (ASC-US), four as low-grade squamous intraepithelial lesion (LSIL), and one as adenocarcinoma.
Conclusion: Random rescreening 10% of negative smears can effectively improve laboratory performance and decrease false-negative numbers. Unlike other studies and practices, we do not sign out reports of these selected smears that will be rescreened and wait for the consensus if any discrepancy occurs. So this study can be considered not a retrospective study but rather a prospective practice of our institution.

PS-11-022

HPV-based opportunistic cervical cancer screening in Barcelona. Preliminary results in >30 year old women

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Background & objectives: Cervical cancer screening using HPV detection as the primary test is being implemented in Barcelona in

women > 30 years since 2018. The aim of this study is to analyse the detection of CIN2+ cases within the new screening protocol.
Methods: HPV detection is performed by Cobas-HPV Test (Roche) with cytology as triage test. Colposcopy is indicated when cytology is positive (ASC-US or worse), and in HPV16 and/or 18 cases. Cross-referencing of the HPV screening database and the anatomic pathology database was performed, in order to obtain the CIN2+ detection rate.
Results: HPV test was positive in 16.2 % (n=10,239) of women (range: 22.2% in 30-35 y.o, to 8 % in 51-65 y,). CIN2+ lesions were detected in: 15.9% of HPV16±others, 5.2% of HPV18±others and in 2.6% of non 16/18 HPV. Among HPV+ women 30 to 35 y.o., CIN2+ lesions were more frequent (23.4%) than in >35y.o. ones (18%).
Conclusion: HPV based cervical cancer screening in our region has diminished more than 80% the number of cytologies, however more than 50% of them have abnormalities detected. The protocol has shown a PPV of HPV for CIN2+ higher in HPV 16/18+ women (38 %) than in non-HPV16/18+ (14%). These results are in accordance with those in other countries and validate the new screening protocol.

PS-11-023
Malignancy rate of atypia of undetermined significance/follicular lesion of undetermined significance in thyroid FNAs in Greater Vancouver, Canada
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Background & objectives: Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) is a challenging category comprised of a heterogeneous group of lesions. The objective of this study was to evaluate the malignancy rate of thyroid fine needle aspiration (FNA) diagnosed as AUS/FLUS.
Methods: This is a retrospective population-based study of all thyroid FNAs diagnosed as AUS/FLUS in Fraser Health in Greater Vancouver area during a six-year period (2014-2019). FNA diagnoses were correlated with clinical outcome in subsequent years including repeat FNA, surgery, and clinical/imaging follow-up. Clinical and radiologic factors were compared to identify malignancy-related features.
Results: A total of 443 cases of AUS/FLUS were included. Repeat FNA was performed on 222/443 (50.1%) nodules, and 187/443 (42.2%) underwent surgery. The overall incidence of malignancy when a diagnosis AUS/FLUS is rendered in our study was 11.5% (51/443). Fifty one of 187 patients (27.3%) who underwent surgery had malignant thyroid carcinoma (38 papillary, 8 follicular, 5 with medullary, poorly-differentiated or anaplastic carcinoma). There were no statistically significant differences in age, sex and nodule size between benign and malignant cases. The rate of malignancy was 12.6% (28/222) in patients who underwent immediate surgery following the first AUS/FLUS diagnosis, while it was 10.4% (23/221) in patients who underwent repeat FNA (P=0.2).
Conclusion: The malignancy rate of AUS/FLUS in the study is consistent with the recommended range proposed by the 2017 Bethesda System for Reporting Thyroid Cytopathology. Demographic and radiologic findings were not significantly associated with upgrade malignancy risk. No significant difference was found in malignancy risk between those who underwent immediate surgery versus patients who underwent surgery after a repeat FNA following the initial diagnosis of AUS/FLUS.

PS-11-024
Liquid-based cytology in the detection of premalignant lesions in patients with "Atypia in Squamous Cells" in conventional cytology
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Background & objectives: Management of "Atypical Squamous Cells" (ASC) in conventional cytology (CC) is based on the risk of High-Grade Squamous Intraepithelial Lesion (HSIL). Efficacy of liquid-based cytology (LBC) to detect HSIL is variable, with little evidence of its performance in Colombian patients.
Methods: Were obtained patients who attended colposcopy clinic due result of ASC in CC. A cervical sample for LBC was obtained from these patients which was interpreted by two pathologists without access to other results. The performance of LBC to detect HSIL was determined considering colposcopic/histological diagnosis as a gold standard: negative-satisfactory colposcopy/histopathological report. Two age groups were compared (<30/≥30 years).
Results: Were included 114 patients, with previous report of ASC-US in CC, (there were no reports of ASC-H), with a mean age of 38.4 years (SD ± 13.3). LBC had abnormal results in 40.36% (n=46), with slightly higher proportion of Low-Grade Squamous Intraepithelial Lesion (LSIL) than HSIL. The total of abnormal diagnoses by colposcopy and/or biopsy was 51.75% (n=59) with a predominance of LSIL (36.84%). The sensitivity of the liquid-based cytology to detect premalignant lesions was 76.5%, specificity: 66.0%, positive predictive value: 28.3% and negative predictive value: 94.1%. The Cohen's Kappa index of LBC for detecting HSIL was 0.2492 for the total population and 0.2907 for ≥ 30 years.
Conclusion: This is the first prospective study conducted in Colombian patients with abnormal ASC cervical cytology to assess the diagnostic performance of LBC and CPS in detecting HSIL compared to histopathology. It can be concluded that although LBC decreases the total number of abnormal cytology and increases the detection of HSIL, improving diagnostic precision and decreasing the number of ASC-US, its concordance with the gold standard is discreet, being higher to detect HSIL especially in patients aged 30 years or older.
Funding: Universidad de Cartagena, Cartagena, Colombia.

PS-11-025
Applicability of the Sydney System and touch imprint cytology methodology in lymph node samples obtained by EBUS-TBNA. Three years of experience and 402 cases
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Background & objectives: The Sidney System for reporting lymph node FNA has standardized the diagnostic procedure. We present one of the few case series exploring the usefulness of this classification in EBUS-TBNA specimens.
Methods: Over a 3-year period, EBUS-TBNA attended by the interventional pathologist were quantified. Patient demographics, number of passes, and procedure time, among other variables, were recorded. A modification of the touch imprint cytology and ROSE methodology was used for on-site validation of the cell block sample.

Results: 402 mediastinal lymph node FNA were performed. 69% male. Mean age 65 years old (range 19 - 90). Mean number of passes 3.14 (range 1 - 8). Mean procedure time 25.33 minutes (range 10 - 90). Mean number of cytological smears 13.03 (range 3 - 38). Sydney System first level diagnostic categories: I: 4.48%; II: 36.82%; III: 0%; IV: 0%; V: 58.71%. Immediate sample management (microbiology, molecular tests, flow cytometry, etc.) was necessary in 33% of cases. The most frequent diagnosis of malignancy was metastatic lung carcinoma (218 patients - second diagnostic level).
Conclusion: To date, few scientific publications have highlighted the usefulness of the Sydney System in the categorization and diagnosis of lymph node FNA. The results obtained (with less than 5% of insufficient samples) support the applicability of this classification system in samples obtained by EBUS-TBNA. We consider the modified touch imprint cytology plus ROSE methodology (which allows validation of the representativeness of the cell block) to be a key step in achieving the results obtained.

PS-12 | Poster Session Dermatopathology

PS-12-001
Cutaneous metastases from non-primary skin tumours

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Background & objectives: Cutaneous metastasis (CM) accounts for only 2% of all skin neoplasms. They occur infrequently and usually during the late stages of cancer with poor prognosis. The objective is to analyse the different types of CM, their location and survival.
Methods: We reviewed skin biopsies of cancer patients diagnosed with CM between January 2006 and February 2022 at Donostia University Hospital in Spain. Patients with primary skin cancer and haematological malignancies were excluded. We collected the following data: patient age and sex, the time of cancer diagnosis and CM, location of CM, type of cancer and survival outcome.
Results: We included 16 patients, aged between 48 and 93 years (mean 68), of whom 11 were women and 5 men. Breast cancer was the most common primary cancer (6 cases), followed by gastric adenocarcinoma (3 cases) and clear cell renal cell carcinoma (2 cases). Pancreatic ductal adenocarcinoma, neuroendocrine tumour of the lung and arytenoid cartilage, hepatocellular carcinoma and endometrial serous carcinoma were also found. The most frequent locations for CM were head, neck and chest. Although most skin metastases were solitary, patients presented with advanced-stage cancer with other visceral metastases. Only five patients are still alive.
Conclusion: Cutaneous metastases have an incidence of 0.7% to 9%. In general, men are more commonly affected than women, and most patients are aged between 50 and 70 years. In our study, women are the most affected patients with breast cancer. The most typical locations were scalp, neck and trunk. Despite CM being a sign of poor prognosis may not always indicate a poor survival outcome and depends on each type of cancer.

PS-12-002
Acute generalised exanthematous pustulosis and generalised pustular psoriasis: differential diagnosis in the report of 2 cases

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Background & objectives: Acute generalized exanthematous pustulosis (AGEP) and generalized pustular psoriasis (GPP) share clinical and histopathological similarities, and their classification as separate entities or as diseases within the same spectrum remains controversial. We describe two cases highlighting this diagnostic challenge.
Methods: Case A: 36 year-old man presented a generalized pustular eruption with an erythematous background, especially on the trunk with involvement of the limbs and face, after COVID19 vaccination. Fever and peripheral blood leukocytosis were also present.
Case B: 72 year-old man, previously diagnosed with psoriasis, had a widespread eruption of sterile pustules on an erythematous background, without constitutional symptoms associated.
Results: Case A. Histopathological examination revealed an acanthotic epidermis with occasional exocytosis of neutrophils, reaching the upper layers and the stratum corneum. There was also focal intraepidermal and subcorneal detachment with haemorrhage, neutrophils and eosinophils. The dermis presented a mixed inflammatory infiltrate surrounding vascular and neural structures. Direct immunofluorescence showed granular non-specific IgA deposition at the dermal-epidermal junction.
Case B: Microscopical examination presented an epidermis with moderate acanthosis, hyperkeratosis, parakeratosis, hypogranulosis and intraepidermal and subcorneal pustules at different stages of development. There was also a dermal mixed inflammatory infiltrate with numerous neutrophils and haemorrhage.
Conclusion: Case A was diagnosed as AGEP; despite the overlap with pustular psoriasis, the clinical information, the small intraepidermal pustules and eosinophils favour the former diagnosis. The patient was treated with systemic corticosteroids with good result. Case B was compatible with GPP, given the pre-existing diagnosis of psoriasis and the slightly more pronounced psoriasiform hyperplasia. Despite the high mortality rate associated (30%), our patient had a great response to treatment with acitretin, and a restrict follow-up.

PS-12-003
Basal cell carcinoma with trichogerminoma-like areas, a morphological and immunohistochemical study in a series of three cases

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Background & objectives: We present three patients with basal cell carcinoma (BCC) incorporating trichogerminoma-like cell-balls presented as slow growing pearly nodules in a 76, 81 and 88-year-old patients on the temple, back and forearm. Two were ulcerated and one was variably pigmented.
Methods: Microscopically all BCCs were of nodular subtype. In addition, they showed lobules of epithelioid cells, with a rim of compact cells and central crowded cells expressing concentric whorled nuclei. They were incorporated within the main BCC area. One case showed clefts surrounding these cell balls with increased apoptosis. No significant atypia or increased mitosis was seen. Another showed focal keratinisation.
Results: Immunohistochemistry showed positive staining with cytokeratin 5/6 while BerEP4 was diffusely positive in the BCC and negative in trichogerminoma-like area. They were negative for Epithelial Membrane Antigen (EMA). Cytokeratin 20 did

not highlight Merkel cells in these areas. The diagnosis mainly depends on morphology.
Around 30 trichogerminomas were reported and are included in the spectrum of trichoblastomas. However, their presence within BCCs has not been well described or studied. These cases are not associated with Brook-Spiegler syndrome or any poor prognosis. Grainyhead-like transcription factor (GRHL1/2/3) gene rearrangements including FOXK1:GRHL1/2 fusion transcripts which are recently reported by Kervarrec et al in trichogerminomas have not been yet studied in this BCC subtype.
Conclusion: We report a series of three cases of BCC with trichogerminoma-like areas, which is underreported and rare BCC subtype.
The diagnosis is based mainly on tumour morphology expressing epithelioid cell balls. They also express a distinct immunohistochemical profile.
Pure trichogerminomas have GRHL gene rearrangements but this is yet to be studied in cases associated with BBC.
Complete excision of the tumour with adequate margins is the treatment of choice.
There is no association with poor prognosis or Brook-Spiegler syndrome.

PS-12-004
The value of peritumoral lymphocyte infiltration in progression free survival in BRAF and NRAS mutant stage I and II melanoma: a retrospective cohort study
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Background & objectives: The presence of tumour infiltrating lymphocytes is a favourable prognostic factor in cutaneous melanoma. The current study's objective have been to compare the NRAS and BRAF mutation status with peritumoral lymphocytic infiltration and progression free survival in melanoma.
Methods: Altogether, 85 patients underwent melanoma surgical treatment at the Riga East University Hospital, were retrospectively enrolled in the study. The histopathological characteristics were assessed. The melanoma BRAF and NRAS mutations status were assessed by PCR (ddPCR). Progression-free survival (PFS) was estimated with the Kaplan-Meier method with the log-rank test. Multivariate regression was analysed using Cox proportional hazards model.
Results: There were 56 cases of nodular melanoma and 29 cases with superficial spreading melanoma. The BRAF mutation was observed in 52 patients (61.2%). The BRAF mutation in melanoma correlated with Clark invasion level (p=0.045), patient age (p=0.02) and peritumoral lymphocytes (p=0.04). NRAS mutation was observed in 9 patients (10.6%). NRAS mutation correlated with Breslow thickness (p<0.0001), disease stage (p=0.002) and lymphovascular invasion (p=0.03). Our study showed that melanoma patients with BRAF mutation had significantly better progression-free survival (PFS) than patients with NRAS mutation (HR=4.2, 95% CI=2.8-10.4, p<0.0001). However, in patients with concomitant BRAF and NRAS mutation the PFS was significantly worse compared to patients with only BRAF or NRAS mutation.
Conclusion: To conclude, the strength of our study was the demonstration of significant role of TIL and BRAF, NRAS mutational status in patients with stage I-II melanoma. Patients with NRAS mutation had significantly worse prognosis compared to patients with BRAF mutation. However, the increased TIL infiltration characterized by better prognosis.

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PS-12-005
Clinicopathologic characteristics of BRAF V600K mutant malignant melanoma in comparison with V600E mutant cases: a preliminary study
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Background & objectives: BRAF V600K mutation, the second most common mutation in malignant melanoma with a rate of 10-30%, is related to worse response to treatment and adverse prognosis. However, data for comparing V600K/V600E groups for the histopathologic and prognostic features are limited.
Methods: A total of 23 malignant melanoma cases with BRAF V600E or BRAF V600K mutations detected by pyrosequencing in our department were retrospectively analysed. The associations between the type of BRAF mutations and histopathologic, clinical and prognostic characteristics were statistically investigated.
Results: Of the 23 cases, 7 (30.4%) had V600K and 16 (69.6%) had V600E mutation. Although there was no statistical significance between two groups, most of the cases with V600K mutation were male (85.7%). In BRAF V600K mutant cases, histologic type was mostly superficial spreading melanoma (85.7%), tumour localization was mostly head and neck (57.1%); ulceration and regression were slightly higher. In BRAF V600E mutant group, the number of mitosis (>10/HPF) was higher (81.3%). V600E mutant group was generally more advanced (pT4) at the time of diagnosis (75%). In survival analysis, the estimated survival time was shorter in patients with V600K mutation than those with V600E mutation (17.9 vs 33.2 months).
Conclusion: Although it's a preliminary study and no statistical significance was detected due to the low number of cases, our results emphasize that overall survival time is almost half as short in V600K mutant cases than those with V600E mutation. Considering the prognostic differences, since the double nucleotide change seen in the V600K mutation(GTG to AAG) includes the single nucleotide change seen in the V600E mutation(GTG to GAG), it's important to be careful in the evaluation to distinguish these two mutations.

PS-12-006
The clinicopathologic features of dysplastic nevus with severe cytologic atypia: single centre experience
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Background & objectives: Dysplastic nevus with severe cytologic atypia are accepted as a significant intermediate lesion in malign melanoma progression. We aimed to summarize the clinicopathological findings of cases as diagnosed dysplastic nevus showing severe cytologic atypia at a single institution.
Methods: We reviewed the pathology reports of excisional skin biopsies of 644 cases and 1226 lesions as diagnosed dysplastic nevus between 2010 and 2021, retrospectively. The cases having severe cytologic atypia and their clinicopathologic features were noted.

Results: We detected 49 lesions which have dysplastic nevus with severe atypia belonging to 32 cases (4%, 5%). The sizes ranged from 3 to 20 mm (mean=8.1 mm). The locations of lesions were as follows; trunk: 38; head: 5; lower extremities: 4, upper extremities:1, unknown: 1. While 43 of 49 lesions showed compound morphology (87.8%), 6 of 49 lesions showed junctional morphology (12.2%). At the time of the initial diagnosis; 3 patients had malign melanoma (9.3%), 14 patients had multiple dysplastic nevus (43.7%), histopathologically. 8 of the patients with multiple dysplastic nevus had severe cytologic atypia. The number of dysplastic nevus in these patients was between 2 and 6.
Conclusion: Severe atypia is the most important histopathologic feature in terms of malign melanoma progression for dysplastic nevus. For this reason, after recognizing severe atypia in a dysplastic nevus, screening of all melanocytic lesions of the patients and excision of the lesions which have high risk are recommended.

PS-12-007
Expression of IL-22 in tissue specimens of mycosis fungoides is associated with the involvement of FOXP3+ cells and neutrophils in the microenvironment
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Background & objectives: Recent studies suggest a significant role of the cellular microenvironment, as well as interleukins in mycosis fungoides (MF). We investigated the cellular microenvironment composition and its potential correlation with Interleukin(IL)-22 and IL-17A expression in MF skin lesions.
Methods: We retrospectively collected 16 MF cases of various disease stages, with adequate skin tissue for immunohistochemistry and available frozen tissue for RT-qPCR. Histological assessment of eosinophils, neutrophils, CD20+, CD4+, CD8+, FOXP3+, CD56+ and CD1a+ cells was performed. Expression levels of IL-22 and IL-17 mRNA were measured by RT-qPCR. Statistical analysis was performed using SPSS version 25.
Results: The cases included three in patch stage, eight in plaque stage, and five in transformation to high-grade large cell lymphoma (t-LCL). Overall, eosinophils, neutrophils, and B-lymphocytes were absent or scarce, with the highest numbers being observed in t-LCL cases. IL-22 and IL-17A tissue levels were higher in early than in advanced stages of the disease. IL-22 levels were associated with IL-17A levels (Pearson's, $r=0.961$, $p<0.001$) and showed a statistically significant correlation with FOXP3+ T-regulatory cells (Pearson's, $r=0.851$, $p<0.001$), as well as with neutrophil density (Pearson's, $r=0.586$, $p=0.014$). No association was found between IL-17A values and the estimated cells.
Conclusion: MF lesions with t-LCL present a remarkable different microenvironment regarding cellular composition and IL expression levels, compared to early MF. FOXP3+ cells may regulate the expression of IL-22 in the MF microenvironment. Investigating the role of the cellular microenvironment and certain cytokines, including IL-17A, and -22, in MF, can significantly contribute to a better understanding of the pathogenesis and progression of the disease and possibly to novel targeted therapies.

PS-12-008
Dermatomyofibroma: a series of five cases
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Background & objectives: Dermatomyofibroma (DMF) is an infrequent mesenchymal benign tumour of uncertain nature. It usually affects young women and is preferentially located in the upper trunk. Its diagnosis relies on its distinct clinical, histological and immunohistochemical features.
Methods: We retrospectively collected five cases of DMF from the files of the Department of Pathology of the University Hospital of Santiago de Compostela. All cases had blocks and sections available for review. The demographic, clinical and immunohistochemical characteristics of the cases were studied.
Results: Cases corresponded to one male and four females, with ages which ranged from 4 to 48 years (average 32). Three cases were located in the shoulder girdle and two in the upper chest. They were all superficially located and diameter was around 1cm. Treatment was conservative resection and no relapses were noted. Histologically, they were constituted by multiple fascicles of regular spindle-shaped cells parallel to the epidermis, showing no mitoses or pleomorphism. Immunohistochemical study was performed in all cases to confirm the diagnosis.
Conclusion: DMF are unusual lesions whose clinical and histological features overlap with those of dermatofibroma (DF). Location in the upper part of the trunk is unusual for DF and histologically, the characteristic disposition of fascicles parallel to the dermoepidermal junction allow the differential diagnosis. Immunohistochemical findings suggest not muscular, but myofibroblastic differentiation.

PS-12-009
GATA3 evaluation on primary cutaneous CD30-positive lymphoproliferative disorders and its mimics
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Background & objectives: Primary cutaneous CD30+ proliferative disorders (CD30+ LPD) represent second largest subcategory of skin lymphomas. The purpose of the study was to assess the GATA3 expression in CD30+ LPD and its mimics for better characterization of malignant T cell features.
Methods: We identified 18 cases of CD30+LPD and 13 cases of pityriasis lichenoides et varioliformis acuta (PLEVA), diagnosed in our department between 2009 – 2022. Immunohistochemical staining was performed on all cases for CD4, CD8, CD30, ALK and GATA3. Results were compared between CD30+ LPD group including lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (pcALCL) and PLEVA group.
Results: We identified 11 cases of Lyp (2 type A, 2 type B, 2 type C, 4 type D and 1 case of LyP not otherwise specified) and 7 cases of pcALCL. All cases of pcALCL (variable CD4/CD8; CD30+) and three out of four cases of LyP type D (CD4-/CD8+/CD30+) showed diffuse and variable positivity for GATA3 in both CD4 and CD8 dermal T cells and in epidermal extravasated lymphocytes. The rest of LyP and all PLEVA cases stained negative for GATA3. The correlation of the percentage of GATA3+ lymphocytes with CD4/CD8 profile of T cells, subgroups or age showed no statistical significance.
Conclusion: GATA3 is a transcription factor associated with LTh2 differentiation and function and activation of CD8+ T cells, and our study showed GATA3 positivity in both CD4 or CD8 predominant CD30+ LPD. The tumour microenvironment remains unclear in CD30+ LPD but GATA3 may play a role in cytokine

local response. CD30+ LPD and PLEVA may show similar histopathological patterns and may be difficult to differentiate without clinical data on small biopsies and GATA3 expression may be a clue for diagnosis.

PS-12-010

NTRK fusion in pigmented spindle cell nevus/Reed nevus: an immunohistochemical study on a large multicentric Italian cohort

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Background & objectives: Pigmented spindle cell nevus/Reed nevus (PSCN/RN) is a Spitz nevus variant genetically characterized by NTRK (mainly NTRK3) gene fusions, but the data about the frequency of this genomic alteration are widely discordant and range from 14 to 52%.
Methods: All PSCN/RN diagnosed at our institutions (February 2017-December 2021) were collected and stained with pan-TRK antibody (EPR17341; rabbit monoclonal; Ventana, OptiView RED Detection Kit). We evaluated the percentage of positive cases and analysed the association between pan-TRK(+) and other clinical-pathological features [$\chi 2$ tests for dichotomous and categorical data; Student t-test (normal distribution) and Mann-Whitney U-test (non-normal distribution) for continuous data].
Results: A total of 44 PCSN/RN were collected and histologically confirmed, according to 2018 WHO Classification of Skin Tumours. pan-TRK(+) was detected in 6 (13.6%) cases and exhibited a specific expression pattern [cytoplasmatic, granular, diffuse (4/6, 67%) or not (2/6, 33%)]. pan-TRK(+) was significantly associated with localization [4/6 (67%) on trunk/dorsum and 2/6 (33%) on extremities, p=0.008] and cytological atypia [1/6 (17%) mild, 2/6 (33%) moderate and 3/6 (50%) high, p=0.004]; no other clinical-pathological features were significantly associated with pan-TRK(+).
Conclusion: This is the largest case series of PSCN/RN tested for NTRK fusions. We found that a subgroup of PSCN/RN is characterized by NTRK fusions, with a percentage of positive cases (13-14%) similar to what was previously shown by Kervarrec T. et al. Furthermore, we found that PSCN/RN pan-TRK(+) are preferentially localized on trunk/dorsum and extremities, and display moderate/high cytological atypia. We will integrate our data with molecular techniques to support our results and better compare them with previous studies.

PS-12-011

Approaching the cellular origin of Merkel cell polyomavirus (MCPyV) associated Merkel cell carcinomas: effects of MCPyV Gene expression in epithelial and lymphoid cells

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Background & objectives: Merkel cell carcinoma (MCC) is a rare but deadly non-melanoma skin cancer. Although there is accumulating of evidence that Merkel cell polyomavirus (MCPyV) contributes to the etiopathogenesis of MCC, the cell of origin of MCC remains elusive.
Methods: We stably introduced MCPyV small and large tumour antigens in two MCPyV-negative cell lines, an epithelial and a leukaemia B-cell line and compared the gene expression changes induced thereafter. We assessed the MCPyV effects through functional and pathway enrichment analysis of MCPyV-T antigens expressed in the cell lines with immunological and neurological terms and validated their expression in primary MCCs.
Results: The results revealed that in the epithelial background, the global effects of MCPyV T antigens are higher compared to the lymphoid background, mainly attributed to the higher differential expression of genes caused by the LT antigen. Genes upregulated by MCPyV sT antigen were associated with neurological gene-ontologies in both cell lines. Key genes in neuronal development, differentially expressed in the lymphoid background were enriched in pathways that have been implicated in human cancers such. Validation of significantly enriched genes was assessed in the primary MCC cell lines and tumours, of which all genes were highly expressed, suggesting the involvement of MCPyV T antigens in regulating neuronal pathways involved in tumorigenesis.
Conclusion: We conclude that the expression of MCPyV T antigens in epithelial and lymphoid background affects neurological pathways in both. However, more effects are seen by the introduction of sT antigen expression in the lymphoid background. These novel established cell lines comprise an important tool to study the cell of origin of MCPyV- associated MCCs.

PS-12-012

Micromorphometric parameters of B16 melanoma cells and their circadal

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Background & objectives: Violation of the circadian rhythm is a risk factor for the development of melanoma. Tumours are also characterized by a change in the normal daily rhythm. Micromorphometric parameters of B16 melanoma cells and their circadian rhythms were investigated.
Methods: The study was conducted on 50 male BDF1 hybrid mice divided into 2 equal groups. First - control, mice of the second group were transplanted with B16/F10 melanomas. On the 15th day, the animals were withdrawn from the experiment at 9.00, 15.00, 21.00 and 3 hours. Conducted studies of micromorphometric parameters of tumours and their daily dynamics using cosinor analysis.
Results: It has been established that atypical melanocytes are characterized by significantly larger nuclei with a decrease in its elongation and contour indices with an increase in the shape factor. Daily fluctuations in the size of the nucleus of tumour cells are of a significant circadian nature, with acrophase rhythm of 7^24 in the control and 4^12 in the experiment at amplitudes of 1.48 and 4.52 sq.μm, respectively. The tumour cell size circadian rhythm was characterized by an acrophase in 19^32 and an amplitude of 10.07 sq.μm. According to the cosinor analysis, for the nucleo-cytoplasmatical ratio, circadian rhythm was not significant.
Conclusion: The data obtained indicate a change in rhythmostasis in mice with experimental melanoma B16. The features of the organization of the rhythm of the tumour itself can be used in its targeted experimental therapy, taking into account chronobiological features. The results of the study can be used for further studies of the effect of various lighting modes on the morphofunctional state of the animal organism in the pathology under study.

PS-12-013

Detection of clonal T cell receptor gamma gene rearrangements in mycosis fungoïdes

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Background & objectives: The diagnosis of Mycosis Fongoides (MF), especially early MF, is challenging. It might be difficult to distinguish it from inflammatory disorders. Monoclonal rearrangement can be helpful. The aim of the study was to describe molecular aspects of MF.
Methods: We conducted a retrospective study that included all cases of MF confirmed by histopathological and immunohistochemical (IHC) examination in the Pathology Department in collaboration with the Dermatology Department at Habib Thameur Hospital of Tunisia from 2008 to 2020. Genomic DNA was extracted from lesional tissues and rearrangements of TCR-gamma chain gene were amplified using the IdentiClone polymerase chain reaction (PCR).
Results: We enrolled 56 patients. The mean age at diagnosis was 51.8 years (15 - 83 years) with a male to female ratio of 1.94. Cases were: 35 classic MF, 12 pilotrope MF, five CD8-positive MF, three granulomatous MF and one hypopigmented MF. The rearrangement of the TCR-ϒ was performed in 30 cases. It was monoclonal in 18/30 cases (60%) and polyclonal in 12 cases (40%). At an early stage, monoclonality was present in 6/13 cases (46%) and polyclonality in 7/13 cases (54%). Polyclonality was found in 11 biopsies (73%) dating back more than 5 years, with a statistically significant association between clonality and the year the sample was received (p=0.05).
Conclusion: The detection of clonal TCR rearrangement can be helpful in establishing the diagnosis of MF. In fact, the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) support a diagnostic algorithm for early MF which includes TCR gene rearrangement analysis. However, some benign and reactive inflammatory lesions may also have clonal rearrangement. As a result, MF diagnosis should be based on confrontation of clinical, histological, immunohistochemical, and molecular data.

PS-12-014

Histopathologic features of mycosis fungoides: a morphologic study on 134 biopsy specimens from 56 patients

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Background & objectives: The diagnosis of mycosis fungoides (MF) is very challenging especially at early stage. The aim of this study was to describe histologic and immunohistochemical presentations of MF.
Methods: We retrospectively reviewed 134 biopsies from 56 patients with documented MF in patch, plaque and tumour stages.
Results: A total of 134 biopsies from 56 patients were reviewed. The 43 cases of early MF showed epidermotropism in 42 biopsies (98%), pilotropism in 37/38 (97%) and syringotropism in 25/39 (64%). Lymphocytic dermal infiltrate was superficial and perivascular in 22/43 biopsies (51%). Necrotic keratinocytes were noted in 3/43 biopsies (9%). Band-like lymphocytic infiltrate of superficial dermis was seen in 30 biopsies (56.6%) at plaque stage and was extended to the entire dermis in 36 biopsies (26.9%) at tumour stage. Fibrosis of papillary dermis was observed in 90 biopsies (67.2%). At immunohistochemistry, 129 biopsies (96.3%) demonstrated CD3+, CD4+ and CD8- phenotype and lack of CD7 expression was observed in 17/22 biopsies.
Conclusion: The histologic diagnosis of MF especially at early stage is one of the most vexing problems in dermatopathology, because the histopathologic features may simulate a variety of inflammatory skin disorders. Immunohistochemistry can help in diagnosis in some cases. Hower, clinicopathological correlation remains the "gold standard" for making an accurate diagnosis.

PS-12-015

Immunohistochemical staining for p16 is a useful adjunctive test in the diagnosis of Bowen's disease

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Background & objectives: Bowen's disease (BD) and actinic keratosis (AK) are squamoproliferative disorders of the skin. Histologically, they may mimic each other and they might be misinterpreted. p16 has been suggested to be a useful tool to make the differential diagnosis between them.
Methods: We gathered 13 cases of BD and 9 cases of AK. The cases were stained for p16 using standard immunohistochemical techniques, and the staining patterns were categorised into one of five different patterns of the classification proposed by Harvey.
Results: Mean age patients with BD and AK were 69 and 68 years respectively. All cases of BD and AK were positive to p16 with both nuclear and cytoplasmic staining. Intensity and extension of staining were different between BD and AK. For BD cases, the anti-p16 staining was pattern 1 for 12 cases (92%) and one case pattern 5. Concerning AK cases, staining was pattern 2 in 5 cases, pattern 3 in one case and pattern 5 in one case. Immunohistochemistry was not contributive in one case.
Conclusion: We have confirmed the previously published findings that immunohistochemistry for p16 in BD shows a consistent pattern of strong staining of all abnormal cells, presenting at least focal palisaded basal cell sparing. This pattern is not seen in AK. Where the staining is typically patches or scattered single cells of weak or moderate intensity.
We believe that p16 can serve as a useful adjunctive test in supporting a diagnosis of BD in difficult cases and in separating it from AK.

PS-12-016

Eccrine porocarcinoma: a clinicopathological study of 8 cases

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Background & objectives: Eccrine porocarcinoma (EPC) is a rare malignant eccrine sweat gland tumour characterized by locally aggressive growth and high rates of extracutaneous metastasis. The aim of this study is to describe clinical and histopathological features of EPC.
Methods: A retrospective review of medical records and histopathology slides of EPC cases between January 2000 and December 2022 was conducted using the cancer registry database of the centre of Tunisia.
Results: Eight EPC cases were included in this study. The mean age of diagnosis was 53.50 years (range 46-70 years) with seven females and one male. Systemic comorbidities were present in one patient. Clinically, EPC was described as ulcerated nodular lesion mimicking a squamous cell carcinoma in half of the cases. The most common localization was the scalp reported in 3 cases. Histopathological analysis revealed a tumour arising from the epidermis

and showing deep anastomosing cords in the dermis. Tumour cells were polygonal with irregularly-shaped nuclei and numerous mitotic figures. Ulceration was found in four cases. Squamous cell differentiation was observed in five cases. Perineural invasion was observed in one case.
Conclusion: This study underlines that EPC is a challenging diagnosis and that careful clinicopathological correlation is the key to differentiate this malignant tumour from other skin tumours.

PS-13 | Poster Session Digestive Diseases Pathology – Liver / Pancreas

PS-13-001
Treatment with activin receptor-like kinase 5 inhibitor (ALK5i) differently affects collagen 1A1 deposition in mouse models of toxic and metabolically induced liver fibrosis

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Background & objectives: Chronic liver diseases of various aetiology lead to liver fibrosis/cirrhosis. Aim of the study was to explore pattern of de novo collagen 1A1 (COL1A1) deposition in two mouse models of liver fibrosis and to evaluate therapeutic effect of ALK5 inhibitor.
Methods: Liver fibrosis was developed in 41-days CCl4 and 70-days high-fat diet induced models. Animals were treated with ALKi (SB525334); D21-D41 in CCl4 model and D29-D70 in NASH model. De novo collagen deposition was analysed by hydroxyproline content, COL1A1 content (anti-COL1A1 antibody, #72026, CST & digital pathology software, Visiopharm). Distribution of fibrous tissue was evaluated by NAFLD Activity and Fibrosis Score.
Results: In both models, vehicle treated disease control mice, showed significantly higher liver hydroxyproline level and percentage of COL1A1-positive area accompanied by formation of bridging fibrosis, as compared to naïve animals. Treatment with ALK5i significantly decreased hydroxyproline levels and percentage of COL1A1-positive area in liver. There was no effect of ALK5i treatment on bridging fibrosis formation in CCl4-induced model. On the other hand, in high-fat diet model, decreased number of animals with bridging fibrosis was observed following treatment with ALK5i; periportal and perisinusoidal fibrosis prevailed.
Conclusion: It was shown that formation of bridging fibrosis in liver fibrosis model induced by high-fat diet can be influenced by ALK5i treatment. Influencing the pace of bridging fibrosis formation could be of utmost clinical relevance, since disrupted intrahepatic blood flow, due to presence of bridging fibrosis/cirrhosis, is a major cause of portal hypertension.

PS-13-002
Utility of intraoperative pathology consultations during pancreatic surgery and impact on final margin status: a single institution analysis

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Background & objectives: Intraoperative consultations (IOCs) are widely used to assess surgical margins during pancreatic resections. The impact of this practice on patient management is often debated. Herein, we reviewed the utility of IOCs and its impact on final postoperative surgical margin status.
Methods: Retrospective review of all patients who underwent pancreaticoduodenectomy (Whipple) and distal pancreatectomy (DP) at our institution (2018-2020) was performed and data from pathology reports was recorded. From this cohort, cases of adenocarcinomas resected with Whipple surgeries were further analysed. A positive permanent margin (R1), including pancreatic, bile duct or other margins, was defined as margin involved by a known neoplasm.
Results: During a 3-year period, 213 Whipple and 62 DP procedures were performed at our institution for neoplastic lesions. Of these, IOCs were completed for 112 pancreatic margins and 94 bile duct margins. Comparative analysis identified that although there was a significant difference in the frequency of margins submitted for IOC among four pancreatic surgeons ($P<0.001$), there was no significant difference in the postoperative final R0 rate ($P=0.637$ for Whipples and 0.653 for DP) for neoplastic lesions examined and for adenocarcinomas resected with Whipple surgeries, particularly ($n=170$, $P= 0.612$). Postoperative positive margins (R1) reported for Whipple adenocarcinoma cases also include other margins ($n=41$) that were not amenable to be assessed intraoperatively.
Conclusion: Our data suggests that IOCs for margins did not seem to improve postoperative R0 on pancreatic resections. The current findings add to a growing body of studies that question whether intraoperative margin assessment of Whipple surgeries performed for adenocarcinomas contributes to reducing the risk of R1 or improving long-term patient outcomes. The significant difference in frequency of IOC requests for margins among surgeons also suggests the development or redefining of guidelines for IOCs during pancreatic surgeries.

PS-13-003
Central histopathology review of hepatocellular carcinoma: impact of the WHO 2019 classification on histological diagnosis and TNM staging

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Background & objectives: The updated World Health Organization (WHO) 2019 classification of hepatocellular carcinoma (HCC) introduces new histological subtypes with unique characteristics. Our aim was tumour reclassification and frequency estimation of new variants after review of histological slides from curative HCC surgical resections.
Methods: We centrally reviewed all histological slides of 73 liver resection specimens from 73 patients with HCC (60 male, median age 72, IQR 64-76 years, BCLC stage 0-C) operated from 2001 to2018. Histological slides and reports were retrieved from the Department of Pathology, Aretaieion Hospital. All cases were reclassified according to WHO 2019 and re-staged according TNM 2017 system.
Results: Twenty-two HCC (30%) were reclassified into new subtypes: 14 macrotrabecular-massive (19%), 4 steatohepatitic (5.5%), 2 chromophobe (2.7%), 1 lymphocyte-rich (1.4%), 1 neutrophil-rich (1.4%). Histological grade changed in 35/73 (48%) HCC: Initial grade 1 n=21, 2 n=27, 3 n=25; revised grade 1 n=3, 2 n=48, 3 n= 22 ($p<0.001$). TNM stage was modified from 1 to 2 in 16/73 HCCs ($p <0.001$). The main histological pattern was solid (48%), trabecular (36%) or pseudoglandular (16%). Microvascular invasion was detected in 49/73 (67%) HCC. The non-neoplastic parenchyma showed steatosis (42.5%), steatohepatitis (20.5%), chronic

inflammation (71%) and no fibrosis in 29%. Fibrosis was staged as F1 22%, F2 12%, F3 10% or F4 27%.
Conclusion: Central histopathology review according to WHO 2019 and TNM 2017 modifies histological grading and staging in about 1/2 and 1/4 of resected HCCs, respectively, with clinical implications. One third of HCCs are re-classified into new histological subtypes, some with known molecular background, prognostic and/or predictive impact, important for patient management.

PS-13-004
The site of metastatic lymph node has prognostic significance in pancreatic ductal adenocarcinoma
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Background & objectives: Pancreatic ductal adenocarcinomas (PDAC) have poor survival rates and prognosis. Important prognostic parameters are; tumour size/stage, metastatic lymph nodes count and vascular invasion. In the current AJCC staging system, there is no recommendation to specify metastatic regional lymph node localization.
Methods: Metastatic sites of 82 patients with regional lymph node metastases out of 101 patients with PDAC who underwent pancreaticoduodenectomy were classified as peripancreatic, perigastric, hepatico-communis, hepatic pedicle and other regions. Each region's number of metastatic lymph nodes was determined. The associations between the presence of metastases in each lymph node region and overall survival and disease-free survival were determined statistically.
Results: Eighty cases (79.2%) had peripancreatic, 7 cases (6.9%) had perigastric, 6 cases (5.9%) had hepatico-communis, and 7 cases (6.9%) had hepatic pedicle lymph node metastasis.
In survival analysis, the estimated overall and disease-free survival time were significantly shorter in patients with hepatic pedicle lymph node metastasis (35.5 vs 11.24 month; p= 0.001, 18.55 months/3.68 months; p <0.001, respectively). Although not significant, the estimated overall survival time was shorter in patients with hepaticocommunis lymph node metastasis (34.7 months/20.5 months; p= 0.32)
Hepatic pedicle lymph node metastasis was an independent predictor of mortality (p=0.005) and recurrence (p=0.003) in multivariate analysis.
Conclusion: The presence of hepatic pedicle lymph node metastasis is an independent poor prognostic factor for mortality and recurrence risk, according to our findings. Although not significant, patients with hepaticocommunis lymph node metastasis have 14-month shorter life expectancy than those without. With these findings, we conclude that the metastatic lymph node site may have an impact on the prognosis, and may be included in pathology reports.

PS-13-005
Ground-glass change: think beyond chronic hepatitis B infection
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Background & objectives: Ground-glass change (GGC) corresponds to hepatocytes with eosinophilic granular, glassy cytoplasm on light microscopy, induced by proliferated smooth endoplasmic reticulum. GGC has been classically associated with chronic hepatitis B (HBV) infection but can be induced by drugs.
Methods: Analysed liver biopsies and surgical resections with GGC hepatocytes between January 2007 and December 2021, in "Centro Hospitalar e Universitário de Coimbra". Sex, age, nature of the product and the GGC aetiology were collected. The quantity of GGC was divided into the following categories: mild (1-30%), moderate (30-70%) and severe (70-100%).
Results: 79 patients with GG hepatocytes, 49 were male and 30 female. The average patient age was 39 years. Seventy of the samples came from native livers (88.6%) and remaining 9 from allograft livers (11.4%). The main cause identified was HBV infection (74.7%). The remainder were due to drug-induced liver injury (12.7%), hepatocellular carcinoma (2.5%), and autoimmune hepatitis (2.5%). In 4 cases the exact aetiology could not be identified (5.1%), and 2 are still under investigation (2.5%). The GGC ranged from mild (48.1%), moderate (34.2 %) to severe (17.7%). Mild GGC was more frequent in non-viral aetiologies and moderate/severe was more frequent in HBV infection, but without statistical significance (p=0.324).
Conclusion: GGC mimicking the appearance of HBV infection may be seen in other conditions and are the result of cytoplasmic accumulation of glycogen, fibrinogen or cellular organelles. GGC are distinguished from HBV infection based on clinical information as well as lack of immunopositivity for hepatitis B surface antigen. Despite not statistically significant in our study, mild GGC should arise suspicion for non-HBV related causes.

PS-13-006
The influence of pancreatic regression characteristics on outcome of neoadjuvant treated pancreatic cancer in two Austrian university centres
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Background & objectives: Neoadjuvant treatment strategies for extended pancreatic cancer could improve the outcome of this dismal disease entity now and in the future. Our histopathological knowledge of pancreatic regression phenomena are thereby sparse.
Methods: We investigated retrospectively the pathological regression grading of neoadjuvant treated pancreatic cancer of two university clinical centres of Austria using all known grading systems. Furthermore, extensive clinic-pathological data as well as different histomorphological and immunohistochemical (e.g. different markers of proliferation, tumour associated inflammation and chemoresistance) findings were collected and correlated to clinical and pathological endpoints.
Results: Overall, 22 patients (female/male: 16 (72.7%)/ 6 (27.3%) with a mean age of 64.6±8.9 years) with pancreatic cancer were enrolled in this study until now. The pretreated pancreatic cancer revealed more low grading (G1-G2: n=16 (72.7%)) and more high T-stages (T3-T4: n=17 (77.3%) as well as more high regression grade (CAP 0-2: n=13 (59%) according the 4-tired CAP regression grading system). Looking in detail, the statistical analysis indicated that some clinic-pathological, histomorphological and immunohistochemical parameters were statistically associated to endpoints (survival, recurrence, metastasis and regression grading) and could predict therapeutic response, overall.
Conclusion: We demonstrated that the classical and deep investigation of such neoadjuvant treated pancreatic cancer specimen could be helpfully for stratify the therapeutic success. In the future, the definitive predictive and prognostic role of the regression

grading and associated parameters needs to be more evaluated in prospective, controlled and international clinical trials of cases with neoadjuvant treated pancreatic cancer.

PS-13-007

Comprehensive histologic evaluation of venous invasion in pancreatic neuroendocrine carcinomas

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Background & objectives: Pancreatic neuroendocrine carcinomas(PanNECs) have aggressive clinical behaviour with distant metastasis at the time of diagnosis. However, our understanding of various histologic features of venous invasion and association with clinicopathologic characteristics in PanNECs have not been systematically well elucidated.
Methods: Various histopathologic features of venous invasion, including status, type (lymphatic and venous), number of invasion foci, and histologic patterns [pancreatic intraepithelial neoplasia (PanIN)-like, conventional, and destructive] were evaluated in 14 PanNECs and compared with 471 pancreatic ductal adenocarcinomas (PDACs).
Results: Mean patient age was 67.1±13.1years with male-to-female ratio of 1.3. Mean tumour size was 3.8±1.6cm. Twelve(86%) were small and 2(14%) were large cell types. All had extrapancreatic extension, and lymphovascular and perineural invasions. Venous invasion was present in 11cases(86%), and associated with higher nodal category(p=0.028). Conventional and destructive patterns were identified in 10(71%) and 8(57%) cases, respectively. Compared with PDACs, PanNECs had higher foci of venous(4.3±5.4 vs. 2.2±3.4; p=0.039) and lymphatic(14.9±15.6 vs. 1.7±4.7; p<0.001) invasion. Unlike PDACs, PanIN-like pattern was absent and conventional pattern was dominant in PanNECs(p<0.001). Higher nodal category, frequent distant metastasis, and lymphatic invasion were noted in PanNECs(all, p<0.001). PanNECs showed significantly poor overall-survival(OS) than PDACs(p<0.001).
Conclusion: PanNECs show more conventional patterns of venous invasion and frequent venous and lymphatic invasion than PDACs. These higher frequency of lymphatic and venous invasion are associated with frequent nodal and distant metastases and poor OS comparing with venous invasion in patients with PDACs.

PS-13-008

Influence of constant lighting on liver

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Background & objectives: The current study was undertaken to evaluate the effect of prolonged exposure to light, simulating urban light pollution, on liver health. We examined the morphofunctional state, immunohistochemical and micromorphometric parameters of rat liver in normal conditions and prolonged lighting exposure.
Methods: The study was carried out on 120 Wistar rats divided into 2 equal groups. The control group is kept in standard laboratory conditions, the experimental group was kept under constant illumination. The following were studied: morphological features of the liver, micromorphometric parameters of hepatocytes, expression of Ki-67, Per2, Bmal1 and p53 in them and circadian rhythms of these parameters.
Results: Our results show that nocturnal light disruption triggers a cell death in the liver within three weeks (necrosis and apoptosis of hepatocytes) and stimulates a change in normal cellular karyometric parameters. At the same time, intracellular regeneration takes place within the organ, which manifests through hepatocyte hypertrophy. Under the influence of constant illumination, the circadian rhythms (CRs) of the size of hepatocytes and their nuclei are restructured, the rhythm of the nuclear-cytoplasmic ratio is destroyed. The destruction of the CR of expression of p53 and Ki-67 also occurs against the background of the rearrangement of the daily rhythmicity of Per2 and Bmal1.
Conclusion: The revealed changes in the morphofunctional state of the liver under the influence of light pollution indicate that a violation of normal illumination regimes is a potent factor leading to significant structural changes in the liver. Despite this, our results show a link between light pollution and liver damage, which warrants further research into specific effect of light pollution of different extent on human liver health.

PS-13-009

Prognostic implication of leptin-signalling proteins, PD-L1 and tumour-infiltrating lymphocytes in surgically resected biliary tract cancers

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Background & objectives: Biliary tract cancers are rare malignancies with a dismal prognosis. Leptin and PD-L1 influence CD8+ and FOXP3+ lymphocytes, and then cancer cell growth. We aimed to define prognostic implications of these variables and clinicopathological features in surgically-resected biliary tract cancers.
Methods: Immunohistochemistry for leptin signalling-related proteins (leptin, leptin receptor, pSTAT3, ERK, mTOR), PD-L1, CD8 and FOXP3 and in situ hybridization for Epstein-Barr virus-encoded small RNAs were performed in 186 cases of surgically-resected biliary tract cancers. Prognostic significances on 5-year survival and recurrence-free survival of patients were evaluated through multivariate analysis using a Cox proportional hazards model.
Results: Immune cell PD-L1 (+), tumour size < 3cm, application of adjuvant chemotherapy, no recurrence and early-stage tumours were correlated with better 5-year survival of patients in the entire cohort through multivariate analysis ($P < 0.05$, respectively). However, in tumoral PD-L1-positive subgroup or leptin-positive subgroup, immune cell PD-L1, adjuvant therapy and tumour stage lost their impact on patient survival. The significance of immune cell PD-L1 and adjuvant chemotherapy on patient survival retained in extrahepatic cholangiocarcinoma only among subgroups by tumour location ($P < 0.05$, respectively). Regarding recurrence-free survival, leptin and ERK expressions revealed prognostic value in the entire cohort, tumoral PD-L1-negative subgroup or gallbladder cancer subgroup ($P < 0.05$, respectively).
Conclusion: Immune cell PD-L1 (+) and adjuvant chemotherapy favourably affected patient survival in the entire cohort, however, it was not relevant in tumoral PD-L1-positive subgroup or leptin-positive subgroup. PD-L1- or leptin-targeted therapy rather than conventional chemotherapy may be beneficial for these subgroups. Regulating leptin and ERK expressions may improve recurrence-free survival in tumoral PD-L1-negative subgroup or gallbladder cancer subgroup.

PS-13-010

Venous invasion of undifferentiated carcinoma and undifferentiated carcinoma with osteoclast-like giant cells of the pancreas

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Background & objectives: Venous invasion (VI) is frequent in pancreatic ductal adenocarcinoma (PDAC) than other cancers and it explains why PDAC is deadly. However, our understanding of VI in pancreatic undifferentiated carcinoma (UC) and undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) is limited.
Methods: Histopathologic characteristics of VI were evaluated with 44 (30 UCs and 14 UCOGCs) cases using triple CD31─D2-40─desmin and e-cadherin immunostaining and clinicopathologic factors were compared with those of 471 PDACs. VI patterns were divided into three groups: conventional, intraepithelial neoplasia (IN)-like and destructive patterns.
Results: VI was frequent in 3 cancers (PDAC, 64.3%, 303/471; UC, 70.0%, 21/30; UCOGC, 50.0%, 7/14; p=0.43). Mean VI foci number was higher in PDAC (3.3±3.6, p=0.004) than UC (2.0±2.1) and UCOGC (1.1±1.6). Mean number of IN-like (p=0.002) and destructive (p=0.033) patterns on H&E slides were higher in PDAC than UC and UCOGC. Triple CD31─D2-40─desmin staining detected more foci of destructive pattern (p=0.018) than H&E, but no difference for detecting IN-like and conventional patterns. E-cadherin expression was lost in tumour cells invading stroma but was re-expressed within venous lumen of UCs and UCOGCs. Median survival time of UCOGC was significantly better compared to UC (UC, 5.52 months; UCOGC, 19.9 months; p<0.001).
Conclusion: 1) VI was frequent both in UC and UCOGC like PDACs. 2) Triple CD31─D2-40─desmin staining could detect more VI foci of destructive pattern. 3) Sustained epithelial─mesenchymal─transition may not require for VI of UC and UCOGC. 4) VI alone could partly explain for different survival between UC and UCOGC patients, as all the measured indexes of VI, such as its overall prevalence, the mean number of foci, and the mean IN-like and destructive patterns, showed the lowest values in UCOGC.

PS-13-011
Ex vivo patient-derived pancreatic cancer organoids to uncover individual therapeutic vulnerabilities and model acquired resistance

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Background & objectives: The acquisition of drug resistances contributes to poor survival of pancreatic cancer patients. Tumour organoid models not only bridges the gap between research and clinics but also offer a platform to study intrinsic drug sensitivities and predispositions to drug resistances.
Methods: After establishing patient derived tumour organoids from a rare BRAF mutated pancreatic cancer patient and their genetic evaluation, we performed an ex vivo functional drug testing in order to identify specific drug vulnerabilities. The continuous exposure with trametinib lead to the formation of drug resistant organoid clones used for the subsequent RNA sequencing and expression analysis.
Results: In an ex vivo functional drug testing, the BRAF organoids revealed a genotype specific sensitivity towards the MEK inhibitor trametinib when compared to other drugs. The induction of a drug resistance by continuous trametinib selection pressure further lead to the formation of resistant clones indicating a change in Wnt signal regulation compared to their untreated counterparts. Sequencing analysis performed on the patient's primary tumour specimen and the metastatic lesion revealed the acquisition of a GATA6 amplification, indicative for the underlying resistance mechanism, which resulted in the progression of the disease.
Conclusion: We conclude that the use of patient derived tumour organoids represents a patient centered approach to investigate drug sensitivities and explore predispositions for drug resistances. The results generated by this approach assist in guiding and customizing therapy decision with the fundamental goal to improve the survival of pancreatic cancer patients.

PS-14 | Poster Session Endocrine Pathology

PS-14-001
Molecular pathological characteristics of benign thyroid nodules with poorly differentiated component

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Background & objectives: Thyroid follicular tumours (TFTs) showing nodule-in-nodule (NN) appearance with poorly differentiated component (PDc) but neither invasion nor metastasis are diagnosed as benign nodules regardless of high-grade histological features. This study aims at elucidating the malignant potential of PDc.
Methods: This study analysed the profile of TP53 binding protein-1 (53BP1) expression by dual-colour immunofluorescence with Ki-67 and NRAS codon 61 mutations by droplet digital PCR in 16 cases of TFT showing NN with PDc compared to 30 adenomatous goiter (AG), 31 follicular adenoma (FA), 15 minimally invasive follicular carcinoma (MFC), and 11 widely invasive FC (WFC) cases.
Results: The incidence of abnormal type 53BP1 expression in TFTs was significantly higher in the outer nodule (Out-N) (11.7%) and PDc (10.3%) in NN than AG (5.6%) and FA (6.5%) but not in MFC (14.2%) and WFC (17.1%). Furthermore, the frequency of double-positive cells with Ki-67 was significantly higher in PDc (0.36%) than in AG (0.03%), FA (0.12%), and Out-N (0.08%) but not in MFC (0.67%) and WFC (0.66%). The NRAS codon 61 mutation was the most frequently detected in both Out-N and PDc tumour areas (56.3%), and significantly higher than in AG (3.3%), FA (20.0%) but not in MFC (26.7%) and WFC (36.4%).
Conclusion: This study demonstrated that the prevalence of abnormal type 53BP1 expression and NRAS mutations in PDc was comparable to FCs, suggesting a malignant potential at the molecular pathological level. Because co-localization of 53BP1 and Ki-67 can be an indicator of altered DNA damage response (DDR), the development of PDc may be associated with DDR impairments after harbouring an NRAS mutation. Thus, we should pay more attention to PDc as a precursor lesion associated with poorly differentiated thyroid carcinoma.
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PS-14-002
Histology of distant follicular cell–derived thyroid carcinomas metastases can be misleading to identify the primary tumour

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Background & objectives: Follicular Cell–Derived Thyroid Carcinomas (FCDTC) harbour targetable molecular alterations according to their histology. It has been proposed that molecular screening to drive treatments should be based on histological classification. However, we found that distant metastases histology can be misleading.
Methods: We review the features of distant metastases of FCDTC registered in our centre from 2010 to nowadays, blinded to the primary tumour.
Histological criteria evaluated included the presence of follicular pattern, colloid, papillae, psammoma bodies, squamous differentiation, tumour necrosis, prominent mitoses, and nuclear features of papillary carcinomas. Then, a presumed diagnosis was stablished and compared with the original primary tumour.
Results: We review 15 metastases, located in bone (8), skin (3), soft tissues (1), liver (1), lung (1), and cerebellum (1). Our presumed diagnosis was follicular variant of papillary carcinoma (7 biopsies), another variant of papillary carcinoma (3 biopsies), and follicular carcinoma (3 biopsies). Two biopsies had insufficient material. Our diagnosis was concordant with the primary in 7 cases (54%) and discordant in 6 (46%). Among discrepant cases, three primary follicular carcinomas were identified as papillary carcinomas by their nuclear features. Moreover, three primary poorly differentiated carcinomas were identified as papillary carcinomas (2) and follicular carcinoma (1).
Conclusion: Identification of primary FCDTC based on the histological features of distant metastases can be misleading in almost half of cases. Most common causes of discrepancy are the presence of nuclear features of papillary carcinomas in the metastases and the difficulty to determine characteristics of poorly differentiated thyroid carcinomas in the metastases.

PS-14-004
Peculiar facets of medullary thyroid carcinoma
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Background & objectives: Medullary thyroid carcinoma (MTC) is characterized by a relatively aggressive biological behaviour, responsible for a high number of deaths compared to other thyroid cancers. We aimed to analyse the clinicopathological profile of MTC, pointing on cases with increased oncological risk.
Methods: The study group comprised a single centre case series of 59 patients diagnosed at a referral hospital in North-Eastern region of Romania. The histological diagnosis of MTC was confirmed by immunohistochemical exam. Correlations between the classical clinico-pathological variables and three parameters considered elements of aggressiveness (thyroid capsular invasion, lympho-vascular invasion and lymph node metastasis) were settled by using statistical analysis.
Results: Histopathologically, we identified the following types of MCT: conventional (35 cases/59.32%), spindle cell (12 cases/20.33%), oncocytic (5 cases/8.47%), follicular/glandular (3 cases/5.08%), pseudopapillary (2 cases/3.38%), with giant cells (1 case/1.69%) and with small cells (1 case/1.69%). Statistical analysis revealed significant correlations between tumour size and lympho-vascular invasion ($p < 0.0001$), and lymph node metastasis ($p = 0.0220$); tumour focality was significantly correlated with lymph node metastasis ($p = 0.0230$). The chances of risk for lympho-vascular invasion and lymph node metastasis were associated with tumour size over 40 mm (OR=13.69, respectively OR=6). In addition, the chance of risk for lymph node metastasis was associated with multifocal primary tumour (OR=9.428).
Conclusion: Our results indicate that, despite the variability of histological MTC subtypes, they do not significantly influence the prognosis. A particular aspect identified in our MTC series was the association, in 7 cases, with papillary thyroid carcinoma, tumour with different cell origin; the coexistence of the two thyroid malignancies is rarely reported in the literature. Moreover, our data confirm that lympho-vascular invasion and lymph node metastasis are relevant indicators for aggressiveness, whose presence can explain the worse course of disease.

PS-14-005
Non-syndromic familial non-medullary thyroid carcinoma in the area of Santiago de Compostela (northwest Spain)
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Background & objectives: Non-syndromic familial non-medullary thyroid carcinomas (NSFNMTCs) are a heterogeneous group of hereditary cancers whose genetic basis is poorly understood. It has been suggested that some of their clinicopathological features may suggest a familial character. We investigated a series of NSFNMTCs.
Methods: Follicular cell-derived thyroid carcinoma was identified in ≥ 2 first-degree relatives in 43 cases. Most patients were women (69.76%), with a female-to-male ratio of 3:1.3. The mean and median age (and range) was 42.5 and 67 (25-73) years for women, 43.08 and 43 (18-68) for men and 42.33 and 41 (18-68) for the total number of patients, respectively.
Results: All cases (97.67%) were papillary thyroid carcinomas (PTCs) except one case of oncocytic thyroid carcinoma. PTC subtypes were: follicular (54.76%), conventional (28.57%), tall cell (11.9%), oncocytic (2.38%) and Warthin-like variant (2.38%). Multifocality was detected in 31/43 cases (72.09%) and bilaterality in 24/42 cases (57.14%). Tumour size ranged from 3 to 56 mm (mean 17.55; median 12). Venous invasion was found in 1 case (2.32%); extrathyroidal extension in 6 (13.95%) and lymph node metastases in 10 (23.25%). Follicular nodular disease and/or follicular adenoma was detected in 30 cases (69.76%); lymphocytic thyroiditis in 13 (30.23%); Graves disease in 2 (4.65%); intrathyroidal parathyroid in 3 (6.97%) and thymic tissue in 1 case (2.32%).
Conclusion: NSFNMTCs are typically PTCs, mainly of the follicular, conventional and tall cell variants, associated with multifocality and bilaterality, as well as with a high frequency of extrathyroidal extension. The combination of PTC with a background of benign lesions is also frequent.
Funding: Partially supported (JMC-T) by grant PI19/01316-FEDER, Instituto de Salud Carlos III, Spain.

PS-14-006
The incidence trend of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in Mures county, Romania, five years after the introduction of this new entity: a retrospective cohort study
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Background & objectives: NIFTP nomenclature was proposed in 2016 and revised in 2018. The aim of our study was to retrospectively assess the incidence and the epidemiological trend of NIFTP in Mures county, Romania, five years after the introduction of this new entity.

Methods: All NIFTP cases registered in Targu-Mureş Pathology Department between 2016-2021 were reviewed. The incidence of NIFTP was calculated in relation to the number of papillary thyroid carcinomas (PTCs) registered over the study period. Then, the incidence of NIFTP between 2016-2018 was compared to the incidence between 2019-2021, 2018 marking the year when the diagnostic criteria of NIFTP were revised.
Results: A total number of 43 cases of NIFTPs were diagnosed in our department between 2016-2021, with an overall NIFTP incidence of 13.5% [CI 10.06-18.11], among the 319 PTCs cases registered over the same period. When the incidence of NIFTP was compared between the two periods (2016-2018 versus 2019-2021), we found out that the overall incidence of NIFTP has dropped from 15.13% [CI 10.0-22.83] to 11.97% [CI 7.77 -18.42] in the second evaluated period.
Conclusion: In this study, we documented a low NIFTP incidence in our institution over the last 5 years. The fact that NIFTP incidence decreased after refining the diagnostic criteria in 2018, emphasize the need to apply very stringent histomorphologic criteria when making a diagnosis of NIFTP, in order to avoid overtreatment of a tumour with indolent behaviour.

PS-14-007
A 20- year retrospective analysis of adrenal tumour pathology in Mureş County, Romania. What has changed?
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Background & objectives: Primary adrenal malignancies are rare tumours. The aim of the study was to examine time-trends of tumour adrenal pathology and to analyse the distribution of their different histology in a 20-year retrospective study (2000-2019), in Mureș County, Romania.
Methods: Patients clinic-pathological features were obtained from database registries of Department of Pathology, County Emergency Clinical Hospital, Târgu-Mureș. Histological types of adrenal tumours were classified according to WHO 2017 criteria. Due to a small number of cases, in order to establish a trend for incidence, we analysed the cases distribution in 4 periods of 5 years:2000-2004, 2005-2009, 2010-2014 and, respectively, 2015-2019.
Results: We first identified 101 patients who underwent an adrenal surgery between 2000-2019. Subsequently, the analysis included only cases classified as tumours of the adrenal cortex (62,72.9%) or adrenal medulla (23,27.1%). The most common adrenal tumours were adenomas 35%, followed by pheochromocytomas 24%, carcinomas 15%, metastatic tumours 14%, myelolipomas 7%, neuroblastic tumours 4%, lymphomas 1%.
The average age at the time of diagnosis was 54.13 year-old for adenomas, 49.73 for carcinomas and 47.85 for pheochromocytomas. The average size of the carcinomas was 88.2 mm, and 60.4 mm for pheochromocytomas.
An increased number of adrenal adenomas (56,26%) was noticed in the last period 2015-2019, increasing the total number of adrenal tumours (37.64%).
Conclusion: Although not very common, adrenal tumours express a varied pathology with special features that must always be in the pathologist's attention for a diagnosis as accurate as possible. The recent increase in adrenal tumours cases, due to benign and probably non-secretory tumours, could be attributed to the frequent use of imaging methods. The incidence of adrenal cancer did not have an upward trend.

PS-14-008
Evaluating proliferation in medullary thyroid carcinoma
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Background & objectives: Medullary thyroid carcinoma (MTC) is a rare malignant neuroendocrine neoplasia. Recent studies demonstrated that proliferation is one of the most important prognostic factors. Various methods are available for the measurement of proliferation, including mitotic counts and immunohistochemistry of proliferation-associated antigens.
Methods: A total of 100 initial thyroidectomy specimens were examined microscopically. The mitotic index (MI), Ki67, PHH3 and MCM6 proliferative indexes were evaluated. Measurements were obtained in the area showing the highest proliferative activity. MI and PHH3 were assessed per 2mm2. For the Ki67 and MCM6 proliferative indexes, 500 to 2000 tumour cells were counted per tumour.
Results: All of the four proliferative indicators were significant predictors of overall survival (OS), biological (B-DFS) and morphological disease free survival (M-DFS). MI was associated with a decrease in OS (hazard ratio [HR]=1.26, 95% confidence interval [CI]=1.18-1.35, p<0.001), M-DFS (HR=1.2, CI=1.13-1.27, p<0.001) and B-DFS (HR=1.13, CI=1.08-1.19, p<0.001). PHH3 was associated with a decrease in OS (HR=1.15, CI=1.05-1.28, p=0.022), M-DFS (HR=1.09, CI=1.02-1.16, p=0.036) and B-DFS (HR=1.10, CI=1.05-1.16, p=0.001). MCM6 was also associated with a decrease in OS (HR=1.06, CI=1.03-1.08, p<0.001), M-DFS (HR=1.03, CI=1.00-1.05, p=0.049) and B-DFS (HR=1.04, CI=1.02-1.06, p<0.001).
Conclusion: We demonstrateded that all proliferation measurement methods are significant prognostic predictors. These indicators are continuous variables, and as each variable increases, prognosis worsens. We recommend reporting at least one of these proliferation indexes in addition to conventional prognostic factors for MTC.

PS-14-009
Neuroendocrine metastasis in the digestive system
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Background & objectives: Metastasis of neuroendocrine carcinomas (NEC) in the digestive system are possible and present an unusual mode of revelation. They represent a real challenge for the pathologist since they mimic primary neuroendocrine pancreato-gastrointestinal tumours.
Methods: A review of all neuroendocrine metastasis in the gastro-intestinal tract and pancreas of the Gustave Roussy Campus Cancer pathology department was performed between 2015 and 2021.
Results: Three cases of secondary NEC in gastro-intestinal tract and pancreas were found. They were all men aged 58, 68 and 73 years old. Two had pancreatic tumours and one had a small intestine tumour. Diagnosis was made on the second opinion expert consultation. The two pancreatic tumours showed

positivity for neuroendocrine markers, SATB2 and had a proliferative index Ki67 between 40 and 50%. They both expressed Polyomavirus on immunohistochemistry. Final diagnosis was Merkel cell carcinoma. Intestinal tumour was positive for neuroendocrine markers and TTF1. Ki67 labelled 80% of the cells. Final diagnosis was metastasis of large cell neuroendocrine carcinoma of lung. Chest tomography was secondarily performed and confirmed this diagnosis.
Conclusion: NEC of the digestive system are rare tumours with multiple morphological mimics. The pathologist must always favour the diagnosis of a secondary localization and push the investigations before making the diagnosis of primary NEC of the digestive system.

PS-14-010
Different patterns of prostate specific membranous antigen expression in tumour-associated neovasculatur among neuroendocrine neoplasms of GI-tract - an immunohistochemical study targeted on its theranostic use
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Background & objectives: Tumour vascularization as a therapeutic target is gaining importance in an increasing number of solid tumours. In this context, the expression of prostate specific membranous antigen (PSMA) in intratumoral vessels has led to increased interest with regard to PSMA-directed therapy.
Methods: We examined PSMA expression on tumour-associated vessels in specimens of different neuroendocrine neoplasms of the digestive system (n=16 NET-G1, n=16 NET-G2, n=8 NET-G3 and n=14 NEC) by immunohistochemistry. If positively stained vessels were present, their number was counted in hotspot regions and related to the area.
Results: PSMA expression in intratumoral vessels was detected in 2/16 NET-G1 (12,5%), 3/16 NET-G2 (18,7%), 5/8 NET-G3 (62,5%) and 7/14 NEC (50%). We found differences in the distribution (intratumoral versus marginal or in the area of the invasion front) as well as in the number and density of stained vessels.
Conclusion: Comparable to other solid tumour entities, in neuroendocrine neoplasms PSMA expression in intratumoral, tumour-derived vessels is associated with higher tumour-grade and aggressiveness. As PSMA-directed therapy in metastatic prostate cancer is an already well-established theranostic concept, opportunities are now also emerging in the context of vascular PSMA expression of solid tumours. This could open up the possibility of PSMA-directed diagnostic work-up and therapy in aggressive neuroendocrine neoplasms whose therapeutic options have been limited so far.

PS-15 | Poster Session Molecular Pathology

PS-15-001
Digimir test: a novel pipeline for mir-371a-3p quantification using droplet digital PCR in liquid biopsies of testicular germ cell tumour patients
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Background & objectives: miR-371a-3p is the most reliable liquid-biopsy biomarker for diagnosis and monitoring of testicular germ cell tumour (TGCT) patients. Current studies have focused on RT-qPCR methodologies, but some challenges remain (pre-amplification and normalization). Droplet digital PCR (ddPCR) may overcome these challenges.
Methods: In this work, we provide a report of a ddPCR-based pipeline for quantification of miR-371a-3p (the DigiMir pipeline) and compare it with two common RT-qPCR protocols. A total of 107 plasma samples were investigated in the validation setting. All requirements for validation of ddPCR pipelines were followed, including appropriate controls, spike-in, temperature gradient and limits of blank, detection and quantification.
Results: The DigiMir pipeline showed a good performance in the intra-operator, inter-operator, inter-synthesis and inter-extraction tests. It detected TGCTs in a manner representative of tumour burden, with a sensitivity and specificity of 94% and 100%, respectively, outperforming the combined sensitivity of all three classical serum tumour markers available currently in routine (61.5%). All non-TGCT testicular masses were negative, as was a patient with hepatocarcinoma showing high serum levels of AFP, further assuring the specificity of the test. One patient with constitutive slight elevation of AFP (generating clinical challenges) was negative for the miR-371a-3p and remained disease-free under surveillance. The single patient showing disease progression maintained high miR-371a-3p levels at follow-up.
Conclusion: Therefore, in this proof-of-concept investigation, we have showed that the DigiMir pipeline constitutes a new promising methodology for accurately reporting miR-371a-3p in the clinical setting. ddPCR is a suitable methodology for quantifying microRNAs in liquid biopsy samples of patients with the accuracy needed for precision medicine.
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PS-15-002
Differential gene expression of nystagmus-associated genes in chronic traumatic encephalopathy, Parkinson`s disease, and Alzheimer`s disease
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Background & objectives: The research aimed to determine whether the genes that presented with nystagmus as part of their clinical presentation were differentially expressed in the brains of patients with Parkinson's Disease (PD), Chronic Traumatic Encephalopathy (CTE), and Alzheimer's Disease (AD).
Methods: The data was derived from the available NCBI SRA datasets that allowed public domain use. The database search yielded 10 PD patients, 13 AD patients, 10 CTE patients, and 6 CTE with AD patients. The RNA sequence from the brain samples of the patients underwent differential expression analysis using the web-based platform Galaxy and R version 4.1.0 with R Studio.
Results: Identifying the nystagmus-associated genes among the genes that were expressed in the brain samples of patients with PD, AD, CTE, and CTE with AD showed that there were only 21 genes out of the 28,395 retrieved genes in the mRNA sequence of the

patient groups and the control group that were identified to have a reported association with nystagmus. Post Hoc evaluation showed that the identified genes from all of the patient groups were significantly under-expressed compared to the control group ($p<0.001$). The genes that were identified can be divided into those involved in protein synthesis, cell cycle regulation, gap junction formation, transcription regulation, signal transduction, and synaptic function.
Conclusion: The relationship illustrated that the common genomic changes may indicate how the pathways that have been altered due to the diseases have intersecting gene expression alteration that lead to visual motor control pathology. Performing differential gene expression studies in the brain samples of post-mortem cases illustrates how autopsy pathology and computation pathology can elucidate the common genomic changes and molecular mechanisms that can present across different diseases which may be significant in the field of both neuro- and ophthalmic pathology.

PS-15-003
Determination of Ly6E and Ly6K gene expression levels in soft tissue tumours and investigation of their correlation of these levels with tumour aggression
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Background & objectives: Soft tissue tumours are rare heterogeneous group of tumours. In recent years, cancer research has gained a different approach with the discovery of cancer stem cells. We aimed to evaluate the expression of Ly6E and Ly6K genes in these tumours.
Methods: The study was performed with 45 patients, aged between 20-80, diagnosed with soft tissue tumours. In the study, there were patients diagnosed with dermatofibroma and leiomyoma; leiomyosarcoma, pleomorphic sarcoma and synovial sarcoma. Paraffin blocks sections were taken and deparaffinised, total RNA isolation and cDNA were obtained. Ly6E and Ly6K expression levels were determined by PCR, the results were compared.
Results: When all groups are evaluated together; there was a statistically significant increase in Ly6E and Ly6K gene expression in the benign and malignant tumour groups compared to the control group. However, the increase in Ly6K was statistically insignificant. Especially in leimyosarcomas, there was a statistically significant increase of Ly6E gene expression. In synovial sarcoma and pleomorphic sarcomas, it was observed that Ly6E expression increased compared to the control group, but it was insignificant. A statistically significant increase in Ly6K gene expression level was found in malignant tumours originating from smooth muscle compared to the control group. There was no statistically significant difference between other tumour groups in Ly6K expression levels.
Conclusion: The expressions of Ly6E and Ly6K in human soft tissue tumours were discussed for the first time in the literature. Especially in well-differentiated malignant soft tissue tumours, the aforementioned markers were found to be elevated and tumour aggressiveness is related with them. Therefore, with more comprehensive studies, the importance of Ly6E and Ly6K genes in cancer development and their potential roles in the therapy will be better understood and our study will make an important contribution to the literature.

PS-15-004
Setting up an ultra-fast next-generation sequencing approach as a reflex testing at diagnosis in non-squamous non-small cell lung cancer
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Background & objectives: The number of targetable genomic alterations in non-squamous non-small cell lung cancer (NS-NSCLC) patients increased these last few years, while the tissue material reduced in size. Therefore, molecular pathologists are facing challenges to maintain a strategy allowing a rapid diagnosis.
Methods: We report here our experience (LPCE, Nice, France) between September 20, 2021 and December 31, 2021 for the development of an optimal workflow for genomic alteration assessment as a reflex testing in routine clinical practice at diagnosis in patients with NS-NSCLC using an ultra-fast next generation sequencing approach (Genexus OPA DNA RNA panel, Thermo-Fisher).
Results: 325 patients were included in the study. 74% of patients had stage IIIB-IV NS-NSCLC, and 26% were stage I-IIIA. Ultra-fast NGS was performed in 182 bronchial biopsies, in 68 transthoracic biopsies, in 50 surgical specimens and in 25 cellblocks from 16 pleural effusion and 9 EBUS with a short mean turnaround time of 72h. Mean tumour cell was 40% (ranging from 5% to 95%). The analytical validation of the Genexus OPA workflow, performed on 30 NS-NSCLC cases, demonstrated 100% concordance with the gold standard methods.
Conclusion: We demonstrate that molecular targets accessible to personalized medicine in NS-NSCL were identified using the Genexus system in a rapid turnaround time. Ultra-fast NGS integration as a reflex testing can be an optimal option for genomic alteration assessment at diagnosis for all stage NS-NSLC. This approach enables for a sensitive and a specific identification of mutations, CNVs, and fusion variants types across 50 key genes, on tumour material with a low amount of nucleic acids.

PS-15-005
KRAS mutations in 1355 Italian patients with lung adenocarcinoma
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Background & objectives: Targeted therapies against KRAS mutations in patients with non-small cell lung cancer (NSCLC) were recently introduced in clinical practice. The aim of this study was to investigate the molecular landscape of KRAS mutations in Italian patients with lung adenocarcinoma.
Methods: Consecutive Italian patients with histologically diagnosed lung adenocarcinoma who underwent molecular analysis for KRAS mutations were enrolled into the study. Mutation analysis was carried out initially by quantitative measurements of mutations with pyrosequencing (PyroMark Q24 system, Qiagen Inc., USA), replaced in 2021 by next generation sequencing (NGS) techniques on Ion S5 GeneStudio (Life Thermofisher) platform.
Results: 1355 patients were enrolled. Among them 850 (62.73%) were males, and the mean age was 67 ($\pm$10.3) years. A KRAS mutation was detected in 324 patients (23.9%); most of them were males (238, 73.46%). Considering the male population, KRAS mutations were found in 238 out of 850 (28%), while they were detected in 86 out of 505 (17.03%) women ($p<0,0001$). No statistically significant difference in the age of mutated and non-mutated patients (68, 95% CI: 67 – 70 vs 68, 95% CI: 67 – 68.5 years) was

found. Globally, 14 subtypes of KRAS mutations were detected, the most common being G12C (103, 31.79%), G12V (79, 24.38%), and G12D (45, 13.89%).
Conclusion: KRAS mutations occurred in 23.9% of the patients enrolled in the study, and KRAS G12C was the most common one, detected in 103 patients (7.6%); these figures are slightly lower in comparison to those reported for other Caucasian populations.

PS-15-006
Increased expression of the CST2 gene is associated with lymphatic dissemination of prostate cancer
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Background & objectives: Locally advanced prostate cancer (LAPC) is characterized by invasion of the prostatic capsule, in which lymphatic dissemination is also frequently observed. For this category of patients, the search for reliable prognostic markers for choosing further treatment tactics is especially relevant.
Methods: Total RNA was obtained from 73 LAPC samples, from which libraries were prepared and RNA-Seq on the Illumina platform was performed. Differential expression analysis was performed between samples with (N1 group) and without lymphatic dissemination (N0 group) in R (edgeR). Validation of gene expression was performed by qPCR on an independent sample of LAPC patients based on 37 FFPE samples.
Results: According to the obtained RNA-Seq data bioinformatic analysis results, a statistically significant increase in the differential expression of the CST2 gene in the N1 group by 3.27 times was found (LogFC = 1.71; FDR-value QLF test = 0.01). Spearman's rank correlation analysis showed a correlation between CST2 gene expression and lymphatic dissemination (rs=0.47; p-value = 0.00009). Based on the results of CST2 gene relative expression validation in an independent sample of LAPC patients, a statistically significant increase in expression in the N1 group by 3.24 times (p-value = 0.002) was also confirmed.
Conclusion: Thus, based on the study, it was shown that an increased level of CST2 gene expression is statistically significantly associated with lymphatic dissemination and can be considered as a potential prognostic marker in prostate cancer.
This research was financially supported by the Russian Science Foundation, grant 18-75-10127.

PS-15-007
NTRK fusion genes in cholangiocarcinoma
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Background & objectives: Cholangiocarcinoma (CCA) is an uncommon and aggressive adenocarcinoma with poor long-term survival. As current treatment options for CCA patients are restricted and systemic, new therapies are urgently needed. Here we studied if NTRK fusion genes exist in CCAs.
Methods: CCA cohort retrieved from Helsinki Biobank (Finland) included 93 primary CCAs and 25 metastatic samples. Tumours were histologically re-evaluated, processed into TMAs and labelled with pan-TRK antibody (clone EPR17341, Roche Tissue Diagnostics, Tucson, AZ). Tumours expressing TRK were further analysed with Idylla GeneFusion Assay (Biocartis, Mechelen, Belgium) and FusionPlex Comprehensive Thyroid and Lung (CTL) panel (Invitae Corporation, San Francisco, CA).
Results: Altogether 9 primary tumours showed TRK expression in immunohistochemistry (IHC), indicating putative NTRK fusion. Metastatic samples showed no expression. The amount of TRK positive cells was low with an average value of 15 cells per tumour (median 4, range 1-100). In 7 of the tumours the expression was nuclear and 2 tumours showed cytoplasmic expression. Real-time RT-PCR-based Idylla GeneFusion Assay was performed to all 9 tumours. It identified NTRK3 expression imbalance in the tumour with cytoplasmic TRK expression. No other fusions were detected. Next-generation sequencing (NGS)-based FusionPlex CTL panel was performed for 8 tumours. No NTRK fusions were detected.
Conclusion: We identified NTRK3 expression imbalance in one (1.1%) of 93 CCA tumours but this could not be confirmed with NGS. Our results show limited specificity of pan-TRK IHC to identify NTRK fusions. Pan-TRK IHC can thus be utilized as a screening technique for NTRK fusions in CCA, but positive samples require confirmatory testing with RNA-based methods. As there is a tumour agnostic oncological treatment for patients with an NTRK fusion, also CCA patients should be screened for this gene rearrangement.
Funding: This work was supported by the Cancer Foundation Finland [no grant number], the Helsinki University Hospital Research Fund [grant number TYH2019205] and Bayer Oy.

PS-15-008
Analysis of PINK1 immunoexpression in primary lung adenocarcinomas revealed a group of patients with a poorer prognosis
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Background & objectives: In lung adenocarcinoma, high PINK1 expression was correlated with poor response to chemotherapy. Our aim was to study the immunoexpression of PINK1 in samples from lung adenocarcinoma and their respective brain metastases and its possible clinical relevance.
Methods: Twenty-six consecutive patients with lung adenocarcinoma and subsequent brain metastasis surgically removed between 2007 and 2019 were studied. Tissue arrays were produced using a 2 mm diameter needle. Immunohistochemical studies were conducted and analysed by the H-Score method. Statistical analysis of these findings was carried out using the SPSSv25; $p<0.05$ program.
Results: Positive immunoexpression for PINK1 was detected in more than 90% of both primary tumours and their brain metastasis without significant differences (70,91 ± 43,46 vs 77,61 ± 43,69; p= 0,565). More than 80 points of PINK1 immunoexpression in primary lung adenocarcinoma showed a group of patients with a significant lower overall survival (46,63 ± 17,44 vs 98,79 ± 15,02 weeks; p= 0,018) and post-metastasic survival (18,86 ± 6,61 vs 84,78 ± 14,88 weeks; p= 0,002).
Conclusion: Non-significant differences for PINK1 were noted between primary and metastatic adenocarcinoma samples. More than 80 points of PINK1 immunoexpression in primary lung adenocarcinoma revealed a group of patients with a poorer prognosis.
Funding: A competitive grant to IFV in the intramural call for the promotion of research projects of the Institute of Health Research of the Principality of Asturias, ISPA (2020-2022).

PS-15-009

Analysis of p62 immunoexpression in metastatic samples of lung adenocarcinomas to the brain revealed a group of patients with a poorer prognosis

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Background & objectives: p62 is a multifunctional adaptor protein implicated in the crossroads of autophagy, apoptosis, and cancer. Our aim was to study the immunoexpression of p62 in samples from lung adenocarcinoma and their respective brain metastases and its possible clinical relevance.
Methods: Twenty-six consecutive patients with lung adenocarcinoma and subsequent brain metastasis surgically removed between 2007 and 2019 were studied. Tissue arrays were produced using a 2 mm diameter needle. Immunohistochemical studies were conducted and analysed by the H-Score method. Statistical analysis of these findings was carried out using the SPSSv25; $p<0.05$ program.
Results: Positive immunoexpression for p62 was detected in more than 80% of both primary tumours and their brain metastasis with significant differences (112,38 ± 101,28 vs 85,71 ± 88,97; p= 0,035). More than 60 points of p62 immunoexpression in metastatic brain samples of lung adenocarcinoma showed a group of patients with a significant lower overall survival (56,61 ± 15,21 vs 111,03 ± 11,21 weeks; p= 0,039) and disease-free survival (4,55 ± 1,91 vs 82,47 ± 20,10 weeks; p= 0,005).
Conclusion: Significant overexpression of p62 was noted in primary lung adenocarcinomas compared to the metastatic tissue in the brain. More than 60 points of p62 immunoexpression in metastatic brain samples of lung adenocarcinoma revealed a group of patients with a poorer prognosis.
Funding: A competitive grant to IFV in the intramural call for the promotion of research projects of the Institute of Health Research of the Principality of Asturias, ISPA (2020-2022)

PS-15-010

NGS-based molecular profiling and liquid biopsies: an assessment of pathologists and oncologists knowledge and attitudes

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Background & objectives: This activity investigated the knowledge gaps of haematologists/oncologists (hem/oncs) and pathologists regarding the use of next generation sequencing (NGS)-based molecular profiling and liquid biopsies in clinical practice.
Methods: A CME-certified clinical practice assessment comprising 30 multiple-choice questions that measured knowledge, attitudes, and perspectives regarding NGS-based molecular profiling and liquid biopsies was developed. The self-assessment was available online to physicians without monetary compensation. Respondent confidentiality was maintained, and responses were deidentified and aggregated prior to analysis. The activity launched June 8, 2021; data through December 1, 2021, are presented.
Results: The number of hem/oncs and pathologists answering each of these 30 questions ranged from 58 to 340. Only 54% of hem/oncs and 52% of pathologists knew that the turnaround time of NGS analysis of liquid biopsies is approximately 50% shorter compared to NGS analysis of tissue biopsies. Furthermore, only 44% of hem/oncs and pathologists were aware that real world data in NSCLC showed that patients receiving matched targeted therapy after genomic profiling of tissue biopsy versus ctDNA had similar PFS and ORR. The percentage of hem/oncs who answered each of the 20 knowledge questions correctly ranged from 17% to 83% while the range for pathologists varied from 16% to 89%.
Conclusion: NGS-based molecular profiling and liquid biopsies are becoming increasingly important in informing treatment decisions for patients with cancer. However, only 26% of hem/oncs and 35% of pathologists are confident in explaining to their colleagues how to apply NGS in clinical practice, and only 27% of hem/oncs and 28% of pathologists are confident in their ability to use liquid biopsies in clinical practice. This demonstrates the importance of further educating clinicians on these topics.
Funding: This activity was supported by an independent educational grant from Thermo Fisher Scientific

PS-15-011

Study of gene expression by in situ hybridization in tissues with prostate adenocarcinoma routinely processed

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Background & objectives: The chromogenic in-situ hybridization (CISH) RNAscope® amplifies specific mRNA signals without background noise, and detects individual molecules as points feasible to be quantified. It allows high resolution in the study of the expression of each cell within its morphological context.
Methods: The in situ gene expression was evaluated by CISH in routinely processed prostate tissue. CISH assays were performed under standard conditions of the RNAscope® 2.5HDBrown ISH protocol, in a tissue microarray. Considering a positive stain easily visible under the microscope, nuclear and cytoplasmic dotted staining and signal strength for mRNA of each gene in the tissue cores were measured.
Results: Expression of the endogenous gene Hs-PPIB (Peptidylprolyl-Isomerase-B) as a positive control, the bacterial gene dapB (dihydrodipicolinate-reductase) as a negative control for the background signal, and the target gene CXXC5, were evaluated in a prostate tissue microarray constructed from prostatectomy samples of patients with localized prostate cancer, including 381 cores of benign prostate tissue and prostate adenocarcinoma. The quality of the mRNA was variable along the tissue cores of the microarray, most showed moderate to strong staining of the positive control with little background staining. There was a correlation between mRNA expression of the constitutive endogenous gene Hs-PPIB and the target gene CXXC5.
Conclusion: CISH makes it possible to detect isolated mRNA molecules in routinely processed tissues, study cell gene expression in context without destroying tissue morphology, compare it between heterogeneous cell populations, and locate molecular markers within the tumour microenvironment. Analysing the expression of mRNA in prostate cancer (PCa) tissues routinely processed by CISH would allow risk stratification and prognostic markers.
Funding: Universidad de Cartagena, Cartagena, Colombia.

PS-15-012

Arylsulfatase B gene expression profile in colorectal cancer

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Background & objectives: Arylsulfatase B (ARSB) is a lysosomal enzyme with specific role in metabolism of chondroitin and dermatan sulfate. Few studies suggested it's role in different carcinogenesis. The aim was to examine the association between ARSB and TP53 gene expressions in CRC.
Methods: In this prospective study, 77 cases of CRCs were included. Gene expression of ARSB and TP53 was analysed after RNA isolation from fresh tissue samples. The expression level was determined using relative quantitation (RQ). RQ>1 was considered highly expressed whereas RQ<1 was used to identify low gene expressions for ARSB and TP53.
Results: The statistical assessment showed a strong direct association between ARSB and TP53 gene expression levels ($p<0.0001$). Low expression was seen in 42 of the cases (54.55%) for both genes. In 15 out of the 77 cases (19.48%) both genes were highly expressed; these cases were mostly diagnosed in locally advanced stages (pT3/4), with high budding grade. The remaining cases (n=20; 25.97%) presented high ARSB and low TP53 expression. From the 62 cases with high ARSB gene expression level, 25 (40.32%) had mutation in one of the exons of the KRAS gene. These cases were mostly G2-adenocarcinomas with epithelial phenotype.
Conclusion: All these findings suggest a possible prognostic role of ARSB in CRC and an association with TP53 gene. Further research might be necessary to understand the exact behaviour of this enzyme in such carcinomas. No similar data were reported in literature.
Funding: This study was partially funded by the CNCS – UEFISCDI, project number 20 PCCF/2018.

PS-15-013
The spectrum of gene fusions in primary epithelial ovarian tumours identified by panel RNA NGS approach
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Background & objectives: Gene fusions represent somatic alterations involved in tumorigenesis of different cancers, and serve as diagnostic markers and/or therapeutic targets, although their incidence in ovarian tumours is unknown. Our aim was to characterize fusions in selected primary epithelial ovarian tumours.
Methods: Sequencing libraries for paired-end capture RNA-Seq (147 genes; 373kbp; HyperCapture,Roche) were prepared using 300ng of total RNA isolated from FFPE tissues including mucinous borderline tumours (MBT;58), mucinous carcinomas (MC;36), high-grade serous carcinomas (HGSC;6), serous borderline tumours (SBT;23), and low-grade serous carcinomas (LGSC;53) and KAPA RNA HyperPrep kit (Roche), sequenced on NextSeq (Illumina), and biostatistically analysed using CLC Genomics Workbench (Qiagen).
Results: A recurrent fusion TFG::ADGRG7 was found in 4/58 (7%) MBT, 2/36 (6%) MC, 1/23 (4%) SBT, and 1/53 (2%) LGSC. Interestingly, a known targetable recurrent fusion FGFR2::KIAA1217 was found only in the LGSC sample set (2/53; 4%). In total, eight different fusions were identified in 6/58 (10%) MBT, 2/36 (6%) MC, 1/23 (4%) SBT, 6/53 (11%) LGSC, and 1/6 (17%) HGSC. The fusion partners included known or potential therapeutic targets, such as BRAF, EGFR, FGFR2, NF1.
Conclusion: The applied RNA-Seq approach revealed several known or novel fusions across different types of primary epithelial ovarian tumours. Extension of the analysed cohort and identification of fusions is ongoing and eventually will show fusion patterns, the role of gene fusions in targeted therapy and differential diagnostics in rare ovarian primary tumours.
Supported by Ministry of Health of the Czech Republic (NV19-03-00007 and RVO64165, General University Hospital in Prague).

PS-15-014
Development of a murine-model of oral carcinogenesis: a rapid tool for biomarker and anti-tumour drug discovery
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Background & objectives: Oral squamous cell carcinoma (OSCC) is the commonest malignancy in Pakistani males and second only to breast cancer in females. We devised a novel accelerated murine model of oral carcinogenesis that can be exploited to identify molecules of diagnostic/therapeutic/prognostic significance.
Methods: Total 40 healthy male, 6-8 weeks-old, 20-22 gram Naval Medical Research Institute(NMRI) outbred-strain mice were recruited. Of these, 25 were topically applied with 0.5% 9,10-dimethyl-1,2-benzanthracene in the lower lip for 20 weeks and 15 were used as controls. Harvested tissues were fixed and stained with hematoxylin and eosin. Additionally, expressions of CK 5/6, p53, and Ki-67 were investigated by immunohistochemistry.
Results: All 25 mice (100%) who underwent accelerated carcinogenic regime developed tumours/lesions. The earliest lesion was developed on day 33 while the highest number of days taken for development of a lesion was 126. Average number of days taken by our mice to develop lesion was 84.56 days. Of 25 mice, 21 developed moderately differentiated squamous cell carcinoma and 1 showed dysplastic features with foci of invasion. Three mice were found dead despite developing lesions. CK 5/6 showed strong positivity (100%) and p53 and Ki-67 showed patchy (<30%) strong positivity in OSCC suggesting the similarity of our model to human OSCC. Controls did not show any morphological changes throughout the study.
Conclusion: We present an accelerated, immunocompetent murine model of oral carcinogenesis using 9,10-dimethyl-1,2-benzantharacene in NMRI outbred strain mice. This model is close to human carcinogenesis that can be exploited as a tool to investigate and underpin molecular circuitry involved in oral carcinogenesis and to investigate various bio-molecules of diagnostic, therapeutic and prognostic significance.

PS-15-015
The effect of mitochondrial energy metabolism modulators on cytotoxicity of cisplatin and pemetrexed in mesothelioma
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Background & objectives: The aim of this experiment was to investigate whether pharmacological modification of mitochondrial energy metabolism together with high glucose concentrations could potentially be used for a more successful treatment of malignant mesothelioma.
Methods: To access the resistance of mesothelioma cells to antineoplastic agents, cell proliferation was quantified in the Mero-14 mesothelioma cell line after a 3 day treatment with different concentrations of antineoplastic agents pemetrexed and cisplatin (C/P) together with high glucose concentration alone or combined with mitochondrial energy metabolism modulators UK-5099, DNP, DCA. Cell proliferation was estimated using the MTT assay.
Results: The addition of glucose alone did not significantly alter the cytotoxic effect of C/P and neither did UK-5099, DNP, nor DCA show an effect on cell proliferation when used at lower

concentrations. The obtained results did not show a significant difference between C/P alone and C/P in combination with low doses of mitochondrial energy metabolism modulators. In contrast, at higher concentrations, UK-5099, DNP, and DCA potentiated the cytotoxicity of C/P. When combined with a high glucose concentration, lower concentrations of DNP and DCA potentiated the cytotoxic effect of C/P and at higher concentrations this effect was annulled.
Conclusion: The presented results showed that all three tested mitochondrial energy metabolism modulators, UK-5099, DNP and DCA, when used in higher concentrations, have a similar pattern of action; potentiating the cytotoxic effect of cisplatin and pemetrexed. This suggests a synergistic effect of antineoplastic agents and mitochondrial metabolism modulators on reducing mesothelioma cell proliferation. Mitochondrial metabolism modulators have potential for mesothelioma treatment. However, further studies are needed to examine their precise mechanisms of action.
Funding: These findings are a part of the research project Reprogramming cytoprotective pathways in malignant mesothelioma (IP-2014-09-4173), funded by the Croatian Science Foundation.

PS-15-016
The clinical significance of epigenetic and RNAPII variabilities occurring in clear cell renal cell carcinoma as a potential prognostic marker
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Background & objectives: Patients diagnosed with clear cell renal cell carcinoma (ccRCC) have poor prognosis. For this reason, the more detailed molecular characterisation of the primary tumour, and metastasis, are crucial to select the proper adjuvant therapy.
Methods: As a potential molecular biomarker, to follow the transcriptional kinetics in 30 ccRCC patients, we analysed γH2A.X, H3K4me3, and H3K9me3 and the alterations of RNAPII by immunohistochemical staining. The variabilities between the tumorous and non-tumorous parts of the tissue were detected using quantitative image analysis by monitoring 100 cells either the tumorous or the control part of the tissue sections.
Results: We detected a synergistic elevation both in H3K4me3 and RNAPII level which confirms the reliability of our data. The present study also establishes a strong correlation between H3K4me3 and RNAPII marks. We also found that the alteration in the global level of H3K9me3 corresponding with changes in the level of H3K4me3 and RNAPII was correlated with the presence of ccRCC. Finally, in ccRCC tumour-derived specimens, we observed increased γH2A.X level, which is the hallmark of persistence DNA damage. In correlation with the perpetual presence of γH2A.X, in ccRCC patients considerable number of DNA damage or insufficient DNA repair takes place.
Conclusion: Data obtained from the analyses were used to identify potential prognostic features and to associate them with the progression. These markers might have a value to predict patient outcomes based on their individual cellular background. These results also support that detection of any alteration in the level of H3K4me3, H3K9me3, and γH2A.X can account for valuable information for presuming the progression of ccRCC and the clinical benefits to select the most efficient personalised therapy.
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PS-15-017
Long non-coding RNA H19 expression in rectal cancer and therapy response
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Background & objectives: Long non coding RNA, H19 is an imprinted, maternally expressed gene, usually deregulated in different cancer types, including rectal cancer. This study aimed to investigate H19 role as a potential biomarker to predict therapy response in rectal cancer patients.
Methods: The study included 14 patients diagnosed with rectal cancer, treated with neoadjuvant chemoradio therapy (nCRT). RNA was isolated by TRIzol reagent from samples of rectal cancer tissue before and after nCRT. Relative expression of H19 was normalized to housekeeping GAPDH gene, and expression was analysed by quantitative real-time PCR. Relative expression of H19 was calculated by 2-ΔCt method.
Results: Relative expression of H19 was significantly increased in rectal cancer tissue after nCRT (0.244±0.408) compared to the tissue before nCRT (0.043±0.055), p=0.004, Wilcoxon test. According to tumour regression grade (TRG), 85.71% (12/14) of patients did not respond, while 14.28% (2/14) responded to preoperative CRT. Responders (TRG1, TRG2) and non-responders (TRG3, TRG4) did not differ in H19 expression in tumour tissue before (p=0.659, Mann-Whitney U test) as well as after nCRT (p=0.999, Mann-Whitney U test). Receiver operating curve analysis indicates that H19 expression in colorectal tissue before nCRT can not be used as a biomarker for distinguishing responders from non-responders (AUC=0.625, 95%CI=0.257-0.992, p=0.583).
Conclusion: Our study suggests H19 upregulation upon neoadjuvant chemoradiotherapy in rectal cancer. The potential predictive value of H19 as a biomarker of therapy response should be studied in a larger group of patients.

PS-15-019
BRG1-deficient non-small cell lung carcinomas. Clinicopathologic characteristics and correlation with SMARCA4 mutations
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Background & objectives: SMARCA genes are responsible for chromatin remodelling. Inactivating mutations in SMARCA4 induce BRG1 deficiency and thus a set of malignancies, mostly undifferentiated carcinomas. To facilitate translation of preclinical findings into clinical studies, we assessed clinicopathological features of BRG1-deficient tumours.
Methods: Data sets from our department were reviewed to determine the prevalence of SMARCA4-mutant non-small cell lung carcinomas (NSCLC) and describe their clinicopathologic characteristics. Genetic alterations were identified

using Oncomine Comprehensive (Thermofisher) NGS. BRG1 expression was evaluated by immunohistochemistry and correlated with SMARCA4. Medical records were retrospectively reviewed for clinicopathologic, molecular characteristics and treatment outcomes. Survival analyses were performed using Kaplan-Meier.

Results: We detected SMARCA4 genomic alterations in 11.6% (n=34/292) of NSCLCs. Truncating missense mutations comprised 22 cases, nonsense 9, frameshift 3 and INDEL 2. 44.1% of SMARCA4-mutant NSCLCs (n=15/34) showed loss of expression of BRG1, most (80%) of which had truncating SMARCA4 mutations. Overall, 92% (n=12/13) of evaluated NSCLCs with nonsense, frameshift or INDEL mutations lacked BRG1 expression. Deficient BRG1 expression was detected predominantly in solid adenocarcinomas (G3) and NSCLC-NOS with co-occurring mutations in KRAS (n=8; 3 G12C), TP53 (n=4), STK11 (n=4) and MAP2K2 (n=3). Deficiency on BRG1 was associated with lower disease-free survival (log rank p=0.049) and a tendency to associate with lower overall survival (p=0.2) in comparison with non-BRG1-deficient.

Conclusion: BRG1 deficiency is enriched in NSCLCs with truncating SMARCA4 mutations. Clinical outcomes are poor in this molecular subgroup, highlighting the importance of developing novel strategies to target unique vulnerabilities associated with the BRG1-deficient state.

PS-15-020

Validation of RNAseq as first approach: results of the real-world study at the Lorraine Cancer Institute

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Background & objectives: Next-generation sequencing has become the standard for tumour sequencing, but most laboratories use sequential workflows.

We optimized our workflow by using RNA-based FusionPlex® assay as the primary approach and assessed the ability of this assay to detect fusions and mutations.

Methods: A total of 43 formalin-fixed paraffin embedded (FFPE) tissues from patients with various cancer types (colorectal, lung, sarcoma, and pancreatic cancers) were included in this study.

After RNA and DNA extraction, all samples were assessed using the FusionPlex® assay for gene fusions, SNVs/indels and custom STS, for the detection of SNVs /indels and sequenced using Illumina platform or Idylla assay.

Results: Repeatability of the assay was assessed using a triplicate within the same run, and reproducibility by analysing 3 different samples in two different runs. Limit of detection was evaluated using RNA input from 20 to 250ng.

Among the 43 analysed samples, 35 SNVs or indels were previously identified using DNAseq or Idylla. The total concordance for indels and SNVs for ALK, BRAF, EGFR, KRAS, RET and ROS1 genes was 97.1% (Sensitivity=0.97, Specificity=1.0). Only one mutation G12V of KRAS with a VAF of 3.3% has not been found using RNAseq. Repeatability and reproducibility of the assay were both 100%. Finally, 20ng of RNA were found sufficient as a minimal input.

Conclusion: Analytical concordance, repeatability, reproducibility, and a robust limit of detection was documented in this assessment of the RNAseq approach. This data supports the RNAseq first approach, using FusionPlex® research assay (Invitae), and a decision has been made to adopt this workflow in our laboratory.

PS-15-021

Proof of concepts for automated extraction of mutation status from narrative pathology reports: KRAS G12C mutations and NTRK fusions in non-squamous non-small cell lung cancer

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Background & objectives: Manual extraction of molecular diagnostic results from narrative pathology reports is labour intensive, causing delay in analysis of real-world data. The aim of this study is to develop an automated method for data extraction from narrative pathology reports.

Methods: For automated selection of reports indicating the presence of the *KRAS* p.(G12C) mutation, a 5-fold cross validation Random Forest model was performed using TF-IDF transformed report text. For analysis of *NTRK* fusions, an SVC model was used with a supplementary word-association model. Previous manually extracted results from PALGA reports were used as a gold-standard.

Results: Pathology reports deposited in the Dutch nationwide pathology databank (PALGA) of all NSCLC patients in 2015 were manually curated (n=2,427) for reporting of the *KRAS* p.(G12C). The algorithm achieved high sensitivity (98.7%) and specificity (100%) to identify this mutation in narrative text. In addition, pathology reports mentioning TRK or *NTRK* between 2017 and 2020 were manually curated (n=7,457) for reporting of TRK protein expression and/or *NTRK* fusions. A first validation cohort demonstrated an acceptable sensitivity (88.0%) and specificity (95.0%) of the algorithm. TRK expression was generally not described as a dichotomous result, leading to large variation in reporting. All false-negative cases were ambiguous reporting of TRK immunohistochemistry results.

Conclusion: The algorithm that was developed for identification of pathology reports mentioning *KRAS* p.(G12C) demonstrated high accuracy. In contrast to *KRAS* mutations, the prevalence of TRK expression or *NTRK* fusion is low, which hampers the training of the algorithm with only a low absolute number of unambiguous TRK/*NTRK* positive cases. The observed variety in reporting of TRK results requires further optimization of the TRK/*NTRK* algorithm. Nevertheless, automation-supported analysis of pathology reports is a promising tool for rapid assessment of real-world data.

PS-15-022

KRAS-G12C mutation in non-small cell lung cancer: prevalence and prognostic significance

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Background & objectives: KRAS-G12C variant, which has recently been proved to be druggable, is the most frequent KRAS mutation, accounting for the 13% of non-small cell lung cancer (NSCLC). We aim to determine its prevalence, concurrent mutations, histopathologic profile and prognostic value.

Methods: We used Next-Generation Sequencing with the Oncomine Comprehensive panel to identify KRAS mutation status and other genetic alterations in 400 patients from our institution. Pathological findings were retrospectively reviewed using previous biopsy slides. Clinical data was extracted from medical records, including age, gender, smoking history, treatment, stage,

disease-free survival (DFS) and overall survival (OS). Survival analyses were performed using Kaplan-Meier.
Results: In this cohort of 400 patients with NSCLC, 120 were detected to harbour KRAS mutation (89% adenocarcinomas, 10% non-specified NSCLC and 1% squamous cell carcinoma). KRAS mutated cases encompassed 63% males and 37% females, with a median age at diagnosis of 66 years, 67% were heavy smokers (defined as greater than or equal to 30 pack-years) and 51% presented at advanced stages. KRAS-G12C was the most common KRAS mutation subtype (46%) and it was associated with a shorter median OS (p=0.006) and a tendency to associate lower DFS (p=0.14) than non-KRAS-G12C. KRAS-G12C subgroup tended to include more females, smokers and elderly patients (p=0.06-0.14) in comparison with non-KRAS-G12C.
Conclusion: G12C subtype, which was the most frequent KRAS mutation in this sample, was related to aggressive behaviour and poor prognosis. No other significant differences were confirmed, except a tendency in KRAS-G12C subgroup to include more females, smokers and elderly patients in comparison with non-KRAS-G12C. Our study could enhance higher levels of accuracy estimating prognosis and response to novel targeted therapies.

PS-15-023
Genomic profile of primary non-small cell lung cancer and matched mediastinal lymph nodes by next-generation sequencing: a pilot study
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Background & objectives: The evaluation of genomic alterations in primary resected NSCLC and matched lymph nodes can be useful in stratifying patients at risk of tumour relapse, in detecting occult metastases, and in selecting patients for adjuvant treatments.
Methods: Genomic DNA (gDNA) extracted from tissue sections of six resected NSCLC (T1-2) and from samples of mediastinal lymph nodes (MLN) with negative cytology were analysed by Next Generation Sequencing (NGS) with a customized SureSelect® XTHS2 kit (Agilent Tech, Santa Clara, CA, USA).
Results: We observed pathogenic variants in 91.7% of the sequenced samples (six tumour and five MLN). Different genetic variants between tumour and lymph nodes were observed in five cases. Only one patient presented the same genetic alteration in both samples.
Conclusion: We demonstrated different somatic pathogenic variants between the tumour tissue and the cytological negative matched lymph nodes, suggesting that these mutations were not drivers for relapse or metastases, and that different subclones carrying other mutated genes might progress to metastatic adenocarcinoma. Thus, combining molecular tests to the cytological analyses of MLN may contribute for the development of an integrative Tumour, Node, Metastasis (TNM) staging.
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PS-15-024
Concordance between FISH and NGS in detecting t(11;14) status in patients with multiple myeloma
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Background & objectives: The t(11;14) translocation has been identified as a predictive biomarker of response to venetoclax in relapsed/refractory multiple myeloma (MM). The objective of this study was to assess the concordance between FISH and NGS for t(11;14) detection in patients with MM.
Methods: This was a retrospective, single-centre, non-interventional study. Bone marrow aspirates were collected from an approved biobank with informed consent. The presence of t(11;14) was detected by FISH using the Vysis IGH/CCND1 XT DF FISH probe kit and NGS using a targeted NGS panel and NextSeq. Cohen's Kappa was used to determine the concordance between the two diagnostic techniques.
Results: A total of 130 samples were analysed for t(11;14) status; 65 at diagnosis, 60 at relapse and 5 unspecified. The samples consisted of 76 males and 54 females with a median age of 69 (range: 43 – 91). Both NGS and FISH detected t(11;14) in 66 samples with a concordance rate of 100% (Cohen's Kappa=1). Concordance rate (100%) was consistent within the diagnostic and relapse samples. The 5 unspecified samples were t(11;14)+. There were no discordant samples.
Conclusion: The results from this study demonstrate that FISH and NGS techniques have a 100% concordance rate for the detection of t(11;14) in MM patient samples. Both FISH and NGS-based testing can detect t(11;14) in patient samples allowing an individualized approach to patient care.

PS-15-025
Stability of t(11;14) status by FISH between diagnosis and relapse in patients with multiple myeloma
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Background & objectives: Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by multistep genetic alterations and frequent relapse. We evaluated the stability of t(11;14), an early genetic event and predictive biomarker for venetoclax activity, in MM patients between diagnosis and relapse.
Methods: This was a retrospective, single-centre, non-interventional study. Longitudinal bone marrow aspirates (BMA) from patients at different subtypes of disease (monoclonal gammopathy of undetermined significance [MGUS]; smoldering MM [SMM]); newly diagnosed MM [NDMM]; relapsed/refractory MM [RRMM]; and plasma cell leukaemia [PCL]) were collected. t(11;14) was detected using interphase FISH analysis of BMA samples enriched for plasma cells using CD138 immunomagnetic beads.
Results: Among 272 patients, 118 were t(11;14)+ and 154 were t(11;14)- with a median age (years [range]) of 60 [37 – 85] and 63 [34 – 85], respectively. The median number (range) of longitudinal FISH assessments were: t(11;14)+: 2 (2 – 4); and t(11;14)-: 2 (2 – 5). All t(11;14)+ patients evaluated between diagnosis and first relapse (n = 87) remained positive with a median of 29.1 months (range, 1.9 – 149.4) between FISH assessments. All t(11;14)+ samples evaluated between diagnosis and multiple relapses (n=16) remained positive with 43.3 months (range, 11.4 – 196.9) between FISH assessments. t(11;14) was detected in MGUS/SMM patients (n=15) from diagnosis to progression (median-time: 28.7 months).
Conclusion: This study is the first confirmation in a large, longitudinal cohort of patients with MM that t(11;14) is a primary genetic event that is stable across the course of disease from MGUS/SMM to MM and across lines of therapy from NDMM to RRMM. All t(11;14)+ patients remained positive from diagnosis to first and any relapse thus providing confidence in this biomarker when considering t(11;14) directed treatment. No t(11;14)- patients acquired the translocation at relapse.

PS-15-026

The frequency of EGFR mutations of non-small cell lung carcinomas in the east Black Sea region of Turkey

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Background & objectives: EGFR gene mutations are most common in exons 18-21. Exon 19 deletions and exon 21 L858R point mutation constitute 90% of them. We aimed to detect the frequency of EGFR gene mutations in the east Black Sea region of Turkey.
Methods: We investigated the mutational status of 488 cases diagnosed with non-small cell lung carcinomas between January 2019 and March 2022 with next-generation sequencing. QIAsec New Solid Custom MSI Panel was used.
Results: We detected EGFR mutations in 10.2% of the cases (50 patients). It is mostly observed in exons 19, 20, and 21 which were 16 cases (32%) in exon 21, 15 cases (30%) in exon 19, and 12 cases (24%) in exon 20. In addition, EGFR mutations were detected in exon 15 in 7 cases (14%). Exon 19 deletions were seen in 14 cases (28%) and exon 21 L858R point mutations were seen in 10 cases (20%). Exon 20 T790M mutation, which causes tyrosine kinase inhibitor resistance, was observed in 3 of the cases. EGFR and TP53 co-mutations were detected in 8 patients.
Conclusion: Consistent with the literature, the most frequently observed mutations were exon 19 deletions and exon 21 L858R mutation. Our results demonstrated the frequency of EGFR gene mutations in the east Black Sea region of Turkey. Although there are no clinical studies on exon 15 EGFR mutations in the literature, exon 15 mutations were detected in 14% of the cases in our study. This result may shed light on future studies.

PS-15-027

Tumour PD-L1 expression and molecular profiling are not associated with immune checkpoint inhibitor-induced thyroid dysfunction in advanced non small cell lung cancer (NSCLC) Patients

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Background & objectives: Immune-checkpoint-inhibitors (ICIs) has been revolutionary in treating advanced NSCLC, however- frequently associated with thyroid-related adverse events. We aimed to explore the association between patient characteristics, tumour PD-L1 expression and molecular profile with the development of thyroid dysfunction in these patients.
Methods: Single centre, retrospective study assessing the association between clinical parameters, tumour PD-L1 expression, molecular profiling, and the development of thyroid irAEs in 107 NSCLC patients treated with PD-1 or PD-L1 inhibitors from April 2016 to July 2020. All patients were euthyroid at baseline and had at least two TSH measurements post treatment initiation.
Results: Overall, 37 (34.6%) patients developed any thyroid dysfunction and 18 (16.8%) developed overt thyroid dysfunction. There was no association between PD-L1 staining intensity in the tumour and the development of thyroid dysfunction. TP53 mutation was less likely to be associated with the development of any thyroid dysfunction ($p < 0.05$). There was no association found between the development of thyroid dysfunction and EGFR, ROS, ALK or KRAS mutations. There was no association between PD-L1 expression and time to develop thyroid dysfunction.
Conclusion: This study did not demonstrate an association between PD-L1 expression and the development of thyroid dysfunction in advanced NSCLC patients treated with PD-L1 or PD-1 inhibitors, suggesting that the thyroid-related adverse events are unrelated to PD-L1 expression in the tumour.

PS-15-028

Identification of Maml1 as a novel negative regulator of Itch E3 ubiquitin ligase activity: new insights in cancer biology

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Background & objectives: Maml1 is a transcriptional coactivator in several pathways, such as Notch and Hedgehog, directly involved in the onset/development of several cancers. Here, we demonstrate that Maml1 can control the expression levels of Gli1 and Notch1 proteins at post-translational level.
Methods: We utilized different experimental approaches: immunoprecipitation and ubiquitination assays in both in vitro and ex vivo (Maml1-/- murine model) cell lines; Maml1 silencing with CRISPR/Cas9 technology; analysis of Itch post-translational modification; siRNA-mediated depletion of Maml1 in breast and colon cancer cell lines; wound healing assay; proliferation assays.
Results: Gli1 and Notch1 are both regulated at post-translational level by Itch/E3 ubiquitin ligase. We demonstrate Maml1 capability to regulate Notch1 and Gli1 expression levels through Itch inhibition. For the first time, we identify the functional role of Maml1 C-terminal domain as a post-translational regulator of target proteins. Moreover, we pinpoint the molecular mechanism through which Maml1 acts as negative regulator of Itch, by inducing auto-ubiquitination events. Therefore, Maml1 increases the expression levels of Gli1 and Notch1 oncogenic proteins, by switching off Itch activity. Accordingly, in pathological contexts, such as breast and colon cancers, Maml1 silencing impinge on Notch1 and Gli1 protein levels, hindering proliferation and epithelial-mesenchymal transition events.
Conclusion: Overall, our data suggest a protective role mediated by Maml1 on Itch-target proteins involved in cancer biology. Indeed, the ability of Maml1 to negatively regulate Itch activity could have an impact in the activation of oncogenic pathways, such as Hedgehog and Notch. The identification of Maml1 as a novel negative regulator of Itch adds a piece in the understanding of tumour biology and could help to set out new therapeutic approaches based on the dual role of Maml1.

PS-15-029

Characterising the cellular architecture of the tumour microenvironment using imaging mass cytometry and digital image analysis with the HALO® and HALO AI™ platform

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Background & objectives: The identification of biomarkers, and their spatial distribution in the tumour microenvironment (TME) can help establishing a prognosis and cure. Here we show the analysis of the TME using the HALO® and HALO AI™ platform in mass cytometry multiplexed images.
Methods: Here, we present image analysis of more than eight different cancer types, such as bladder urothelial carcinoma, prostate adenocarcinoma, and lung adenosquamous carcinoma, using the HALO and HALO AI software (Indica Labs, Inc.). Samples are formalin-fixed paraffin-embedded (FFPE) primary tumour biopsies prepared for imaging mass cytometry using Marpar® reagents from Fluidigm. Images were acquired with the Fluidigm Hyperion™ platform.

Results: To circumvent morphologic cell variability, HALO AI was used to create a Nuclei Segmentation network that performed well across all cancer types analysed. Rather than relying on PanCK and E-cadherin biomarkers to identify tumour cells, a HALO AI Nuclear Phenotyper algorithm was trained to recognize tumour cells from stromal cells independently of biomarker expression and staining variability. The Nuclear Phenotyper and Nuclear Segmentation networks were embedded into the Highplex FL module of HALO for analysis of tumoral proliferation, using pHH3 and Ki67 biomarkers. The Spatial Analysis module of HALO was used to examine the proximity of cytotoxic T lymphocytes and macrophages and their level of infiltration of the tumour margin.
Conclusion: HALO and HALO AI software provide easily adaptable tools for the analysis of the TME in any tissue type and with any set of markers. It can be applied to IMC images in order to standardise cell segmentation, tissue segmentation, cell phenotyping and spatial analysis.

PS-15-030
Genomic landscape analysis of ERBB3-mutated human cancers reveals common co-occurrence with activating ERBB2 alterations
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Background & objectives: ERBB3 is a member of the ERBB receptor tyrosine kinase (RTK) family, which includes EGFR, ERBB2 and ERBB4. In this study we describe the prevalence of activating ERBB3 mutations across human cancers and analyse the genomic landscape of ERBB3-mutated tumours.
Methods: Retrospective review of MSK-IMPACT (DNA-based NGS) data (January 2014-June 2021) was performed (n=72000 pts). ERBB3 mutations were annotated as hotspot and/or activating using OncoKB database and current literature. Data analysis, visualization and statistical analysis were performed using R Studio and GraphPad PRISM.
Results: Out of 72000 patients tested, 582 patients (1%) harboured an activating ERBB3 alteration. The majority of tumours with ERBB mutations were colorectal, gastric and oesophageal cancers, small bowel carcinomas, bladder urothelial carcinomas, uterine endometrioid carcinomas, and breast cancers. Most mutations in ERBB3 occurred in the extracellular domain (85%) with only 15% found in the kinase domain, consistent with the allosteric activator function of this receptor. Concurrent alterations in ERBB2 were found in 19% of ERBB3-altered tumours and were present across the above tumour types. Of note, no such association was observed for EGFR.
Conclusion: ERBB3 mutations are potential driver alterations with no FDA-approved therapy. A significant proportion of activating ERBB3 mutations co-occur with activating ERBB2 alterations suggesting synergistic tumourigenic effects. Our work highlights the importance of broad genomic testing to detect ERBB3 mutations, as these may identify patients potentially responsive to ERBB2 inhibition or antibody-mediated targeting of ERBB3.

PS-15-031
Mir-9 and their putative targets expression in prostate cancer
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Background & objectives: There are divergent descriptions of the role of mir-9 in terms of its support or suppression of tumour development and metastasis in different tumours. It has been found overexpressed in prostate cancer (PCa) tissue compared to benign prostate tissue (BPT).
Methods: In a prostate tissue microarray with 145 BPT and 149 PCa cores, from prostatectomy samples of patients with localized PCa, using miRNAscope® 2.5LSRedISH, miR-9-5p expression was scored and compared between both conditions. Possible mir-9 targets were sought in miRTarBase, their expression was explored in the tumour tissues of the Cancer Genome Atlas (TCGA) through bioinformatics tools of GEPIA2 web server.
Results: MiR-9 was overexpressed in PCa compared to BPT. In the miRTarBase, 526 mir-9 target genes validated with at least one experimental assay were identified, and 24 genes with the strongest evidence of interaction with miR-9 were selected. The higher expression level in PCa was for CDH1, RAB34, AP3B1, CCNG1, SRF, TGFB1, ID2, FOXO3 y CCND1. When compared with BPT, the expression of 3 genes (BCL6, RAB34 and NTRK3) was downregulated in PCa, while CDH1 was overexpressed in the prostate cancer tissues ($P < 0.001$). Moreover, miR-9 gene targets CDH1, BCL6, CCND1 and PRDM1 showed truncating mutations, amplifications, deep deletion and splice mutations in some of the cancer datasets.
Conclusion: The analysis of the mir-9 and their target genes expression in normal versus cancer prostate tissues suggest that this miRNA may be regulating tumour initiation, progression, and metastasis processes through the downregulation of the Neurotrophic Receptor Tyrosine Kinase 3 (NTRK3), which has been found altered in breast carcinomas and other cancers, or the downregulation of Cadherin 1 (CDH1), whose loss of function is thought to contribute to cancer progression by increasing proliferation, invasion, and metastasis.
Funding: Universidad de Cartagena, Cartagena, Colombia

PS-16 | Poster Session Pulmonary Pathology

PS-16-001
Clinicopathological features of primary pulmonary Hodgkin lymphoma: a multicentre study and literature review of 110 cases
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Background & objectives: Primary pulmonary Hodgkin lymphoma (PPHL) is extremely rare compared to secondary lung involvement by Hodgkin lymphoma. And overall clinicopathological characteristics has been unclear because of its low prevalence.
Methods: We proceeded the multicentre retrospective study of ten cases histologically confirmed as PPHL from 1995 to 2019. With analysing clinicopathological features of these 10 cases, additional literature review of 100 cases was conducted together. We analysed the total 110 cases of PPHL about sex/age distribution, radiologic findings, histologic subtype and treatment.
Results: Female to male ratio was 6:4 and mean age was 41 years old. Although three patients had no symptom, seven had several localized and general symptoms including cough, sputum, chest discomfort/pain and weight loss. With chemotherapy, five had complete remission and three had partial response. Some cases had not been diagnosed as PPHL in initial needle biopsy, so that three patients underwent surgical resection. Differential diagnosis of PPHL included epithelial malignancy, such as adenocarcinoma, inflammatory diseases like tuberculosis, inflammatory myofibroblastic tumour, IgG4 related lung disease and other hematologic malignancy. With literature review, female predominance and a single peak at younger age were identified. Radiological findings were variable often with cavitation.

Conclusion: Histologically, differential diagnosis can be extremely challenging on small needle biopsy or frozen procedure. Especially, if biopsy is not satisfactory, PPHL can mimic infectious or inflammatory disease (tuberculosis, granulomatous inflammation, etc.) as well as other pulmonary malignancy (adenocarcinoma). This study and literature review can be helpful for pathologists to diagnose PPHL properly.

PS-16-002

Five-year experience of evaluation of PD-L1 expression on advanced non-small cell lung carcinoma – single centre study

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Background & objectives: About 80% of all diagnosed lung carcinoma is of non-small cell lung carcinoma (NSCLC) histological type. The aim was to evaluate results of PD-L1 expression on advanced non-small cell lung carcinoma (NSCLC) in five-year period.
Methods: The percentage of expression PD-L1 (clone 22C3) in malignant cells was correlated on small and surgical samples according to the following parameters: age, gender, histological subtypes of NSCLC, stromal immunological/inflammatory cells and adequacy of samples. PD-L1 testing on demand and its expression was divided into three groups: low, middle and high.
Results: PD-L1 expression was evaluated in 802 patients, 2/3 of them were male and the most frequent in age 61-70, 64% ADC, 20% SCC and 13.3%-NOS. Low PD-L1 expression was found in 53%, weak in 19% and high in 28% NSCLC. Inflammatory/immunological cells were registered in 45% of samples with high PD-L1 expression. Weak and moderate PD-L1 expression among genders was similar, without significance (p=0.689). Weak and high PD-L1 expression among aged groups was similar (p=0.645). PD-L1 expression according to histological subtypes of NSCLC was not significant (p=0.455). Low PD-L1 expression was found in inadequate samples (p<0.001). Inflammatory/immunological cells with PD-L1 expression were significantly higher in patients with higher expression (p<0.001).
Conclusion: High PD-L1 expression was found in 28% NSCLC without correlation with histological subtype, gender and age of patients. High PD-L1 expression was associated with PD-L1 expression in stromal immunological cells. Presented results was similar with published ones in relevant literature.

PS-16-003

Role of microRNAs miR-193b, miR-7, miR-25 and miR-301a as potential diagnostic marker in non small cell lung cancer (NSCLC)

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Background & objectives: NSCLC is leading cause of cancer-related death world over. MicroRNAs are emerging as potential non-invasive biomarker for early detection. We studied the role of circulating microRNAs miR-193b, miR-301a, miR-7 and miR-25 as non-invasive biomarker in NSCLC in Indian population.
Methods: Plasma samples from histology proven 101 NSCLC cases and 28 non-neoplastic controls including 18 chronic obstructive pulmonary disease and 10 healthy individuals were tested for expression of microRNAs miR-193b, miR-7, miR-25 and miR-301a by real time PCR. Dysregulated microRNAs were correlated with clinicopathological features.
Results: miR-193b (p=0.034) and miR-7 (p=0.4) were upregulated while miR-25 (p=0.2) and miR-301a (p=0.5) were downregulated in NSCLC compared to controls. The AUC was 0.636 (95% CI, 0.522-0.750; p =0.03). There was no significant association of microRNA dysregulation with age, gender, smoking, alcoholism, tuberculosis, lymph node status, pleural effusion and disease stage. miR-25 downregulation correlated with adenocarcinoma histology (p=0.03). miR-193b downregulation significantly correlated with survival (14.9 ± 1.5 months (p=0.03). Disease progression was seen in 12 patients in upregulated and in 3 patients in downregulated group with progression free survival of 9.7 ±1.1 months in upregulated 12.3 ±0.5 months in downregulated group (p value =0.04).
Conclusion: miR-193b was significantly upregulated while miR-25 and miR-301 were downregulated in NSCLC but were statistically non-significant. These may act as pointers towards NSCLC diagnosis and suggest diligent search of malignancy in these patients. However, microRNA profiling and validation studies are required to develop microRNAs as a diagnostic tool.

PS-16-004

Alveolar adenoma - clinicopathological characteristics of four cases

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Background & objectives: Alveolar adenoma is a rare, benign tumour of the lung which have broad spectrum of differential diagnosis. In order to minimize the possibility of errors in the diagnosis of similar lung lesions, pathohistological finding should be completed with immunohistochemistry.
Methods: Retrospective study included 4 cases of lung alveolar adenoma, diagnosed between 2010 and 2020. All patients were treated surgically, in one case with video-assisted thoracoscopy, while in others a thoracotomy was performed. The type of resection performed was wedge resection and lobectomy (3:1). In all cases, the tumour was located in the lower lobes.
Results: Frozen section findings in all cases were classified as benign lesions. On FFPE sections, tumours showed characteristic multicystic morphology with cystic structures lined with regular pneumocytes separated by septa, built of spindle cells with lymphocyte infiltrates. Granular eosinophilic detritus was found in the cysts lumens. Tumours were relatively clearly demarcated from surrounding parenchyma, without capsule and with expansive growth compressing the lung parenchyma. Immunohistochemical analysis in all cases showed immunoreactivity of epithelial component to TTF-1, panCK, EMA, while the immunomarkers D2-40, HMB45, MelanA and S-100 were negative. The stromal component was Vimentin positive in all cases, while in one case in addition to vimentin, SMA and CD34 were positive too.
Conclusion: The features of alveolar adenoma may mimic other types of lung tumours, consequently leading to difficulties in the differential diagnosis. Thus, accurate diagnosis of alveolar adenoma is based on a combination of pathological and immunohistochemical findings.

PS-16-005

Is imprint cytology an efficient alternative to traditional frozen section in intraoperative diagnosis of lung adenocarcinoma?

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Background & objectives: Frozen section (FS) histology is the most commonly used method for intraoperative evaluation of the lung lesions, however it requires significant capacity in equipment, staff and time. Imprint cytology (IC) is a fast, cheap and reliable alternative.
Methods: The retrospective study included 193 patients who were hospitalized to clarify aetiology and treat the infiltrative lung lesion. During the diagnostic/therapeutic surgery, tissue sample was obtained and imprint was taken. The samples were processed as standard procedure for FS histological analysis. Sensitivity, specificity, positive and negative predictive value for determining adenocarcinoma were calculated in a relation to final pathohistological diagnosis.
Results: Sensitivity, specificity, positive and negative predictive value for IC were, respectively, 89,86%, 100%, 100% and 94,66%, while the same parameters on FS were, respectively, 94,2%, 100%, 100% and 96.86%. The adequacy of IC was 96,37%. Cytological findings, of later proven adenocarcinomas, were characterized as adenocarcinomas (33,33%), NSCLC-NOS (11,59%), malignant tumour (44,93%), benign tumour (2,90%), non-diagnostic (1,45%), and inadequate (5,80%). Average area of lesion section from which imprint was taken was significantly higher in lesions whose findings were characterized as adenocarcinoma, compared to the findings characterized as malignant (p=0,025). There wasn't statistically significant difference in average area of lesions section between the true positive and false negative IC findings of adenocarcinoma.
Conclusion: IC provides a reliable alternative to the traditional histological diagnosis in the intraoperative evaluation of lung adenocarcinoma. The area of the section wasn't significant factor in intraoperative diagnosis of adenocarcinoma by IC.

PS-16-006
Pulmonary adenofibroma: a clinicopathological analysis of a case series
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Background & objectives: Pulmonary adenofibroma (AF) is an extremely rare benign tumour not yet described in the WHO classification of lung neoplasms. It is frequently misdiagnosed as solitary fibrous tumour. Approximately 40 cases have been described.
Methods: We searched the pathology archives of two major university Spanish hospitals for cases of pulmonary AF over a period of 10 years (2012-2022). We retrospectively analysed clinical, radiological, histopathological and immunophenotypic features.
Results: Our series included five cases middle aged (35-68 years) with male preponderance (4 male and 1 female). All cases were detected incidentally on radiology as a solitary well-defined lung lesion with a diameter ranging from 0,5 to 2,5 cm. Grossly they were whitish with a smooth surface. Histological examinations revealed biphasic tumours with epithelial component with gland-like spaces lined by respiratory epithelium, surrounded by a stromal component with spindled-cell fibroblastic or myofibroblastic proliferation. There were not necrosis, atypia or signs of malignant transformation. Immunohistochemistry studies were performed and all were EMA and TTF1 positive in the epithelial component and actin positive in the stroma. STAT6 resulted negative in all cases.
Conclusion: Pulmonary adenofibroma is a rare benign pulmonary tumour whose morphological pattern could be mimic by various lung tumours. Breast and pulmonary AF show a significant overlap of their morphological characteristics. Biphasic morphology and immunohistochemistry are helpful to distinguish it from other potentially aggressive tumours like solitary fibrous tumour.

PS-16-007
Use of insulinoma-associated protein 1 in small biopsy samples of small cell lung carcinoma (SCLC)
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Background & objectives: Recent publications point out that insulinoma-associated protein 1 (INSM1), as nuclear marker, demonstrates superior performance to the individual and combined use of synaptophysin (Syn), chromogranin A (ChA) and CD56 for diagnosing neuroendocrine tumours of lung.
Methods: Retrospectively reviewed small biopsy samples of previously diagnosed SCLC at the Institute for pathology, Medical Faculty, University of Belgrade. Immunohistochemistry was performed using mouse monoclonal INSM1 antibody (Santa Cruz Biotechnology, Dallas; clone A-8). Positivity was assed as clear nuclear reactivity, and the intensity of immunoreactivity (1+, 2+, 3+) combined with percentage of positive cells (0% to 100%).
Results: A total of 62 eligible cases in the period of 2019-2021 were reviewed. An initial standard IHH panel, based on neuroendocrine morphology, for all cases included S, CD56, TTF-1 and Ki-67. Four cases (6.5%) were negative for S, focally or diffusely positive for CD56 in initial ICH panel, and negative for INSM1. Two cases (3.2%) were negative for all three markers. Another four cases were negative for S, but showed focal or diffuse CD56 positivity, and all were strongly positive for INSM1. The rest of cases (83.9%) were positive for all three markers; S and CD56 with variably immunoexpression, while INSM1 showed strong immunoexpression.
Conclusion: Having in mind that in pulmonary pathology "tissue is issue", and a need to preserve any tissue collected or further molecular testing, it is recommended to use as less as possible IHC markers to post accurate and precise pathologic classification possible. In our work, INSM1 showed good concordance related to immunoexpression of membranous markers. Thus, use of single IHC marker, which is nuclear and more specific than two membranous markers, could save time and tissue for further testing as well.

PS-16-009
Clinicopathologic and molecular characteristics in ERBB2 (HER2)-altered non-small cell lung cancer
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Background & objectives: Anti-ERBB2 therapies have been proven to be effective in ERBB2-altered cases of non-small cell lung cancer (NSCLC). The goal of this study is to demonstrate the clinicopathologic and molecular features of ERBB2-altered NSCLC to enrich the potential candidates.
Methods: We found 66 cases of ERBB2-altered NSCLC including 28 amplified [copy number (CN) $\geq$ 4] and 41 mutated cases from the next-generation sequencing (NGS) data of 969 NSCLC patients tested from 2018 to 2021. Their clinicopathologic data and tissue slides were reviewed. Immunohistochemistry (IHC) and silver in situ hybridization (SISH) were performed and assessed referring to the breast cancer guideline.
Results: SISH-confirmed ERBB2 amplification and oncogenic ERBB2 mutation were identified in 24 and 41 patients, respectively. They were all in advanced stages ($\geq$ III, AJCC, 8th). They mostly demonstrated adenocarcinoma with micropapillary pattern

and lung-to-lung metastasis. ERBB2 mutated cases with exon 20 insertions showed heterogeneous immunoreactivity with mostly weak basal cytoplasmic and membranous patterns (0, 35%; 1+, 40%; 2+, 25%). Two out of five point mutations displayed moderate membranous staining (2+, 100%). Among the 19 ERBB2-amplified cases with CN ≥ 7, 14 cases exhibited a strong complete circumferential pattern (3+). The remaining 5 cases displayed moderate basolateral staining (2+) and were accompanied by actionable EGFR, KRAS, and ERBB2 exon 20 mutations.
Conclusion: ERBB2 amplification shows a high correlation with protein overexpression, being predicted by IHC. ERBB2 amplification can be accompanied by other actionable mutations with discordant ERBB2 protein expression. On the other hand, ERBB2 mutations usually occur in a mutually exclusive manner with other driver mutations. They show heterogenous ERBB2 expression with negative to moderate cytoplasmic and membranous staining.

PS-16-010
A single-institution experience of pulmonary sarcomatoid carcinoma
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Background & objectives: Pulmonary sarcomatoid carcinoma (PSC) is an uncommon tumours, accounting 0.1 to 0,4 % of all lung cancers. It is a highly invasive tumour. The WHO distinguish 3 subgroups: pleomorphic carcinoma, carcinosarcoma and pulmonary blastoma. The aim: discuss clinicopathological characteristics and immunohistochemical features of these tumours.
Methods: This retrospective study included all patients with a pathologically confirmed diagnosis of PSC treated at our department of pathology between 2005 and 2021.
Results: There were 78 male and 11 female patients, aged between 6 and 82 years with a mean of 61. The diagnostic was made on surgical resection (n=56), on transparietal biopsy (n=27) and on a resection of metastatic location (n=10). An intraoperative frozen section was performed (n=36) showed inflammatory lesion (n=5) and non small cell carcinoma (n=31). The histological examination revealed pleomorphic carcinoma (n=66), Carcinosarcoma (n=9), pulmonary blastoma (n=5) and unclassified tumour (n=9). Immunohistochemically, the tumour cells were positive for vimentin (n=50), TTF-1 (n=19), EMA (n=14), cytokeratins (n=41). However, they were negative for muscle actin, PS100, actin, and calretinin.
Conclusion: The rarity PSC and the difficulty of pathological diagnosis make it a difficult malignancy to study. It pose a significant challenge due to their rare occurrence, heterogeneous histology, and unclear histogenesis.

PS-16-011
Complexity of screening methods for gene fusions in molecular pathology labs
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Background & objectives: Gene fusion in NSCLC involving ALK, ROS1, and RET are demanded for benefit from targeted tyrosine kinase inhibitors. Detection and identification of fusion events might be complex even with specific screening methods.
Methods: Fluorescence in situ hybridization (FISH) has currently been used as a sensitive method for screening ALK, ROS1 and RET fusions. RT-PCR specificity is recognized for target specific primers, of known fusions and exon skipping events. DNA/RNA NGS methods have evolved to detect fusions without previous information of gene partners and for diverse genetic events.
Results: Breakapart FISH with 5´/3´probes for screening ALK, ROS1 and RET rearrangements lack information regarding the gene partner fusion. Aberrant FISH patterns and false-positive results may be due to a possible non-functional oncogenic fusion. Immunohistochemistry (IHC) is accurate for protein detection for ALK, but not for ROS1 and RET, due to poor specificity in the lung. RT-PCR as less sensitive method, only detects known gene partner fusions and unknown or new partners will be missed. DNA-NGS reads at specific base position breakpoints and can identify fusion variants, while RNA-NGS identifies known and unknown fusions at the transcript level.
Conclusion: FISH is a sensitive method for detecting breakapart rearrangements but also unspecific due to the lack of information regarding functional fusions. A validated method must be used to confirm aberrant cases. DNA-NGS has revealed many uncommon ALK, ROS1 and RET fusions, events at genomic level not corresponding to fusion transcripts at the RNA level. Molecular Pathology Labs validated RNA-NGS level as necessary to detect rare fusion events, to determine which patients will benefit from actual targeted therapy.

PS-16-012
A multicentric Portuguese study for the assessment of PD-L1 score in NSCLC using 22C3 and SP263 clones on Ventana's platform: a stepping stone for the IVDR legislation landscape?
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Background & objectives: Anti-PD-L1 immunotherapy is used for NSCLC treatment. Different clones, platforms and scoring methods can be used to evaluate PD-L1 expression as a predictive biomarker. We compared the performance of 22C3(LDT) and SP263(IVDR) assays, in a prospective non-interventional multicentric Portuguese study.
Methods: 391 lung cancers; 264 adenocarcinomas (ADC; 67.5%); 98 squamous cell carcinomas (SqCC; 25.1%) and 29 other subtypes NSCLC (7.4%) were collected from 14 Portuguese centres. 22C3 LDT and SP263 IVDR assays were performed on Ventana platform. PD-L1 expression was determined by TPS(Tumour Proportion Score). Cohen's Kappa coefficients were calculated. Nominal variables were analysed using the chi-square test (statistical significance $p<0.05$).
Results: No statistically significant differences were found between 22C3 and SP263 clones when considering the type of sample [biopsy (n=258, 66%) vs surgical specimen (n=133; 34%)] and the histological subtype. Biopsies demonstrated higher 22C3 scores (TPS>=1 or >=50%) than surgical specimens (p=0.013; p=0.023) and also higher SP263 scores (TPS>=1 or >=50%) (p=0.014; p=0.009). The number of samples 22C3 PD-L1 <1% was significantly higher in ADC when compared to SqCC (p=0.032). Excellent Kappa agreement / concordance was observed for PD-L1

22C3 and SP263 clones in all defined cutoffs (K>0.8), taking into consideration the histologic and sample types.
Conclusion: Excellent concordance was observed comparing 22C3 PD-L1 LDT and SP263 IVDR assays. SP263 assay seemed to be more consistent across histologic types. Validation, quality control, training, and experience are essential, especially in LDT, and may explain the high concordance observed. Considering the need of IVDR tests in the future, our work demonstrated an excellent concordance between SP263 IVDR and 22C3 LDT assays, ensuring the reliability of the former when considering a switch.

PS-16-013
Histopathologic patterns in brain metastases of lung adenocarcinoma: does it affect the survival?
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Background & objectives: Primary lung adenocarcinoma is classified and graded according to histopathological patterns. The main goal of our study is to evaluate the prognostic impact of these patterns in surgically resected brain metastases of lung adenocarcinomas.
Methods: A retrospective review of patients with histopathologic diagnoses of brain metastatic lung adenocarcinoma between the years 2010-2022 was made. The presence and percentage of histopathological patterns including acinar, papillary, solid, micropapillary, cribriform, and complex glandular were noted. A total of 88 patients with brain metastasis of lung adenocarcinoma were included in the study. The mean age was 60.7±9.2 years.
Results: As ALK, ROS, and BRAF mutation was performed on 31, 29, and 4 patients respectively, none of them were mutated. However, as EGFR mutation was evaluated in 31 patients, 4(12.9%) of them were mutated. Predominant patterns of the tumours were; solid 49 (55.7%), papillary 13 (14.8%), cribriform 11 (12.5%), complex glandular 8 (9.1%), micropapillary 4 (4.5%), acinar 3 (3.4%). Predominant patterns were not associated with overall survival in the long-rank test (p=0.87). The age of 55 was found as a cut-off associated with poor overall survival (p=0.029). TTF-1 positivity was found to be associated with better overall survival (p=0.008). Filigree pattern, a micropapillary subtype, was associated with EGFR mutation (p=0.05).
Conclusion: Future studies with larger series are needed to demonstrate the prognostic significance of the histopathological patterns observed in brain metastases of lung adenocarcinomas.

PS-16-014
Regional variability and prognostic value of tumour budding in pulmonary squamous cell carcinoma
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Background & objectives: Grading pulmonary squamous cell carcinoma (pSQCC) is controversial. Tumour budding (TB) is a prognostic biomarker in colorectal carcinoma, but its significance in pSQCC is unclear. We compared inter-region variability of TB and its prognostic value in pSQCC.
Methods: We retrospectively included 249 patients resected at the University Hospitals Bern (2000-2013) and Lausanne (2005-2020) with available tissue from diagnostic biopsy and surgical specimen. TB was scored on H&E-stained slides according to the CRC consensus criteria at the tumour centre (TC), infiltration front (IF) and in the biopsy (B). Associations of TB with clinicopathological parameters and survival were assessed.
Results: TB was low (0-4 buds/0.785 mm2) in 128 (IF), 119 (TC) and 184 (B), intermediate (5-9 buds/0.785 mm2) in 68 (TC), 65 (IF) and 34 (B) and high (≥10 buds/0.785 mm2) in 51 (TC), 65 (IF) and 26 (B) cases.
Both the absolute number of buds and the TB score (1 to 3) were similar when comparing TC and IF (pbuds = 0.194, pscore = 0.383) but significantly different when comparing TC and B (pbuds < 0.001, pscore < 0.001).
Only TB scored at the IF showed prognostic potential regarding 5-year overall survival (p = 0.045), which was mainly driven by a poorer survival of patients with high TB scores.
Conclusion: IF and TC were comparable but only TB assessed at the IF showed prognostic significance. Furthermore, TB assessed in biopsies was different from resections, limiting the use of budding as a preoperative prognostic marker.

PS-16-015
Another retrospective study to throw more light on prognostic implications of STAS (tumour spread through air spaces) in lung adenocarcinoma
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Background & objectives: STAS is a recently described prognostic factor mostly studied in lung adenocarcinoma, although the concern it could represent a grossing artifact remains. This study aimed to assess the clinical implications of STAS in lung adenocarcinoma.
Methods: We retrospectively reviewed 118 cases of lung adenocarcinoma from 2015 to 2018 at La Paz University Hospital, Madrid (Spain). The distance from the edge of the tumour to the farthest STAS was measured and the cutoff for this distance was assessed by ROC curves. RFS and OS were compared considering presence of STAS and distance of STAS.
Results: STAS was found in 68,6% of adenocarcinomas. Patients with STAS had shorter median RFS (52,7 months) than patients without STAS (70,2 months) [p=0,028], showing a 2,29 times greater risk of recurrence (HR=2,29; p=0,03). Multivariant analysis with histological grade 3 adenocarcinomas showed no statistical significance.
Two possible cutoffs of 1,5 or 2,5 mm from the edge of the tumour to STAS were established. RFS and OS were shorter when STAS was farther than 1,5mm (p=0,045 and p=0,05), with a 2,06 times greater risk of death (HR=2,06; p=0,05). Statistical significance was found only in OS for a 2,5mm cutoff (p=0,013) and risk of death was 2,39 greater (HR: 2,39; p=0,01).
Conclusion: STAS is a predictive factor of recurrence risk mostly associated with high-grade lung adenocarcinomas and should prompt pathologists its identification in surgical specimens of lung cancer. A cutoff of 1,5mm for assessing distance of STAS to the tumour margin could be acceptable. Further investigations are needed to validate these cutoffs and prognostic implications of STAS in other histological types of lung cancer.

PS-17 | Poster Session Thymic and Mediastinal Pathology

PS-17-001
Mature teratoma in the anterior mediastinum: a retrospective study of 34 cases
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Background & objectives: Mature mediastinal teratoma is a rare entity, accounting for approximately 8% of all tumours in this area. They are usually cystic benign tumours. The aim of this study was to describes the clinicopathological characteristics and discuss the differential diagnosis of this disease.
Methods: We performed a retrospective study of 34 cases of mature mediastinal teratoma diagnosed at our department between 1992 and 2020.
Results: There were 15 male and 19 female patients, aged between 5 and 61 years with a mean of 30,87. All patients underwent a surgical resection. On gross examination, mean size of the masses was 9,5 cm. The outer surface was smooth and tan-white, and the cut inner surface contained multiple cystic structures filled with a tanbrown substance and a strands of hair. Microscopy showed variable mature elements comprising of cysts lined by ciliated stratified epithelium and secretory epithelium, intestinal mucosa, sebaceous glands, smooth muscle, adipose tissue, abortive hair follicles, bone, cartilage, and pancreatic tissue. The cyst wall was fibrous with hyalinised areas. There was no evidence of immature, neuroepithelial elements. Outside the cyst, thymic remnants was identified (n=16)
Conclusion: Mature mediastinal teratomas are rare tumours but should be considered in the differential diagnoses for mediastinal anterior lesion. Complete surgical resection is recommended in all mature teratomas with favourable survival rates.

PS-18 | Poster Session Autopsy Pathology

PS-18-001
Coinfection of HIV and COVID-19
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Background & objectives: Coincidence of HIV and COVID-19 is high. In spite of clinical publications depicting the prevalence of HIV and its complications, many items related to formulation of postmortem diagnosis and aspects of histopathology of lesions related to different pathogens remain unclear.
Methods: We analysed all (148) autopsy cases where in clinical and/or pathological diagnosis were mentioned HIV and COVID-19 in the period from March 2020 till September 2021.
Results: In the pathological diagnosis HIV was considered as main disease in 95 cases, COVID-19 - in 40 cases. In 9 cases other diseases were considered as main cause of death. In 4 cases new coronavirus infection was not included in pathological diagnosis. In majority of cases there were no difficulties in constructing the schema of tanatogenesis with the only exception when secondary infections in HIV were moderately expressed and lesions we considered as manifestation of coronavirus infection were prominent. Most problematic were cases in which was present the combination with secondary pneumocystosis. Taking in consideration that interstitial lung fibrosis in both infections is similar special investigation including immunohistochemistry is necessary.
Conclusion: The rules of optimal formulation of pathological diagnosis has to be discussed internationally, because of influence upon lethal statistics. Many aspects of relations between pathogens in the mixed infection needs further study.

PS-18-002
Clinical and pathological data analysis in 73 deceased patients with previous SARS-CoV-2-associated pneumonia during convalescence period
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Background & objectives: It is still not clear whether new coronavirus infection (COVID-19) has a long-lasting impact and can cause delayed sequela. The study aimed to analyse clinical and pathological data in patients who had previously had COVID-19 during early and late convalescence.
Methods: We analysed medical history data and pathology findings of 73 deceased patients who survived COVID-19 and died from other causes in 2020-2021. The data included gender, age, data on previous coronavirus infection, disease duration, IgG and IgM antibody titers, CT scan results. We analysed initial and immediate causes of death in deceased convalescents of a new coronavirus infection were analysed.
Results: Twenty six men and 47 women, aged from 33 to 104 years, were enrolled in the study. The antibody titer tests were performed at the time of hospital admission: the IgM level amounted from 0.31 to 1013.5 OCE, IgG from 0.1 to 17.43 U/ml. The initial causes of death included circulatory system diseases in 63 patients (86.3%), digestive system diseases in 18 cases (24.7%), respiratory system diseases in 5 patients (6.9%). The cerebral oedema was considered as the immediate cause of death in 31 patients (42.5%), multiple organ failure in 13 cases (17.8%), heart failure in 13 patients (17.8%), endogenous intoxication in 6 patients (8.2%), other in 8 cases (13.7%).
Conclusion: The period from clinical recovery to lethal outcome ranged from 2 to 300 days: 40 patients (54,8%) died after 2-30 days (early convalescents) and 33 (45,2%) after 31-300 days (late convalescents). Frequency of acute conditions of cardiovascular (acute myocardial infarction, bacterial endocarditis), respiratory (bacterial pneumonia) and cerebral (cerebral infarction, nontraumatic intracerebral haemorrhage) systems showed no difference in early and late convalescents (37,5% vs 33,3%, respectively, Ficher's exact test: $p > 0.05$). Chronic disease progression prevailed in both subgroups of patients.

PS-18-003
Splenic metastases in forensic pathology
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Background & objectives: Splenic metastases are relatively rare in forensics. The aim of our study was to highlight the features of splenic metastases from our files, in the context of widespread metastatic disease in autopsy, using immunohistochemistry pattern to identify their origin.
Methods: Necroptic examination and collection of specimens from six selected cases (37- 81 years old; equal distribution among genders), have been performed. Routine staining, along with a panel of immunohistochemical markers (Cytokeratin AE1/AE3, CK5, CK7, CK20, CDX2, CD38, CD138, EMA, Cyclin D1, p53, p63, TTF-1, PSA, CEA, Synaptophysin, Chromogranin, and S100) have been used to to discriminate between different possible primaries.
Results: The gross findings were that of multiple tumours with areas of necrosis. The microscopic examination of

tumour cells showed variable morphology and the differentials included primaries in: lung, pancreas, colorectum, stomach, prostate, cervix, added to multiple myeloma, which has been clinically suspicioned in one case. The immunoexpression of tumour cells corroborated with gross findings and routine histology features certified the diagnoses, with primaries in lung, colon, pancreas, cervix, and prostate, associated with splenic metastases, along with lymph nodes, liver, lung, meninges, and/or brain secondaries. Although the primary tumour remained unknown in one case, the morphology and immunohistochemical pattern certified the diagnosis of poorly differentiated carcinoma, excluding the multiple myeloma suspicion.

Conclusion: Our cases certify that the most common sources of splenic metastases are lung, colon, along with pancreas, and reproductive tract, in cases of multivisceral cancers, while other primaries, such as breast carcinomas and malignant melanoma are reported in literature. Immunohistochemistry is useful to distinguish primaries from secondaries in cases with multiple disseminations, including spleen. However, the primaries are difficult to establish in occult poorly differentiated carcinomas/cancer from unknown primary site, without any gross feature favouring a certain primary location.

PS-18-004

Lung COVID-19 infection – morphological spectrum and mortality-related risk factors

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Background & objectives: The lung microscopic features of SARS-CoV-2 infection include diffuse alveolar damage (DAD), atypical pneumonia, microthrombi, its unfavourable evolution being correlated to multiple risk factors. The aim of our study is the presentation of the pathological spectrum registered in our files.

Methods: The reports from autopsies performed in the last two years in our Department have been reviewed, selecting 343 cases of lung COVID-19 disease, with cases age range between 5 to 99 years old (81.34% males vs. 18.66% females). The cases have been investigated by routine paraffin-embedding sections, followed by hematoxylin and eosin staining, along with histochemical stains in selected cases.

Results: Grossly, pulmonary changes were variable, from pulmonary oedema to lung consolidation, haemorrhagic areas, and pulmonary thrombosis or microthrombi. The microscopic exam showed severe capillary congestion ± hyaline membranes, alveolar haemorrhage corresponding to exudative DAD, reactive pneumocytes changes and syncytial cells, microthrombosis, interstitial and intra-alveolar fibroblastic proliferation. Foci of pneumonia, as superimposed secondary infection, have been observed (37.02% of cases). In a decreased order of frequency, different chronic comorbidities have been registered: ischemic coronary disease, benign nephroangiosclerosis, liver steatosis ± chronic hepatitis/ cirrhosis, diabetes mellitus, chronic pyelonephritis, and emphysema, along with rare diseases, such as lung tuberculosis, gastric carcinoma, Down syndrome, liver hydatid cyst, atherosclerotic aortic dissection, stroke, and traumatic injuries.

Conclusion: Pathologists have an important role in the diagnosis and management of COVID-19 infections, with a magnitude of 506 million confirmed cases, resulting in over 6.2 million deaths worldwide, in April 2022. This study provides an overview of the post-mortem lung lesional spectrum in patients with COVID-19 lesions and the risk factors that may contribute to their fatal outcome. Our findings can also provide valuable data for COVID-19 disease management perspectives, according to the assessment of categories of patients' risk factors.

PS-18-005

Morphological peculiarities of liver in patients died of Coronavirus disease: a series of autopsy reports

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Background & objectives: Coronavirus infection (COVID-19) caused by SARS-CoV-2 remains a global pandemic problem today. In respect that Coronavirus disease frequently accompanied with a high aminotransferase rate in some patients, the detection of the pathological effect of coronavirus on liver becomes especially relevant.

Methods: We described 25 liver section from patients who died of disease related to COVID-19 at the Kharkiv Regional Clinical Infectious Diseases Hospital. Coronavirus disease was detected with PCR isolation of SARS-CoV-2 RNA from nasopharyngeal lavage. All liver sections were taken from representative appearing areas, formalin fixed, paraffin embedded, stained with Hematoxylin and Eosin and analysed under light microscopy.

Results: In our study 72 % of patients had elevated serum levels of aminotransferases. We identify local disorder of hepatic lobules with huge amounts of apoptotic hepatocytes and areas of necrosis in the central part of hepatic lobules. The majority of portal tracts showed a mixed inflammatory infiltrate consisted of lymphocytes, macrophages and plasma cells. The central veins and centrilobular sinusoids were full-blooded with lymphocytic infiltration in the endothelium. Sings of macrovesicular fatty degeneration with accumulation a huge amount of lipids were detected in the hepatocytes. Eosinophilic inclusions in the cytoplasm and nuclear pyknosis of the cholangiocytes were found in the interlobular bile ducts as a sing of apoptosis.

Conclusion: Detected changes in the liver of patients with COVID-19 are regarded as an acute reactive interstitial hepatitis on the diffuse steatosis background with severe bile ducts damage. Histological changes in sinusoidal and central veins endothelial cells may be related with a direct cytopathic viral influence. The mechanism of liver injury from SARS-CoV-2 which includes both inflammatory response and a direct cytotoxic damage requires further study.

PS-18-006

Paraneoplastic syndromes associated with cancers of unknown primary

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Background & objectives: Cancers of unknown primary (CUP) are metastatic tumours without an identified primary lesion. Paraneoplastic syndromes (PNs) occur independently of the physical presence of the tumour. In our study, we aimed to assess the characteristics of PNs in patients with CUP.

Methods: We examined 12837 autopsy cases between 1993 and 2019 in the electronic register of the II. Pathology Department of Semmelweis University, Budapest. Out of 3691 cancer cases we found 135 CUPs, The PNs of this cohort were compared to the clinicopathological features of the tumours. For further

assessment, PNs were classified based on their clinical characteristics (hematologic, myopathic/neuropsychiatric and endocrine/metabolic).
Results: PNs were present in 33,3% of CUP cases. Most of these PNs were hematologic symptoms (62,2%), followed by endocrine or metabolic diseases (26,7%). Myopathic and neuropsychiatric PNs were found only in a small fraction of cases (11,1%). Based on histological classification, PNs occur most frequently alongside anaplastic or neuroendocrine carcinomas (50-50%), whereas in adenocarcinomas (which is the most common cancer type histologically) the occurence of PNs were lower (27,3%).
Conclusion: To our current knowledge, the PNs associated with CUPs has not been studied comprehensively. PNs occur in a third of CUP cases, which is significantly more frequent than the general estimation of PN occurence in cancers, which is 10-15%. The former support the data suggesting CUP is a clinical and biological entity amongst malignant tumours.

PS-19 | Poster Session Cardiovascular Pathology

PS-19-001
Morphometric analysis of aortic wall main components depending on age

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Background & objectives: Morphological and functional changes appearing in all tissues with ageing affect also all vascular structures, including aorta. The authors assessed the densities-D of aortic wall main components (Elastic fibres–FE, Collagen fibres-FCOL, smooth muscle fibres-FM) with ageing in both sexes.
Methods: Four aortic rings (base, cross, thoracic, abdominal) were taken during autopsies from 90 autopsied cases (55 men and 35 women). Samples were processed using the classical HP technique and stained with Orcein, and Goldner's trichrome. Quantitative measurements were made using custom-made software, developed in Matlab (Mathworks, USA) on virtual slides. Average values were compared with "t" test and Pearson's test.
Results: FE-D and FM-D had an obvious descending trend with age in all main aortic regions and in both sexes with no significant differences between sex descending patterns.
FCOL-D, in turn, had an obvious ascending trend with age in all main aortic regions and in both sexes with no significant differences between sex descending patterns.
All three types of fibres had no significant variation along the aortic length in any of the four main periods of live. FE-Ds and FM-Ds were higher in men than in women in all aortic regions excepting cross region while FCOL-Ds were higher in women than in men in all aortic regions excepting cross region.
Conclusion: Ageing brings a remodelling process of aortic wall main components densities (FE-D, FCOL-D and FM-D) similar in both sexes. There were no significant changes of densities values along the aortic length in all main age periods but there were differences between sexes in each type of fiber density along the aortic length.

PS-19-002
An etiological approach to a regional sudden death series

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Background & objectives: In some countries, Sudden death (SD) of persons aged 1 to 40 years-old require further characterization, in order to provide Health Preventive Measures. The authors aim to study the SD causes of young adult victims in an European Country region.
Methods: Cases from the Legal Medicine and Forensic Sciences National Institute's database concerning unexpected sudden death young adults (1-40 years-old) victims, who underwent autopsy, between 2012-2016, at a region comprising 6 mainland and insular districts, were retrospectively reviewed. The Institute Ethics Committee approved this study. Demographic, clinical, autoptic, anatomopathological and toxicological data was collected. Statistical analysis (Stata 13.0 software) was performed.
Results: 175 SD, out of 2101 deaths in ages 1 to 40, were identified. SD victims had a mean age of 32±9 years-old, the majority males (69%,n=120). 115 (66%) SD cases were of cardiovascular origin. The remaining causes were respiratory (18%), cerebral (7%), digestive (6%), endocrinologic (2%), urinary (1%), infectious (1%). The most frequent cardiovascular cause was coronary atherosclerosis and its complications (n=40,35%); whose victims were older (31±8vs35±4,p<0.020), with a minimum age of 26 years, preferentially males (85%vs61%,p=0.011). Hypertrophic cardiomyopathy (HCM) was diagnosed in 3 (3%) victims; with genetic data available in 2, namely through the contribution of molecular autopsy. Six acute myocarditis' cases were identified, in significantly younger patients (23±13vs33±7,p=0,011).
Conclusion: During a 5-year period, the cumulative incidence of sudden and unexpected death of persons aged 1 to 40 years-old, in the studied region, is very low (n=175). Cardiovascular causes are present in 66% of the cases. The most frequent cardiovascular cause is coronary atherosclerosis (35%). Cardiovascular causes vary with age and gender. Epidemiological and Genetic studies are relevant contributes to understand the underlying settings and origins of SD and consequently promote preventive measures, namely of Public Health, and screening programs.

PS-19-003
Study of morphological patterns of acute cellular rejection (ACR) reactions in endomyocardial biopsies (EMBs)

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Background & objectives: Study of ACR reactions in cardiac allograft can assist in determining tissue's immunological injury, presenting accurate information on rejection, and organizing optimal transplanted-heart patient's management. Objective is to identify morphologic ACR patterns of transplanted-heart patients in 3 years of surveillance.
Methods: Transplanted-heart patients with routine surveillance EMBs in 2004 – 2020 were analysed by patient's characteristics and ACR grade (International Society of Heart and Lung Transplantation (ISHLT) nomenclature). Statistical descriptive analysis and Z two-tailed test to assess rejection probability in general population for year 1, 2 and 3 after transplantation were performed. Statistical significance p<0.05. Approval by ethics committee (no. BEC-MF-280).
Results: 70% (n=138) Grade 0 EMBs, 27% (n=53) Grade 1 EMBs, and 3% (n=6) Grade 2 EMBs were detected in 1st post-transplantation year. There were 67% (n=32) Grade 0 EMBs, 31% (n=15) Grade 1 EMBs, 2% (n=1) Grade 2 EMBs in 2nd post-transplantation year, and 54% (n=21) Grade 0 EMBs, 43% (n=17) Grade 1 EMBs, 3% (n=1) Grade 2 EMBs in 3rd

post-transplantation year. Analysis of 1st year's rejection probability resulted in 95% confidence interval (CI) of Grade 0 – 52.9% through 79.1% compared to 2nd year of 95% CI [63.6%; 76.4%] and 3rd year of 95% CI [45.9%; 61.7%] with decrease of Grade 0 EMBs in 3rd year.
Conclusion: Tendencies of no rejection or mild ACR in EMBs suggest that long-term surveillance is irreplaceable tool for effective clinical observation of probable progress of cardiac allograft's injuries. These tendencies detected in study may strongly suggest that procedures of cardiac allograft's pathology testing for transplanted-heart patients are properly prescribed for those patients who demonstrate features of rejection over the years, and 95% CI calculated in this research is a safe indicator that nowadays prescribed EMBs are effectively indicated in risk patients.

PS-19-004
Primary heart tumours, a single-centre, and 11 years of experience
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Background & objectives: In this study, clinicopathological features and follow-up data of 80 primary cardiac tumours diagnosed between 2011-2022 were evaluated.
Methods: The study was a retrospective review of 77 patients.
Results: Of the 77 cases (F/M: 49/28) included in the evaluation, 70 (90.9%) were benign, and 7 (9.1%) were malignant. The mean age at surgery was 53 in benign, and 36 in malignant cases. 60 (86%) of the benign tumours were myxomas. Benign tumours other than myxoma consisted of 5 papillary fibroelastomas, 2 haemangiomas, 1 lipoma, 1 hamartoma, 1 rhabdomyoma. Malignant tumours consisted of 2 spindle cell pleomorphic sarcoma, 2 embryonal rhabdomyosarcoma, 1 angiosarcoma, 1 synovial sarcoma, and 1 myxofibrosarcoma. The follow-up period was 6-140 months in benign cases, 8-56 months in malignant cases. During this period only 5 of the malignant cases died. Mean survival in malignant cases was 21 months.
Conclusion: Surgical resection is the first treatment option for primary cardiac tumours. Histopathological diagnosis of the tumour plays a fundamental role in guiding further follow-up and treatment. While it can be achieved nearly 100% survival with surgical resection in benign cases, the results are not satisfactory in malignant cases.

PS-19-005
Stereological estimation of myocardial fat and its relation to obesity, epicardial and visceral adipose tissue
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Background & objectives: The normal heart includes epicardial adipose tissue (EAT) and myocardial fat – both increase with obesity. EAT is related to risk of heart disease and myocardial fat with arrhythmogenesis. The objectives is to estimate myocardial fat using stereological methods.
Methods: We included 115 deceased with a post-mortem computed-tomography of the eviscerated heart to establish EAT volume. We examined six samples (ant., lat., and post.) from the left (LV) and right ventricle (RV) of the midventricular slice. The percentage of myocardial fat was estimated stereological using Visiopharm software. Kidney and omental fat were weighed at autopsy and waist-hip-ratio calculated.
Results: The group consisted of more males (66/49; 57%), mean age at death was 53.4 years (range 21-93) and mean BMI was 25.4 (±5.6). Females had a slightly non-significant (p=0.054) larger proportion of RV fat (mean 12.1%, range 9.7-16.6) compared to men (10.8%, range 9.4-12.8). We found a positive correlation with BMI and LV fat (p=0.033). In the RV the correlation was only borderline significant (p=0.052). EAT volume was positively correlated with fat in the RV and LV. We found no association with waist-hip-ratio, omental or kidney fat as measures of visceral adipose tissue (VAT).
Conclusion: Myocardial fat is a normal component especially in the RV and correlates with the total volume of EAT. We surprisingly found no association with VAT.

PS-19-006
SET7 methyltransferase mediates the up-regulation of NADPH oxidase expression and oxidative stress in the atherosclerotic aorta of apolipoprotein E-deficient mice
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Background & objectives: Histone methylation-related epigenetic pathways emerged as promising therapeutic targets in atherosclerosis. The study aimed at investigating the functional implication of SET7 in the regulation of NADPH oxidase (Nox) expression, an important source of oxidative stress in experimental atherosclerosis.
Methods: Human non-atherosclerotic and atherosclerotic tissue specimens, apolipoprotein E-deficient (ApoE-/-) mice, and polarized pro-inflammatory (M1) and anti-inflammatory (M2) mouse macrophages (Mac) were investigated employing real-time PCR, Western blot, and microscopy. Male ApoE-/- mice fed a normal or a high-fat, cholesterol-rich diet (HD) were randomized to receive 5 mg/kg (R)-PFI 2 hydrochloride, a selective SET7 inhibitor, or its vehicle for 4 weeks.
Results: Pharmacological inhibition of SET7 had no significant effects on plasma total cholesterol, triglycerides, and body weights as compared with vehicle-treated ApoE-/- (HD) animals. The mRNA and protein levels of SET7 were found significantly elevated in human atherosclerotic lesions, atherosclerotic aorta of ApoE-/- (HD) mice, and in M1-Mac. Inhibition of SET7 suppressed the up-regulation of Nox1, Nox2, and Nox4 subtypes in the aorta of ApoE-/- (HD) mice and in M1-Mac. Treatment of ApoE-/- (HD) mice with SET7 inhibitor reduced significantly the aortic formation of 4-hydroxynonenale-/nitrotyrosine-protein adducts (important markers of oxidative stress). Significant increases in Nox1, Nox2, Nox4, Nox5, and p22phox transcript levels were detected in HEK293 reporter cells overexpressing SET7.
Conclusion: SET7 is a key epigenetic enzyme that methylates nucleosomal histones (H3) and non-histone proteins (transcription factors) at different lysine residues to regulate the expression of the target genes. The novel data of this study indicate that SET7 methyltransferase is up-regulated in human atherosclerosis and mediates NADPH oxidase up-regulation and oxidative stress in experimental atherosclerosis. Pharmacological targeting of SET7 methyltransferase could become an important supportive therapeutic strategy in atherosclerosis.
Funding: Work supported by UEFISCDI (PN-III-P4-ID-PCE-2020-1898, PN-III-P1-1.1-TE-2021-0180, PN-III-P2-2.1-PED-2019-2497, PN-III-P2-2.1-PED-2019-2512).

PS-19-007

Histological analysis of arteriovenous fistula specimens created for haemodialysis

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Background & objectives: Arteriovenous fistula (AFV) creation is the preferred access way for haemodialysis, but their functionality may be limited by pre-existing vascular pathology. In this study was analysed that the pre-existing vascular abnormalities represent a predictive value of AFV no maturation.
Methods: Patients for chronic kidney disease (n=44) undergoing AFV placement were included in this study. The vein samples were processed for light microscopy, stained with H&E, trichrome, and von Kossa. The neovascularization and the chronic inflammatory cell population were analysed using, CD3 and CD68. Intimal hyperplasia and medial fibrosis were quantified using Image J analysis.
Results: 45.45% of 44 biopsies showed concentric intimal hyperplasia, with a 46.2 μm mean by morphometric analysis. Medial fibrosis and expansion interested 54.54% of vein samples with 147.75 μm mean thickness, characterized by conjunctive fibres accumulation. Neoangiogenesis in intima and media layers only in 6.8% of cases was found. In vein walls, calcification and mononuclear inflammatory cells were absent. A subset of 9 specimens obtained from surgical revision patients had substantial luminal narrowing due to irregular neointimal formation (87.27 μm), media thickening (177.34 μm), and neoangiogenesis in intima and media. Foci of microcalcification and luminal thrombus were detected in 5 of 9 cases.
Conclusion: In this study, we observed pre-existing abnormalities in both 9 cases, including neointimal hyperplasia disorganization of the venous wall and neovascularization of intima in veins used for AFV creation, that predispose these venous walls to maturation failure. The intima hyperplasia and neoangiogenesis in fistula without maturation are accompanied by mild inflammatory infiltrate, predominantly in those with thrombosis and calcification.

PS-19-008

Primary heart tumours: a Portuguese case series

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Background & objectives: Primary heart tumours are rare, even in major cardiac surgery centres. We present a retrospective monocentric 5-year case series of resected primary heart tumours at Coimbra Hospital and University Centre.
Methods: All firstly diagnosed primary heart tumours surgically resected at our Institution from 2017 to 2021 were retrieved from hospital registries. From each case, we collected patient age and sex, histopathological diagnosis, and intracardiac tumoral location. Follow-up time varied from 5 to 98 months.
Results: We identified 34 tumours, 32 (94,1%) benign and 2 (5,9%) malignant.
Regarding the benign tumours, we reported 24 (75%) myxomas and 8 (25%) papillary fibroelastomas. As expected, the majority (91,7%) of myxomas arose on the left atrium and papillary fibroelastomas on the valves. Twenty patients were female; the mean age was 62 years (range: 14-79).
During follow-up, one myxoma recurred after eight months and was re-excised. No patient had significant complications nor died of the disease.
The malignant tumours were an angiosarcoma and an EBV-positive diffuse large B-cell lymphoma, the first with a fatal outcome after six months. The patient with lymphoma completed chemotherapy and is well after 11 months.
Conclusion: To the best of our knowledge, we describe the first Portuguese series on primary heart tumours. We report 94,1% of benign tumours, a significantly higher value than the 75% usually described in the literature ($t(33) = -4{,}67$, $p < 0{,}001$). We hypothesize that this difference is due to a higher incidental diagnosis of benign tumours, but further and more recent work is needed.
We also report a myxoma recurrence, a rarely described event, and two uncommon malignant heart tumours.

PS-19-009

Morphometric analysis of arterial wall main components densities depending on the patient's cause of death

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Background & objectives: Cardiovascular-CV diseases are among the most common causes of death. The authors compared the densities-D of aortic wall main components (Elastic fibres–FE, Collagen fibres-FCOL, smooth muscle fibres-FM) of people with CV and non-cardiovascular-NCV diseases causing patients' death.
Methods: Four aortic rings (base, cross, thoracic, abdominal) were taken during autopsies from 90 autopsied cases (62 NCV and 28 CV). Samples were processed using the classical HP technique and stained with Orcein, and Goldner's trichrome. Quantitative measurements were made using custom-made software, developed in Matlab (Mathworks, USA) on virtual slides. Average values were compared with "t" test and Pearson's test.
Results: FE-D and FCOL-D had a continuous descending trend in both CV and NCV groups in all main aortic regions. FE-D were higher in NCV group while FCOL-D were higher in CV group. In turn, FM-D had a general ascending but oscillating trend in both CV and NCV groups, more pronounced in the former.
FCOL-Ds had a pronounced inverse correlation with both FE-Ds and FM-Ds and in both groups (correlation matrices-CMs negative and Pearson's test "p" values <0,0001). In turn, FE-D had a direct correlation with FM-D in both NCV and CV groups, more pronounced in the former (CMs positive and Pearson's test "p" value 0.0384 vs 0.0729).
Conclusion: Our preliminary data show that the remodelling process of the aortic wall components differs between patients with CV and NCV diseases both along the aortic length and in the correlation pattern between the three aortic wall components (FE, FCOL and FM).

PS-20 | Poster Session Electron Microscopy

PS-20-001

Why do some uncemented porous tantalum total knee replacement fail?

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Background & objectives: Porous tantalum has been extensively used in orthopaedic surgery, including uncemented total knee arthroplasty (TKA). We aimed to analyse possible causes for unexpected medial tibia bone loss resulting in porous tantalum tibia component fracture necessitating early revision after primary TKA.
Methods: Retrieved tissue samples collected at revision surgery underneath the tibial baseplate were histologically analysed and scanned with 3 MeV focused proton beam for Proton-Induced X-ray Emission (micro-PIXE) elemental analysis. Fractographic and microstructural analysis were performed by stereomicroscopy. A full 3D finite-element model was made for numerical analysis of stress-strain conditions of the tibial baseplate.
Results: The 65-year old patient was revised 44 months after primary TKA because of suddenly increased pain. His right knee radiographs depicted fracture and displacement of the tibial baseplate. Histological examination of tissue underneath the broken medial part of the tibial baseplate revealed dark stained metal debris, which was confirmed by micro-PIXE to consist of Tantalum and Titanium. Fractographic analysis and tensile testing showed that the failure of the tibial baseplate fulfilled the criteria of a typical fatigue fracture. Microstructural analysis of the contact surface revealed signs of bone ingrowth in 22.5% of the surface only and was even less pronounced in the medial half of the tibial baseplate.
Conclusion: This case details the second known report of failure of a modern cementless modular, trabecular metal (Porous Tantalum™) tibial baseplate in a TKA. Further studies are needed to confirm the responsibility of metal debris for an increased bone absorption leading to catastrophic tibial baseplate failure.

PS-20-002
Characterisation of primary cilium by an ultrastructural study in actinic keratosis and squamous cell carcinoma
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Background & objectives: The primary cilium (PC) is an organelle that plays an essential role in cellular signalling, its aberrant activation is related to an uncontrolled cell division. By an ultrastructural study, we characterised it in relation to squamous cell carcinoma and actinic-keratosis.
Methods: The samples were obtained by a dermatologist, consisting of human skin with suspicion of actinic-keratosis (AK) and/or squamous-cell-carcinoma (SCC). Half of the biopsy was used for diagnosis and the other half for ultrastructural study. The other hemisection was fixed in glutaraldehyde, and then stored in PBS. The sample sections were cut by an ultramicrotome and examined under electron microscope (EM).
Results: From each sample, we got a hematoxylin and eosin (H&E) histological slice and immunohistochemistry: CD31, beta-eosin and immunohistochemistry: CD31, beta- catenin, ki67, vimentin, PTEN, catenin, ki67, vimentin, PTEN, e--cadherin, p63 cadherin, p63 and p53. As for EM, we collected almost 20 images of each sample. We observed a decrease of the cells which expressed the PC in SCC and a gradual loss of AK in their different grades of dysplasia.
Conclusion: We have shown that PC participates in the malignancy process of AK up to SCC. The decreased expression of the PC appears to be directly proportional to the AK grade, which could help to predict the progression to SCC.

PS-21 | Poster Session History of Pathology

PS-21-001
Epidemics in an Atlantic Archipelago
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Background & objectives: Islands, in their natural isolation, are protected from nefarious external influences. Yet, when people and goods movements occur, danger of infectious diseases increases. The authors aim to study epidemics' outbursts throughout History in an Atlantic Archipelago from the XV century.
Methods: A retrospective search for information on infectious diseases / epidemics was performed through Historical, Medical, Literary, Journalistic and Photographic archives and databases of various Institutions of the Archipelago. An analysis of the data, according to the current infectious pathology knowledge, was done.
Results: From the XVth to the XXIst centuries, 9 epidemics' outbreaks occurred and were officially reported at the Archipelago. They were: 1521-1538 – Plague, 1751 – Measles, 1815 – Smallpox, 1856 – Cholera, 1873 – Smallpox, 1905/6 – Bubonic Plague, 1910-1911 – Cholera, 1919-1920 – Pneumonic (Spanish) Influenza, 2020-… – Covid-19. Popular, medical, institutional, governmental and religious interventions tried to overcome each catastrophe; yet, they led to thousands or millions of deaths, sequelae in the survivors and unspeakable suffering.
Conclusion: In a period of seven centuries, 9 major epidemics happened. In an Archipelago where tourism and trade exchanges have been relevant throughout the centuries, the occurrence of epidemics' outbursts are explained. Yet, it is important to understand the socio-economic and medico-sanitary contexts of each outbreak, which may provide data and knowledge to be used / adapted to new – present or future – epidemics, both as preventive and curative measures.

PS-21-002
Smallpox and skin models
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Background & objectives: In pandemic times, science looks back to History trying to learn lessons from the past. Smallpox was among major historical epidemics and was an example in vaccination history. The authors aim to present Variole skin lesions to young medical generations.
Methods: To attain the objective, a search was performed in the collection of the Anatomical Pathology Museum – Medical Faculty, Coimbra University. It is a museum from the XIXth century, UNESCO's World Heritage since 2013, that houses thousands of objects of various natures [from books, photographs, scientific equipment, anatomo-pathological specimens in glass containers with fixative liquid, to artificial (clay, wax) models].
Results: Among the 161 wax models of skin pathology in the Museum, 2 expose Smallpox (Variole) cutaneous lesions. Dating from the XIXth century, acquired in Paris, handcrafted by the French modeler Vasseur, they correspond to human arms with umbilicated vesico-pustular papules. These wax models are three-dimensions representations and present not only anatomic but also pathological accuracy; since they were executed facing the real victims or copied from an original model.

Conclusion: Historical skin wax models from Anatomical-Pathology Museums are priceless and unique tools to teach young medical generations, especially in eradicated diseases, as Smallpox. Knowing how to recognize this entity is of major importance, since the world may unexpectedly face new epidemic waves, in various contexts, namely that of bioterrorism.

PS-21-003

Pathology archives and applicability of immunohistochemistry – 40 years old myocardial infarction samples

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Background & objectives: Our group has recently determined that CD15, C9, C5b-9 and Fibronectin immunohistochemistry can be helpful in Myocardial Infarction (MI) dating. This study aimed to verify antigen preservation for MI diagnosis dating after formalin-fixed paraffin-embedded (FFPE) myocardium stored over 30 years.
Methods: We selected 19 FFPE MIs diagnosed in autopsies between 1970s-1980s from IAP-PM archives. Neutrophils absence/presence was used for dating early/old MI <3days>. IHC panel discriminated between MI/non-MI cardiac tissue, namely CD15, C9, C5b-9 and Fibronectin. Two Pathologists calculated global expression to be compared with global expressions in 24 recent (2017-INMLCF) diagnosed MIs cases, using non-parametric Mann-Whitney test SPSS v27.
Results: Samples reinclusion in new paraffin molding for new microtomes sectioning was performed and 3µm sections were submitted to IHC panel according with manufacturer recommendations for each antibody in BondMax platform. After considering global expression (intensity of expression x percentage of positive myocytes) of CD15 (U=202,500; p=0,531; N=43), C9 (U=214,500; p=0,739; N=43) and Fibronectin (U=147,000; p=0,077; N=43) no statistically significant differences were recognized between archival and recent MIs; C5b9 expression was significantly lower in MIs archived tissue over 40 years (U=138,000; p=0,027; N=43). Fibronectin expression was higher in infarcted tissue in all cases, when compared with normal myocytes.
Conclusion: Our study highlighted performance of immunohistochemistry in archived MI paraffin blocks. It demonstrated that CD15, C9 and Fibronectin can be applied to FFPE archived samples over more than 40 years, enabling and supporting future studies on this material source. Dating MIs was the main goal and fibronectin revealed to be a robust biomarker either for distinguishing between ischemic necrosis and normal myocardium as well as tissue preservation standard biomarker.

PS-22 | Poster Session Infectious Diseases Pathology

PS-22-001

COVID-19 pathology in cases of co-morbidity with malignant tumours

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Background & objectives: COVID-19 infection cases with malignant neoplasms as co-morbidities are associated with increased risk of severe disease' course and higher mortality. The aim of present study was to reveal organs' pathologies induced by COVID-19 infection in patients with various cancers accompanying illnesses.
Methods: Autopsy examinations were performed in fifteen lethal cases of COVID-19 infection with malignant tumours co-morbidities. Clinical and laboratory tests data were recorded and analysed. Gross pathologies of lungs, other internal organs and brain were examined. Tissue samples were taken for histology. Malignancy diagnosis was confirmed in all cases by the oncopathologist's second opinion. Microscopy of H&E stained slides performed at x10,x20,x40.
Results: Results have shown that six patients had concomitant haematological malignancies and nine ones suffered from carcinomas of different localizations. In two cases the causes of deaths were a result of the tumour's growth progression. Present study revealed multi-organ injuries in all cases, but the majority of patients had the most striking lungs pathology. Severe diffuse alveolar damage was diagnosed in thirteen cases with superimposed bacterial bronchopneumonia in two patients. Histologically alveolar epithelial cells dystrophy and necrosis with parallel hyperplasia of type II pneumocytes, hyaline membrane formation, inflammatory infiltration with fibrin plugs in some airspaces were evident. Blood circulation disturbances were found in all autopsies of present study.
Conclusion: The COVID-19 pandemic resulted in a global health crisis with the significant growth of morbidity and mortality. Concomitant malignancies contributed to organ's insufficiency and fatal outcomes. Effective clinical management must be based on the fundamental knowledge of the pathogenesis and pathology of infection combined with neoplastic growth. Postmortem examination is an essential tool in understanding the damages due to this novel infection. Further investigations of the underlying neoplastic diseases' role in lethal outcomes of the COVID-19 are considered essential.

PS-22-002

Mast cells induce fibrosis and thrombosis in lung tissue samples of patients infected with SARS-CoV-2 virus

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Background & objectives: COVID-19 lung tissue shares similar histomorphological features with chronic lung allograft disease, suggesting activation of auto-immune related pathways in COVID-19. Therefore, we analysed the mRNA expression of auto-immune-related genes in post-mortem lung tissue from COVID-19 patients.
Methods: Formalin-fixated, paraffin-embedded post-mortem lung tissue samples of COVID-19 patients were used for targeted gene expression profiling using the autoimmune panel of NanoString technology. To validate the results, multiplex immunofluorescence for tryptase and chymase was applied. Lung tissue samples from influenza patients were used as a control group.
Results: Immune infiltration was broadly similar between COVID-19 and influenza patients. Upregulation of genes related to mast cells (TPSAB1/TPSAB2, CPA3, and HDC) was identified in COVID-19. This finding was strengthened by multiplex

immunofluorescence showing a significant increase of tryptase- and chymase positive cells in COVID-19 as well. Furthermore, AGER (receptor for advanced glycation end-products) and PPBP (pro-platelet basic protein) were upregulated in COVID-19 compared to influenza. IFIH1, IFI44L, IFIT1, and RSAD2, genes related to type I interferon signalling, showed a significant correlation to detected SARS-CoV2 pathway-related genes. A comparison of groups based presence of histomorphological features indicative of ARDS did not show upregulation of any specific gene or pathways.
Conclusion: Through two separate ways of measurement, we show an increase of mast cells in lungs affected by severe COVID-19 compared to influenza. Additionally, several genes involved in fibrosis and thrombosis, among which are AGER and PPBP, are upregulated in COVID-19. Future studies should focus on detecting these markers in bronchoalveolar lavage fluid to predict the severity and course of the disease.

PS-23 | Poster Session Neuropathology

PS-23-001
Expression of LAMP2A, LC3B, and HSP70 autophagy biomarkers in different brain structures during aging

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Background & objectives: Macroautophagy and chaperon-mediated autophagy play a pivotal role in misfolded proteins removal in neurons, whilst their impairment contributes to aging and age-related diseases. We aimed to evaluate biomarkers of abovementioned processes in neurons localized in different brain zones during aging.
Methods: Heat shock protein 70, LAMP2A, and LC3B immunohistochemical staining was performed for FFPE samples of human prefrontal cortex (pyramidal layer), hippocampus, and basal ganglia. Two age groups were studied: young (n=5) and elderly (n=10),whose causes of death were not associated with neurological diseases. The optical density was measured in neuronal perikaryon. Statistical significance was analysed using Kruskal Wallis test.
Results: From the obtained data, it is apparent that in studied groups there was significant difference between macroautophagy (LC3B), chaperon-mediated autophagy (HSP70), as well as lysosome receptor (LAMP2A) biomarkers expression in neuronal perikaryon of large neurons ($p<0.05$). Statistical test revealed increased levels of these autophagy-lysosome pathway proteins in elderly studied groups than in young one. Interestingly, the level of HSP70 in elderly samples was 2-fold higher in comparison with samples obtained from young group. The rates for LC3B and LAMP2A for elderly group were approximately 1.25 times higher than young group, but optical density in each brain zones were not found to differ.
Conclusion: Our demonstration that Heat shock protein 70 expression was significantly increased in elderly samples could indicates its potential role in adaptive mechanisms occurring in aging neurons during chronic oxidative stress and inflammation. Exacerbated levels of all autophagy biomarkers in elderly samples as to young one points out that autophagy seems to support proteostasis in neurons during physiological aging. These findings, while preliminary, suggest that both autophagy-lysosome pathways could contribute to neuronal maintenance during aging.

PS-23-002
Prognosis and outcome of patients with haemangioblastoma based on histopathological features: experience of a tertiary centre

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Background & objectives: Haemangioblastoma is a highly vascular tumour of the central nervous system with clear neoplastic stromal cells, classified as WHO Grade I. The aim of the present study is to investigate the clinical manifestations, histopathological features and prognosis of this entity.
Methods: The characteristics of 25 patients diagnosed of haemangioblastoma were analysed, and a retrospective review of hemangioblastoma of the central nervous system reported in the literature was performed.
Results: 12 patients were female and 13 were men, aged from 9 to 77 years (55 years on average). All cases were wild-type sporadic, except for one associated to Von Hippel Lindau Syndrome. 15 cases were located on cerebellum, 9 on the brain and one on spinal cord. Microscopically, the morphology and immunophenotype of tumoral cells were not different from those mentioned in the literature. 3 patients died during the follow-up period and 4 patients suffered a recurrence of the disease.
Conclusion: Overall prognosis was relatively good, so the presence of tumoral recurrence or malignant transformation was unusual. The most common presentation is a sporadic tumour located on cerebellum. From an histological point of view, only the presence of atypical mitoses correlated with progression of the disease. Cerebral haemangioblastoma often simulates the imaging characteristics of meningioma or glioma. Enough attention should be paid to differential diagnosis before the operation, and exact diagnosis relies on the pathological examination.

PS-23-003
Retrospective multicentric study of patients with histopathological rhabdoid meningioma features

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Background & objectives: Rhabdoid meningiomas (RM) are WHO grade 3 brain tumours, with high rates of local recurrence and heterogeneous mortality. Our aim is to analyse the clinical and pathological characteristics and to establish a possible correlation with the aggressive clinical course.
Methods: We have reviewed the histological, clinical and prognosis characteristics of patients with MR from 17 Pathology Departments and 4 biobanks of Spain. We also review the mitotic index, immunohistochemistry and diagnosis. In cases with aggressive behaviour or successive relapse, we consider to combine a genetic profile through high-density arrays looking for specific genetic abnormalities (loss and gain of chromosomal regions).
Results: From 24 patients only 17 met histological criteria for MR. The age range was 34 to 83 years(10 men, 7 women). In the follow up, we observed 5 RMs with aggressive behaviour, multiple episodes of recurrences and death of the patients (5/17, 3 deceased without recurrences). The sequential analysis of the evolution and genetic changes included tumours at diagnosis and relapse samples. In 2/5 tumours, the genetic pattern at relapse remains identical to that at diagnosis and in the other

3/5, we observed acquisition of new chromosomal abnormalities. 1 to 19 chromosomes were affected, in varying numbers of chromosomes with an average of 5 to 11 chromosomes per tumour altered.
Conclusion: Until now, evidence of rabdoid morphology qualify for a correct diagnosis alone of MR, nevertheless misdiagnosis can be present specially when rabdoid cells are scatter and no other atypical histological characteristic is present. We have established 2 profiles of chromosomal alterations (one with chromosomal losses and one with losses combined with gains of several genetic regions).The most frequent alteration it was the loss of one chromosome 22 (monosomy). Genomic sequencing could help to the graduation of these tumours.

PS-23-004
Grade 2 meningiomas: a retrospective study of 30 cases at a single institution
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Background & objectives: Meningiomas present a broad morphological spectrum. Grade 2 meningiomas (G2M) are aggressive tumours associated with a high recurrence rate. In this study, we aimed to evaluate the epidemiological and histopathological features of G2M in our department.
Methods: This retrospective study included 30 cases of G2M diagnosed during 5 years (January 2012-December 2017) at our department. A review of the slides was performed and the meningiomas were reclassified according to the fifth edition of the WHO Classification of Tumours of the Central Nervous System (WHO CNS5) published in 2021
Results: Our study included 12 men and 18 women (Sex ratio=0.66). The mean age was 56.2 years. The most common symptom was an intra-cranial hypertension. The main localization was the supra-tentorial region (93%). Neurosurgical resection was performed in all cases. Gross-total resection was achieved in 16 cases (53.3%). Histopathologic examination concluded to an atypical meningioma (AM) in 28 cases (93.4%), a clear cell meningioma (CCM) in one case (3.3%) and a rhabdoid meningioma (RM) in one case (3.3%). Ki67 proliferation index was determined in 12 cases. The value varies between 2 and 20%. Recurrence was noted in 6 cases (20%). The progression-free survival and overall survival were 73.3% and 86.7% respectively.
Conclusion: It is now emphasized that the criteria defining atypical or anaplastic (ie, grade 2 and 3) meningioma should be applied regardless of the underlying subtype. As in prior classifications, chordoid and CCM are noted to have a higher likelihood of recurrence than the average WHO grade 1 meningioma and have hence been assigned to WHO grade 2. G2M exhibit a high tendency to relapse with up to 29-52% recurring. The recurrence rate in our study was 20%.

PS-23-005
Epidemiologic profil of primary cerebellar tumour in the south of Tunisia
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Background & objectives: There are several reports regarding the epidemiology of brain tumours. However, little is known about the profile of primary cerebellar tumours (PCT). We report the results of a retrospective study of PCT in an institution of the south of Tunisia.
Methods: We included in our study all cases of PCT diagnosed at our department during 11 years (January 201-December 2020). The tumours were classified according to the fourth edition of the WHO Classification of Tumours of the Central Nervous System (WHO CNS) published in 2016.
Results: Forty-six cases of PCT were included. The average age was 19 years (1-74 years). 45.6% of patients were under 18 years old and 54.4% were over 18 years old. Tumours were located in cerebellar hemisphere in 21 cases (70%), in the vermis in 6 cases (20%) and vermi-lobular in 3 cases (10%). In paediatric population (PP), the sex ratio was 1.1 while in adult population (AP) it was 0.92. Medulloblastoma was the most common histological type for both PP and AP (61.9% and 40% respectively). Pilocytic astrocytoma (PA) represented the second most frequent tumour in PP (38.1%). In AP, haemangioblastoma and PA were diagnosed in 8 and 3 cases respectively.
Conclusion: PCT represent with brainstem tumours 10% of all tumours of the CNS and are frequently encountered in paediatric population. Medulloblastoma and PA are the two most common tumours in childhood as reported in our study. According to the literature, the most common tumour in adults is haemangioblastoma. Contrary to what is reported, our study showed a high proportion of medulloblastoma in adults.

PS-23-006
Analysis of the procedure for extracting, sending and receiving the muscle biopsy. Knowledge, attitudes and practices of the professionals involved
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Background & objectives: The knowledge of professionals related to muscle biopsy has not been estimated at present. The objective of this work is to evaluate the knowledge, attitudes and practices of medical specialists and those in training regarding the muscle biopsy procedure.
Methods: Observational, descriptive, cross-sectional and multicentre study (Provincial hospitals of the Andalusian Health Service. Participants: Specialist physicians and in training randomly selected by sending an anonymous survey, previously validated, by email that included items on the sending of the sample, the excision of the sample, its orientation, volume, etc. . A descriptive, bivariate and multivariate statistical analysis was performed ($p < 0.05$).
Results: Participants: 22 professionals completed the survey (72.7% -16- neurosurgeon; 18.2% -4- plastic surgeons, 4.5% -1- pathologist and 4.5% -1- neurologist. 50% were resident intern specialists. 81.8% -18- were women. 66% of those surveyed did not know the volume of tissue to send to the Pathological Anatomy (AP) service. Only 18.2% informed AP about the shipment. 66.7% considered that they were not well educated about the procedure. 73% did not reference the distal or proximal portion of the sample. 10.1% personally sent the sample to the PC service for its correct reception.
Conclusion: Knowledge and practices about the muscle biopsy procedure in the subjects analysed are scarce, so specific training strategies to increase their knowledge and improve their attitude and skills regarding this procedure should be considered for actual incorporation into the plans training, to avoid diagnostic delays, inadequate handling of the sample and unnecessary reinterventions.

PS-23-007

Clinicopathological characterisation and molecular profiling of H3 G34-mutant high-grade gliomas in paediatric and young adult patients

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Background & objectives: Diffuse hemispheric glioma, H3 G34-mutant is a novel paediatric tumour type in the fifth edition of the WHO Classification of CNS Tumours. We present here a global review of a departmental case series to provide further clarification on this entity.
Methods: Retrospective departmental analysis of 931 paediatric/young adult neuroepithelial tumours identified eleven cases harbouring H3 G34R/V mutation. Clinicopathological and molecular data were reviewed.
Results: H3 G34R/V mutation was a rare molecular event among CNS tumours (1.2%; median age: 17.3 years). MRI revealed features of high-grade gliomas often involving multiple lobes and deep structures that precluded gross total resection. Histologically, the tumours showed marked heterogeneity and aggressive spreading along pre-existing brain structures and leptomeninges. Besides diagnostic H3 G34R/V mutation, most cases harboured pathogenic variants in TP53 and ATRX genes. Potential targetable mutations in PDGFRA and PIK3CA genes were detected in 5 cases. Methylation profiling was a useful diagnostic tool and it also highlighted common structural chromosome abnormalities including PDGFRA amplification, CDKN2A/B deletion and various CNVs in cyclinD-CDK4/6-Rb pathway. The mean overall survival was 19.1 months.
Conclusion: H3 G34-mutant diffuse hemispheric glioma is a distinct CNS tumour type sharing common radiological and pathological features and associated with a dismal prognosis. Genomic landscaping of individual tumours might give an opportunity to tailoring individualised therapies and improve patient management.

PS-23-008

The role of AKT in prognosis of breast cancer brain metastases

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Background & objectives: Brain metastases in breast cancer are linked to a poor prognosis and are a common event. Immunohistochemistry assessment of biomarkers may predict prognosis and guide therapy. Our goal was to investigate the role of the PTEN/AKT/PI3K pathway and androgen receptors.
Methods: A retrospective transversal study of 114 patients (diagnosed between 2000-2016) with breast cancer brain metastases was carried out using archival biological material.
Expression of PTEN, AKT, PI3K and Androgen receptors was assessed by immunohistochemistry.
Clinical and pathological data were retrieved from the hospital database. The local ethical committee approved this study.
Results: After a mean of 20.3±29.5 months, the median overall survival was of 10 months.
The overexpression of AKT was associated with a worse overall survival on univariate analysis (7 months (1.3-12.8) vs 12 months (5.6-18.2), p=0.034), but this finding was not confirmed in multivariate analysis (p=0.090).
No difference in overall survival was seen associated with the expression of PTEN (p=0.608), PI3K (p=0.167) and androgen receptors (p=0.894)
Conclusion: AKT is usually linked to tumour progression and drug resistance, thus it is expected that AKT overexpression is linked to worse overall survival in breast cancer and may have prognostic impact on survival in patients BCBM. Modulation of AKT and its pathway may be a strategy for guiding stratification and therapy of patients.

PS-23-009

Choroid plexus tumours: clinicopathological analysis of 10 cases

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Background & objectives: Choroid plexus tumours are rare intraventricular neoplasms arising from choroid plexus epithelium. 3 histological types have been described by the WHO : Papilloma, Atypical papilloma and Carcinoma. This study aims to highlight the epidemiological and pathological characteristics of this entity.
Methods: Our study is retrospective about ten cases of choroid plexus tumours collected in the pathology department of La Rabta hospital over a period of 22 years from 2000 to 2022. The data on patients' gender, age, pathomorphological characteristics and location of the tumour, clinical presentation and operative details were retrieved from the National Institute of Neurology of Tunis.
Results: 10 cases were evaluable. They were 6female and 4male patients, ages ranging from 5 to 50 years with an average of 16,3 years. The clinical presentation was dominated by intracranial pressure syndrome. The main diagnostic tool was CT-scan and most patients with supratentorial tumour were children. All patients underwent surgical treatment. The histological examination has revealed 6 cases of papillomas and 4 cases of carcinomas. The papillomas corresponded to papillary tumoral proliferations with very low mitotic activity and whose cells were cuboid, resembling those of the normal choroid plexus. Carcinomas, on the other hand, appeared as frankly malignant tumours with significant mitotic activity, less good differentiation and areas of necrosis.
Conclusion: Choroid plexus tumours remain a very rare entity affecting mainly children and are classified into 3 histological types. Higher frequency and better prognosis have been seen with choroid plexus-papillomas. Surgery remains the mainstay of treatment, often followed by adjuvant treatment in case of choroid plexus-carcinomas.

PS-23-010

Hydatid cysts of the nervous cerebral system, an unusual location: about 9 cases

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Background & objectives: Hydatid cyst is a parasitic tapeworm disease caused by the larval stage of Echinococcus Granulosus usually reported in the liver. The NCS is still a rare location. Our aim is to define the epidemiological and pathological characteristics of this entity.
Methods: Our study is retrospective about nine cases of hydatid cysts of the nervous central system (NCS) collected in the pathology department of La Rabta hospital over a period of 6 years from 2016 to 2022. The data on patients' gender, age, histology and location of the cyst and operative details were retrieved from the National Institute of Neurology of Tunis.

Results: 9 cases were evaluable. They were 3male and 6 female patients, ages ranging from 5 to 75 years with an average of 29,5 years. Among these cases, 2 involved the brainstem and 7 involved the parietal lobe. All of patients had a rural origin and contact with dogs. The clinical presentation was dominated by intracranial pressure syndrome with focal neurologic deficit. The radiologic findings range from purely cystic lesions to a completely solid appearance. All of the patients underwent surgical treatment. The histological examination had adjusted the diagnosis showing hydatid membranes with an eosinophilic laminated appearance, containing daughter cysts filled with gel-like fluid and a pericyst on the periphery.
Conclusion: While the liver is usually the most frequently involved organ in hydatid disease, the nervous central system (NCS) is still a rare location leading to several complications in case of late diagnosis. The main diagnostic tool remains always the histopathologic examination

PS-24 | Poster Session Other Topics

PS-24-001
Group work in the annotation of virtual pathological slides

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Background & objectives: One of the important goal of modern medical education is to create a learning environment for interactive discussion and collaboration. The objective of our study was to compare the results of individual and team annotation of digitized pathological slides.
Methods: Based on students' academic performance, gender and ethnicity, heterogeneous teams were created randomly. Students first annotated virtual slides individually and then in a group. Differences in individual and group scores were tested using paired samples T-test. Probability level of $p < 0.05$ was considered significant. Normality of distribution of students' answers was tested using the Kolmogorov-Smirnov test.
Results: General pathology students scored significantly higher ($p<0.001$) in group (Average group score 25.0, SD 2.4) as opposed to individual readings (Average individual score 3.6, SD 1.6). In T4 group studying systemic pathology and working in a group scored significantly higher (Average group score 60.8, SD 6.0, $p<0.00$) compared with individual annotations (Average group score 26.5, SD 11.0). A similar finding was observed when the scores were stratified according to students groups, all groups in Term 3 and in Term 4 achievement was significantly higher ($p<0.003$) in group compared with individual reading. Both the students with lower and with higher academic achievement significantly ($p<0.03$ and $p<0.05$, respectively) improves the results.
Conclusion: Group work in the annotation of pathological slides has learning potential and facilitate interaction between students. This way of analysing pathological slides significantly improves the results of students with lower as well as of students with higher academic achievement. Team work is a part of active learning and is the most important task of modern and high-quality healthcare education. This is supporting students to become reflective and competent physicians.

PS-24-002
Level of IgG to glu-plasminogen in blood plasma as marker of breast cancer

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Background & objectives: Plasminogen plays an active role in tumour metastasis as a proteolytic enzyme. The study aimed to analysed potential diagnostic power of circulating IgG to Plasminogen in blood of mice with and without breast cancer
Methods: Plasma samples were obtained from Balb/c mice with ($n = 25$) and without ($n = 20$) breast cancer. The level of IgG binding plasminogen was analysed by ELISA on 96-well plates with immobilized glu-plasminogen. The comparisons of mean OD between cohorts were performed by the Mann–Whitney U-test. Potential diagnostic power of IgG was investigated by ROC curve analysis
Results: Breast cancer in mice was confirmed using physical examination and biopsies. Plasma samples from breast cancer and healthy mice were incubated in 96-well plates coated with glu-plasminogen and IgG binding was measured by HRP-conjugated anti-mouse IgG Abs. We observed significantly higher circulating levels of IgG to plasminogen in a group of mice with breast cancer compared to a group of healthy mice ($p<0.05$). In ROC curve analysis the sensitivity of the classification of breast cancer from healthy controls was 72%, the specificity was 95% and the area under the curve was 0.93
Conclusion: Our results require further confirmation in women with breast cancer and investigation of the mechanism of IgG binding to glu-plasminogen in blood. The potential diagnostic power of circulating IgG to glu-plasminogen in blood of patients with breast cancer and healthy woman could be a promising candidate biomarker for the early diagnosis of breast cancer.
Funding: The study was carried out within the framework of state assignment to A.P. Avtsyn Research Institute of Human Morphology (No. 122030200534-4)

PS-24-003
Formalin-fixed, paraffin-embedded (FFPE) block stability using PD-L1 IHC 22C3 pharmDx

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Background & objectives: PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical (IHC) assay for PD-L1 expression in FFPE specimens routinely processed for diagnostic evaluation.
A stability study was performed to assess the effects of PD-L1 expression in aged FFPE blocks stored over time.
Methods: Human placenta tissue was used as a model since syncytiotrophoblastic cells have features similar to malignant cells. Fresh tissue was procured and prepared as FFPE blocks to control pre-analytical variables such as processing, ischemic time, and fixation time. Fifteen placenta blocks from 5 cases were stained by IHC at intervals from 0-60 months (5 years) using PD-L1 IHC 22C3.
Results: PD-L1 expression was evaluated and assessed for any changes in overall staining intensity over time compared to the initial Time 0 staining. Our results showed no significant change in PD-L1 expression in sections from aged FFPE placenta tissue blocks stored in the dark with ambient conditions over time for up to 5 years. Similar sensitivity to titrations was observed between placenta and NSCLC.
Conclusion: FFPE tissue blocks stored in the dark at ambient temperature for up to 5 years demonstrated similar PD-L1 expression compared to non-aged blocks and thus, demonstrate stability over time.
Funding: Merck & Co., Inc

PS-24-004

Direct scanning of selected FFPE blocks to reduce workflow costs of routine FFPE controls in histopathology

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Background & objectives: Pathology departments face high costs of slide cutting, staining and coverslipping. We employed a large field-of-view confocal microscope allowing to image thick specimens (Histolog® Scanner) for scanning FFPE blocks to investigate whether this could reduce the number of slide prepared.
Methods: Lung (n=47) and pancreas (n=23) FFPE blocks were imaged with the Histolog Scanner. Pathologists, residents and one grossing room technician were asked to diagnose independently in confocal images if the block is exclusively composed of normal tissue or not. Rate of image rejection prior diagnosis due to insufficient image quality is monitored for further costs saving assessments.
Results: Rate of image rejection were 17% for pancreas and 23% for lung tissues reducing the potential cost savings (these blocks would be processed whatever their content in a routine practice). On the non-rejected images, observers were able to recognize tissue features in FFPE block images despite loss of nuclear detail and lack of colour nuances compared to H&E slides. Accuracy to define that the blocks are exclusively composed of normal tissue yielded high scores for both tissue types: overall sensitivity/specificity of 96%/100% for pancreas (2 pathologists, 1 resident) and of 93%/83% for lungs (4 residents, 7 pathologists, 1 grossing room technician). Similar performances between the three observer populations were found.
Conclusion: Direct image assessment of FFPE blocks by Histolog® Scanner seems to yield acceptable images compared to H&E slides. Preliminary results showed that good performance of FFPE block screening can potentially be achieved for pancreas and lung tissues with very high sensitivity before the preparation of histology slides. This allows potential cost reduction in slide preparation and infrastructure costs for slide storage.

PS-24-005

Audit of pathology quality assurance programmes: assessing efficacy and workload

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Background & objectives: Studies have highlighted significant discrepancies between original and review pathology diagnoses. Quality assurance programmes can improve reporting accuracy. This audit assessed the effectiveness of quality assurance programmes within a single institution and determined the frequency of discrepancies in reporting.
Methods: Retrospective review of cases collected over a one year period was performed. Cases were continuously recorded during this time following review at MDT or clinical meetings and review of randomly selected cases. Frequency of overall reporting errors was calculated and chi square analysis was performed to detect potential disproportionate review of specific specialties.
Results: The continuous quality assurance programme ensured review of 7.7% of the total histology and cytopathology workload over 1 year. Proportionally more histology cases were reviewed compared to cytopathology (p=<0.00001). Randomly assigned review of cases accounted for only 9.7% of the quality assurance programme workload whilst the rest came from review at MDT or clinical meetings.
The proportionate percentage of cases reviewed as per overall specialty workload was significantly different: urology 49.3%, respiratory 37.3%, H&N 16.7%, skin 9.0%, gynaecology 6.2%, gastrointestinal 4.4% and breast 1.7% of cases.
There was complete diagnostic agreement in 94.9% of reports and errors regarded as potentially clinically significant were recorded in 0.9% of cases overall.
Conclusion: Our quality assurance programme ensured review of a significant proportion of overall workload compared to other studies (1.3-8.9%) with comparatively low significant error rates (0.8-5.3%).
Within our institution the combined approach of random plus focused case review effectively detects reporting discrepancies and is pragmatic and efficient.
To our knowledge we are the first to assess whether cases reviewed within a quality assurance programme proportionately reflect overall workload. This information is important to improve effectiveness of quality assurance programmes.

PS-24-006

Extrapulmonary POU2F3-positive small cell carcinoma is associated with variable neuroendocrine marker expression and gallbladder location

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Background & objectives: POU2F3 is recently identified as the defining biomarker of a subset of small cell carcinoma (SmCC) of lung associated with neuroendocrine-low immunoprofile and poor prognosis. Here, we aimed to explore the presence of POU2F3-positive extrapulmonary SmCC and its clinicopathologic characteristics.
Methods: Thirty-four extrapulmonary SmCC from various organs were collected for POU2F3 immunohistochemical staining. The age, sex, primary location, histology (pure versus combined SmCC), and the expression of TTF-1 and available neuroendocrine markers, including synaptophysin, chromogranin A, and/or INSM1, were recorded. To examine its specificity, we also performed POU2F3 staining on 849 cases of 32 different histotypes, including carcinomas, lymphomas, and sarcomas.
Results: POU2F3 immunostaining was positive in 5 (14.7%) extrapulmonary SmCC, originating in the gallbladder (n=3), urinary bladder (n=1), and uterine cervix (n=1). The patients ranged from 52-89 years old. Histologic types were pure SmCC in 4 and combined urothelial carcinoma/SmCC in 1. Synaptophysin was positive in 4 (80%) cases, ranging from strong/diffuse to weak/focal. INSM-1 was positive in both cases with available results (focal/weak and diffuse/moderate in one each). Chromogranin A and TTF-1 were negative. In other tumour types tested, POU2F3 stain was mostly negative, except focal staining in 1 ductal carcinoma in situ of breast (3.4%), 2 gastric adenocarcinomas (1.2%), and 1 invasive carcinoma of breast (0.7%).
Conclusion: Aside from pulmonary SmCC, POU2F3 expression was also found in a minority of extrapulmonary SmCC. Although the case number was small, our data suggested a potential predilection of gallbladder location and a wide range of synaptophysin and INSM1 expressions. Among different tumour types, POU2F3 is relatively specific to SmCC and may serve as a valuable addition to the diagnostic panel for SmCC. Further study is needed to investigate the prognostic and therapeutic significance of POU2F3 expression in extrapulmonary SmCC.

PS-24-007

Influence of tobacco cigarettes on the oral mucosa

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Background & objectives: Despite well-documented adverse effects of tobacco consumption, mechanism of its influence on oral mucosa is not clear. The objective of the performed research was to assess the effect of smoking on the morphofunctional state of periodontal tissues in young animals.
Methods: 30 ten-week-old WAG rats were randomly distributed in two groups, as follows: control animals and tobacco exposed. Smoking was generated using the Boyarchuck chamber operated in a one-pass mode with the smoking feed controlled externally by a metering pump. Morphologic study with morphometry was performed.
Results: Morphological study of oral mucosa was carried out after removing the animals from the experiment on the 90th day. The study of histological specimens of the experimental group showed moderate hyperkeratosis of the epithelium. Own plate was found with acanthotic cords with increased number of fibroblasts, single leukocytes, sclerosis of the reticular layer. The vessels of microcirculatory bed have been characterized by uneven blood filling with background of isolate vessels that have fallen lumens and presence of blood-empty arterioles and capillaries with signs of constriction. Endotheliocytes are flattened with signs of desquamation in focus of ischemia in slides stained according to Rego.
Conclusion: Morphometric study proves reducing vascular density from 19,44±1,97% to 10,01±1,33 %, increasing area of connective tissue from 18,33±2,71% to 29,54±1,87%, spreading area of tissue with ischemia from 1,14±0,70% to 7,44±1,60%. Morphofunctional changes in the periodontium with damage to the structure of the epithelial membrane and changes in its permeability, microcirculatory disorders, sclerotic changes are a manifestation of the initial inflammatory and dystrophic processes that can lead to persistent chronic process in oral mucosa.
Funding: This study is the part of scientific research work "Optimization of early diagnosis, prevention and treatment of oral tissue diseases with smoking addiction", № 0120U102057, Kharkiv National Medical University, and is funded by Ministry of Health of Ukraine.

PS-24-008

Prevalence of vessels encapsulating tumour clusters (VETC) in human cancers

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Background & objectives: VETC shields tumour-cell clusters, promoting free circulation in the bloodstream. This mechanism of metastasization is an alternative to the epithelial-to-mesenchymal transition process, and has been recently described in hepatocellular carcinoma (HCC), however the prevalence of VETC among cancers is unknown.
Methods: We assessed the VETC prevalence on a retrospective series of 1861 neoplastic samples from 1796 patients comprising 24 different histologies. VETC was defined as continuous endothelial covering of neoplastic clusters and highlighted by CD34 immunohistochemistry. Analysis was performed on a tissue microarray by experienced pathologists blinded to clinical and pathological data.
Results: VETC was present in 73/1769 cases (4%) and in 10/23 histotypes (44%). The histotypes that had VETC+ cases were renal cancer (RCC) 29/115 (25%), HCC 23/102 (23%), prostate cancer (PRC) 7/42 (17%), mesotheliomas 2/17 (12%), pancreatic cancer 4/84 (5%), oesophageal cancer 2/72 (3%), and gastric cancer 3/158 (2%). Colorectal, extrahepatic bile duct, and urinary bladder cancer had one VETC+ case each. Cases with VETC+ tended to be associated to the intermediate histologic grade (G2; $p<0.0001$). Age, size, survival, and status were similar between the two groups.
Conclusion: VETC is present across different histotypes and might represent an alternative mechanism of metastasis. Even if present in a minority of cases, VETC was peculiar of some histotypes (especially HCC, RCC, PRC), possibly representing a histotype-specific angiogenetic mechanism. Since VETC predicts response to tyrosine kinase inhibitors, further studies are warranted to assess the prognostic and predictive value of this peculiar vascularization type.

PS-24-009

FABP1 expression in human tumours: a tissue microarray study on 17,071 tumours

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Background & objectives: Fatty acid binding protein 1 (FABP1) is a key protein for the metabolism of fatty acids. It is abundantly expressed in the liver (10%of cytosolic proteins). Because of its high tissue specificity, immunohistochemical FABP1 is thought to have diagnostic utility.
Methods: A set of tissue microarrays containing 17,071 samples from 150 different tumour types and subtypes as well as 608 samples of 76 different normal tissue types was analysed by immunohistochemistry, to comprehensively determine the patterns of FABP1 expression in normal and neoplastic tissues.
Results: Among normal tissues, strong FABP1 immunostaining occurred in hepatocytes, proximal tubuli of the kidney and in epithelial cells of the small intestine, appendix, and the colorectum. FABP1 positivity was found in 24 of 150 tumour categories, including 17 with ≥1 strongly positive case. The highest FABP1 positivity rates were seen in colorectal adenomas (86%), colorectal adenocarcinomas (71.1%) and in hepatocellular carcinomas (65.3%), followed by mucinous carcinoma of the ovary (34.6%), cholangiocarcinoma (21.6%), and various adenocarcinomas from the digestive tract (10-23%). In colorectal cancer, reduced FABP1 expression was linked to microsatellite instability, right-sided tumour location ($p<0.0001$ each), and absence of BRAF V600E mutations ($p=0.001$), but unrelated to pT and pN status.
Conclusion: FABP1 immunostaining has considerably high tumour specificity. As FABP1 expression is virtually absent in adenocarcinomas of the lung, FABP1 immunohistochemistry might be particularly helpful to assist in the identification of metastatic adenocarcinoma to the lung.

PS-24-010

The impact of display variability in digital pathology

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Background & objectives: Digital visualization should enable accurate clinical diagnosis in line with conventional pathology. Therefore, the display plays a crucial role. In this research project we evaluate

various medical displays and quantify their impact on the visual reproducibility of significant clinical structures.
Methods: Using display simulation models, we quantify the impact of modern medical displays on the visualization of whole slide images (WSIs). We included H&E and IHC-stained slides from 400 patients, originating from different laboratories which were digitized with scanners from various vendors. In addition to overall statistics, the perceptual contrast for certain histological structures is measured and compared for various displays.
Results: Using the ΔE method, we found that different displays may introduce a significant difference in perceptual contrast of certain histological structures by up to 2.7ΔE. This effect can further deteriorate over time, due to a decrease in display luminance. This observation advocates the need for continuous display calibration and adequate quality assurance mechanisms. Some medical grade displays for pathology incorporate such quality assurance automatically by factoring in the ambient lighting conditions and optimizing visibility of subtle colour differences. This can increase the contrast of histological features such as nuclei characteristics by at least additional 0.9 ΔE.
Conclusion: In radiology, display systems have been extensively studied, resulting in standardization, clear requirements, and guidelines. However, image data, viewing modalities and ambient conditions in digital pathology differ greatly from radiology. Therefore, independent investigations must be conducted here. The presented experiments illustrate the variability between displays and the perceived image characteristics for specific histological features in order to translate generic display specifications into clinical implications.

PS-25 | Poster Session Pathology in Favour of Developing Countries

PS-25-001
Postmortem ultrasound estimation of foetal gestational age by transcerebellar diameter and cerebellar vermis height

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Background & objectives: Adequate data on gestational age at perinatal autopsy is usually non available in many low-income countries. We aimed to evaluate the usefulness of post-mortem ultrasound measurement of trans-cerebellar diameter and height of cerebellar vermis for gestational age determination.
Methods: Gestational age, intrauterine growth parameters and ultrasound reports were retrieved for all consecutive perinatal autopsy cases from July 2020 to April 2022. A total of 70 cases (68 stillbirths and 2 neonates) with no intrauterine growth restriction or ultrasound brain abnormalities were enrolled. All measurements were performed through the anterior fontanelle. The Pearson correlation coefficient (r) and p-values were calculated.
Results: Mean (SD) gestational age was 22.7 weeks (4.5). Most of stillborn deaths (54; 80%) were due to legal abortion. Other intrauterine deaths (14; 20%) comprised chorioamnionitis (42%), intrauterine hypoxia (42%) and unknown causes (16%). The two neonatal deaths were due to prematurity complications. Trans-cerebellar diameter was measured in all 70 cases (100%) and height of cerebellar vermis in 60/70 cases (85.7%). Trans-cerebellar diameter ranged from 18.5 mm at 17.5 weeks to 56.2 at 40.6 weeks. Height of cerebellar vermis ranged from 8 mm (at 17.5 weeks) to 30.6 at 40.6 weeks. Both trans-cerebellar diameter and height of cerebellar vermis correlated significantly with gestational age ($r=0.84$; $p<0.0001$ and $r=0.87$; $p<0.0001$, respectively).
Conclusion: Post-mortem ultrasound measurements of trans-cerebellar diameter and height of cerebellar vermis could be useful in low-resource settings for obtaining gestational age data. Both measurements can be rapidly conducted with portable ultrasound device. These data are especially useful when evaluating results of minimally invasive tissue sampling (MITS), a procedure based on core needle biopsies, which use is currently expanding in countries of Sub-Saharan Africa and South-East Asia.
Funding: These results are part of the project "Anthropometric parameters and biomarkers for identification of prematurity and pre-eclampsia as causes of perinatal mortality" managed by Barcelona Institute for Global Health (ISGlobal) and funded by Bill & Melinda Gates Foundation (OPP1196642)

PS-26 | Poster Session Uropathology

PS-26-001
The morphological spectrum and molecular features of somatic malignant transformation in germ cell tumours

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Background & objectives: Somatic malignant transformation (SMT) arising in germ cell tumours (GCTs) is an infrequent, but clinically relevant event. There is only limited knowledge on the morphological spectrum of SMT, and therapeutic management of these patients is poorly defined.
Methods: In this work we revisit two consecutive case series (n=756) of GCTs diagnosed at University Hospital Zurich, Switzerland and IPO Porto, Portugal. Clinicopathological data of SMT arising in GCT were determined, with focus on the histopathological spectrum, and molecular aspects were obtained by Fluorescence in situ Hybridization (FISH) and Next Generation Sequencing (NGS).
Results: 30 male patients (28 testicular, 2 extragonadal) were included (representing 4% of GCT patients diagnosed in both institutes). The most common SMT were adenocarcinoma (n=8), embryonic-type neuroectodermal tumours (ENETs, n=8) and rhabdomyosarcoma (n=6), but a wide range of challenging morphologies were depicted, including low-grade neuroglial tumour, adenosquamous carcinoma, neuroblastoma and neuroendocrine carcinoma. SMT was found in 15 primary tumours and in 27 metastases of these 30 patients, the latter showing poorer overall-survival. Adenocarcinoma occurred in metastases post-chemotherapy, but not in the testis. 12p gains were identified in all cases. NGS results were available in 6 patients. Clinical trials/targeted treatments based on the molecular profile were recommended in 4 patients.
Conclusion: SMT arising in GCTs represents a diagnostic challenge and should be confirmed by a specialized uropathologist. NGS based treatment recommendations may improve outcome of these patients.
Funding: JL is recipient of fellowships from FCT – Fundação para a Ciência e Tecnologia (PTDC/MEC-URO/ 29043/2017 and SFRH/BD/132751/2017). JL would like to acknowledge the support of MSD ("Prémio de Investigação em Saúde"), Banco Carregosa / Secção Regional do Norte da Ordem dos Médicos (SRNOM) and Fundação Rui Osório de Castro / Millennium bcp.

PS-26-002
Eosinophilic solid and cystic renal cell carcinoma and renal cell carcinomas with TFEB alterations: a comparative study

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Background & objectives: Eosinophilic solid and cystic renal cell carcinoma (ESC RCC) shows frequent CK20 positivity and TSC mutations. In contrast, frequency of CK20 expression and presence of TSC mutations are unclear in TFEB-amplified RCC and TFEB-translocated RCC, which frequently express Melan A.
Methods: Herein, we compare 6 ESC RCC with 4 TFEB-amplified/translocated RCC. We assess the frequency of CK20 and Melan A expression by immunohistochemistry, and of TSC mutations by next generation sequencing. TFEB alterations were confirmed by fluorescence in situ hybridization (FISH).
Results: All tumours showed voluminous eosinophilic cells with granular cytoplasm, prominent nucleoli, and most showed admixture of solid and cystic areas. CK20 expression was found in all 6 ESC RCC and in all RCCs with TFEB alterations. Melan A positivity was identified in 5/6 ESC RCC and 4/4 RCC with TFEB alterations. We found TSC mutations in 2 ESC RCCs, including in one case also harbouring a CIC fusion, unreported to date. However, we also identified a TSC mutation in one TFEB-amplified RCC.
Conclusion: ESC RCC represents an emerging renal tumour entity with some histological, immunohistochemical and molecular overlap to TFEB-amplified/translocated RCC. FISH for TFEB aids in this differential diagnosis in challenging cases.
Funding: JL is recipient of a fellowship from FCT – Fundação para a Ciência e Tecnologia (SFRH/BD/132751/2017). H.M. receives a Swiss National Science Foundation grant (No. S-87701-03-01).

PS-26-003
Reliability of histological subtyping of penile squamous cell carcinoma in assessing HPV tumour status
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Background & objectives: HPV-positive penile tumours have been associated with higher survival rates. However, HPV analysis is unavailable in many low-income countries. We investigated if histological assessment of penile squamous cell carcinoma subtypes can replace HPV testing in determining HPV-related/non-HPV-related tumour status.
Methods: We reviewed paraffin-embedded tumour tissue from 345 penile cancer patients, surgically treated between 2009 and 2018 at Örebro University Hospital, Sweden. The histological subtype of squamous cell carcinoma was assessed according to the WHO criteria and ISUP recommendations. HPV-DNA genotyping was performed using the PCR method Anyplex II HPV28. Concordance was assessed by calculating Cohen's kappa (κ).
Results: A good concordance was found between histological subtype of squamous cell carcinoma and HPV tumour-status with a Cohen's kappa (κ) of 0,72 corresponding to 86,6% agreement. Of the 46 discordant cases, five had HPV-related histology (mixed subtypes) but were HPV-negative. The remaining 41 cases had non-HPV- related histology (85% usual subtype, 15% mixed subtypes) but were HPV-positive. Noteworthy is that in 21 of the cases with non-HPV-related histology, foci of undifferentiated PeIN was found. In addition, four cases with both undifferentiated PeIN and lichen sclerosus et atrophicus in the tumour margin, 14 cases with both differentiated PeIN and lichen sclerosus et atrophicus and two cases without preneoplastic lesion were identified.
Conclusion: Good concordance between histological subtype of penile squamous cell carcinoma and HPV genotyping shows that when necessary, histological assessment is a good alternative, at least in less resourceful settings, to PCR-based HPV analysis in determining if penile tumours are HPV or non-HPV-related. Discordant cases most likely depend on subjectivity in histological assessment but can also suggest a HPV infection in a non-HPV-related tumour.

PS-26-004
Benign clear cell clusters in non-tumoral nephrectomy specimens
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Background & objectives: Clear cell clusters (CCCs) constitute a benign change occasionally found in the kidney (Virchows Arch. 2021;479:57-67). They must be recognised to avoid a misdiagnosis of renal carcinoma. Etiopathogenesis of CCCs and their frequency in atrophic kidneys are not known.
Methods: 157 consecutive non-tumoral nephrectomy surgical specimens were retrospectively reviewed. Immunohistochemical stainings were performed using an enzyme-conjugated multimer complex (OptiView DAB Detection Kit, Ventana) in an automatic stainer (Benchmarck Ultra). Heat antigen retrieval was done in the automatic stainer. Electron microscopy studies were performed on FFPE tissue. Ultrathin sections were examined with a Philips CM100 electron microscope.
Results: Six cases (3,82%) showed CCCs. This change was multifocal and found in 100% of the samples of five cases and in 83% of the slides of the other one. They were in the renal cortex, predominantly in a subcapsular location. CCCs were composed by large cells with clear/foamy cytoplasm, forming predominantly solid nests, as well as occasional tubules with narrow lumina. Adjacent renal parenchyma showed interstitial fibrosis with tubular atrophy, glomerulosclerosis, and sclerosis of vessel walls. CCCs were CK7, Ksp-cadherin and EMA positive, and negative for RCC marker and AMACR with focal immunoreactivity for CD10. Ultrastructurally, cytoplasms were filled of disrupted organellas with mitochondrial and endoplasmic reticulum ballooning degeneration.
Conclusion: CCCs are rare in nonfunctioning / atrophic kidneys (<5%). It is a multifocal change in the cortex, often subcapsular. Ultrastructural appearance suggests that they are caused by intracellular oedema of tubular cells with disruption of organellas. CCCs show a distal tubule immunophenotype except focal positivity for CD10. The absence of atypia, the subcapsular location and the coexistence of atrophy / ischemic changes help to the diagnosis.

PS-26-006
B7-H3 immune checkpoint molecule in prostate cancer
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Background & objectives: B7-H3 is a newly discovered member of the B7 family of immune checkpoint molecules with both immune and non-immune functions. We investigated the relationship of B7-H3 to the tumour microenvironment as well as its non-immune functions in prostate cancer (PCa).
Methods: We developed a discovery tissue microarray from 94 PCa patients who underwent radical prostatectomy with curative intent. This was stained manually with B7-H3 and correlated to

patient clinicopathological parameters. Also, functional studies of growth, apoptosis, migration and invasion were conducted on PCa human cell lines with transient and permanent silencing of the B7-H3 protein.
Results: High B7-H3 expression correlated with worse clinicopathological patient features in intermediate and high risk PCa patients, including higher T stage ($p<0.0001$), perineural invasion ($p=0.01$) and lymph node spread ($p=0.0006$). Loss of B7-H3 expression did not affect prostate cancer cell growth or apoptosis in vitro. In contrast, there was significant decrease in migration and invasion with scratch wound assays, transwell migration assays and inverted transwell migration assays in vitro following suppressed B7-H3 expression in multiple human prostate cancer cell lines. RNA sequencing identified extracellular space chemotactic cytokines and their receptors, such as CCL2, CXCL1, CXCL8, CXCL6 and CXCL16 to be highly downregulated genes in PC3M cells with B7-H3 knocked out.
Conclusion: B7-H3 protein is overexpressed in PCa making it a promising target for immunotherapies. Examining human tissue samples, we showed an association of B7-H3 expression and aggressive clinical features, including lymph node spread. In vitro experiments with acute and chronic loss of B7-H3 revealed an effect on migration and invasion. Future experiments are required to investigate the mechanistic downstream pathways of this phenotype and further evaluate the role of B7-H3 in metastasis in vivo.
Funding: Cancer research UK

PS-26-007
GATA-3 is a useful immunohistochemical marker to identify periprostatic paraganglia
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Background & objectives: Periprostatic paraganglia (PP) can be a pitfall leading to a misdiagnosis of prostatic carcinoma.
Most of paragangliomas and pheochromocytomas are positive for GATA-3. To the best of our knowledge this fact has not been studied in normal PP.
Methods: Radical prostatectomy surgical specimens in which PP were observed with hematoxylin-eosin were selected for the study. Formalin-fixed paraffin-embedded sections were immunostained with a GATA-3 monoclonal antibody (clone L50-823) using an enzyme-conjugated multimer complex (OptiView DAB Detection Kit®, Ventana Medical Systems, Illkirch, France) in an automatic stainer (Benchmark Ultra®). Heat antigen retrieval was done in the automatic stainer.
Results: Thirteen PP were found in twelve radical prostatectomies (8,1% of the total of the surgical specimens). PP ranged in size from 190 to 1140 µm, with a median dimension of 499,38 µm. They were located within the adipose periprostatic tissue in the middle region (10 cases, of which 8 were in the posterolateral area and 2 were anterior); two at the base and one at the apex. 6 PP were on the right and 5 on the left side; one in the middle line and one was unknown. There was available tissue for immunohistochemistry in 10 cases, all of which showed intense and diffuse nuclear staining for GATA-3.
Conclusion: PP have been found in radical prostatectomy specimens with a frequency similar to previously reported (around 8% of the cases). They are located in the periprostatic tissue, predominantly in the middle region and the posterolateral aspect of the prostate. A frequent clear cytoplasmic appearance of PP cells can lead to a misdiagnosis of prostate adenocarcinoma. GATA-3 is a useful immunohistochemical marker for the differential diagnosis as it is strongly positive in PP.

PS-26-008
Prognostic value of tumour budding in urinary tract cancer: a meta-analysis
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Background & objectives: Recently, tumour budding (TB) has been suggested as a strong prognostic marker in urinary tract cancer. The aim of this systematic review is to test the prognostic value of TB in urothelial cancer by a meta-analysis of previously published studies.
Methods: We systematically reviewed the literature related to TB by using the databases of PubMed and Web of Science. The search was limited to publications in the English language up to and including December 2021.
Results: There were 790 patients from 8 retrospective studies in which TB has been evaluated in urinary tract cancer. The meta-analysis of eligible studies revealed that TB is a significant prognosticator for progression free survival, with a risk ratio (RR) of 3.50 (95% confidence interval (CI) 2.01– 6.08; $P < 0.001$) in univariate analysis, and with a RR of 2.81 (95% CI 1.75–4.51; $P < 0.001$) in multivariate analysis; a significant prognosticator overall survival, with a risk ratio (RR) of 2.80 (95% CI 1.96– 3.99; $P < 0.001$) in univariate analysis, and with an RR of 1.02 (95% CI 1.01–1.03; $P < 0.001$) in multivariate analysis.
Conclusion: We conclude that a high TB score is a promising prognostic marker of poor survival in urinary tract cancer. Because of its simplicity and high predictive power, TB is strongly recommended to be included in the routine pathology report of urinary tract cancer.

PS-26-009
Enhanced TOLLIP expression confers poor prognosis in renal cell carcinoma
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Background & objectives: Renal cell carcinoma (RCC) is a malignancy that in advanced disease, is exceptionally resistant to systemic therapies. TOLLIP protein is a regulator of immune responses. We explored the relationships between the clinical course of RCC and TOLLIP protein expression.
Methods: The tissue microarray (TMA) cohort contained 95 cores of primary tumour, matched metastases and matched adjacent tissues derived from 32 RCC patients. The mean follow-up was 105 months. Immunohistochemical analysis of TOLLIP was performed on all tissue samples. TOLLIP expression was evaluated using the H-score and then analysed with patients' clinical data.
Results: All the examined samples showed cytoplasmic TOLLIP expression with the median value of 100 in primary tumours, 107.5 in metastases, and 220 in the control group. The expression was significantly higher in the normal adjacent tissues compared to

primary or metastatic RCC ($p < 0.05$). We observed moderate positive correlation between expressions of TOLLIP in the primary tumour and its metastases ($p < 0.05$; k=0.48). Elevated TOLLIP expression correlated with worse overall survival (OS) (median OS, 64 vs. 101 months, $p < 0.05$).
Conclusion: High TOLLIP expression predicts poor prognosis in RCC patients. The enhancement of TOLLIP expression probably occurs in the early stages of RCC, before the development of metastatic competence. While TOLLIP reduces immune surveillance and increases autophagy, our results suggest that it could drive the escape phase of immunoediting and compromise both immuno and targeted therapy.
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PS-26-010
Role of epithelial-mesenchymal transition in clear cell renal cell carcinoma
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Background & objectives: Epithelial-mesenchymal transition (EMT) is believed to be the key process in development and progression of cancer, including renal cell carcinoma (RCC), with miR-200 family and miR-205 being key regulators. The exact role of EMT in RCC is not fully understood.
Methods: We analysed the expression of miR-200 family and miR-205 and their targets, ZEB1 and ZEB2, using qPCR and ZEB2 using IHC. Twenty cases (in total 50 samples) of formalin-fixed paraffin-embedded tissue were included, 10 RCC without and 10 with sarcomatoid differentiation (RCC-Sa). In RCC-Sa, sarcomatoid and clear cell component were investigated separately. Microscopically normal renal tissue was used as control.
Results: Interestingly, miR-200 family and miR-205 were downregulated (hallmark of EMT) in both, clear cell component and sarcomatoid differentiation of RCC-Sa when compared to corresponding normal renal tissue. Moreover, they were downregulated even in clear cell component of RCC without sarcomatoid differentiation. Their target genes transcription factors (TFs) of EMT also showed interesting expression: ZEB1 was not expressed, whereas ZEB2 showed variable pattern of expression, being either up- or down-regulated when compared to normal renal tissue irrespective of analysed component. Results of IHC support this information.
Conclusion: Our result on miR-200 family and miR-205 expression suggest that EMT is involved not only in development of RCC-Sa but also in development of RCC. However, their target genes, ZEB1 and ZEB2 seems to have minor role in this process. Our results further confirm that although ZEB1 and ZEB2 are highly related, they may have opposing effects and expression patterns in tumour biology. miR-200 family and miR-205 are probably involved in EMT regulation trough other targeted EMT-TFs.
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PS-26-011
Spontaneous regression - scars of testicular germ cell tumours: association with clinicopathological features - institutional experience
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Background & objectives: Scars in testicular parenchyma as a histological element of GCT spontaneous regression is a rare but well-recognized phenomenon. We analysed the presence and frequency of complete or partial/focal scarring of GCT and their association with clinicopathological features of GCT.
Methods: A surgical pathology archive between 2007 and 2022 has been searched for cases of GCT that had reported in the final diagnosis partial/focal or complete scarring of GCT. The association of scars and following clinicopathological features (patients' age, tumour size, GCT type, lymphovascular invasion, tumour stage, germ cell neoplasia in situ (GCNIS), peritumoral atrophy, and microlithiasis) were analysed.
Results: A total of 322 patients underwent radical inguinal orchiectomy for GCT. Complete GCT regression was reported in 6 cases (1.86%). In 3 of these 6 cases, metastases of mixed GCT were present, whereas GCNIS was diagnosed in 5 cases. Of a total of 316 GCTs, those with partial/focal scars were diagnosed in 68 cases (21.52%). GCTs without scars were diagnosed in 248 (78.48%) cases. Statistical significance in the occurrence of scars in GCT was found in older patients (34.0 ± 8.2 vs 31.0 ± 8.0 without scar; $p=0.001$) and in the seminomatous GCTs in comparison with mixed GCTs ($p=0.027$). Other clinicopathological features were not statistically related to the focal presence of the scar.
Conclusion: Complete GCT regression is a rare event that occurs in GCTs and it is associated with the presence of metastasis and/or associated with the presence of GCNIS at the time of testicular surgery. Partial/focal regression - scarring of GCT is not uncommon. The meaning of focal scars in GCTs is unknown, but in the present study, it looks like it does not have any significant clinical meaning, namely to the lack of their association with the tumour stage.

PS-26-012
Human epidermal growth factor receptor 2 (HER2) expression in urothelial carcinomas of the bladder
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Background & objectives: HER2 is highly expressed in multiple malignancies and associated with patients' prognosis, but its role in urothelial carcinomas remains elusive. To evaluate Her2 expression in urothelial non-muscle-invasive(NMIUC) and muscle-invasive bladder carcinomas(MIUC) by immunohistochemistry (IHC) and gene amplification by insitu hybridization.
Methods: This study involved total of 89 cases (39 muscle-invasive urothelial carcinomas and 50 non-muscle-invasive urothelial carcinomas). Histopathological grading was done as per WHO 2022. All cases were subjected to IHC by HER2 and all equivocal (2+) cases were subjected to FISH using HER2/CEN17 dual colour probe. IHC and FISH analyses were scored per 2018 updated ASCO/CAP recommendations for breast carcinomas
Results: Her2 overexpression (3+) was seen in 11 of 50 NMIUC cases (22%) and 7 of 39 MIUC cases (17.9%). 3 cases of MIUC and 2 of NMIUC showed equivocal (2+) positivity by IHC and were subjected to FISH analyses. None of these cases showed amplification on the dual-probe assay. There was no association between gender of patients and HER2 protein expression. HER2 positivity was associated with a higher tumour grade irrespective of deep muscle invasion. No significant correlation between HER2 expression and lymph node status was found.
Conclusion: The present study shows overexpression of HE2 in high-grade urothelial carcinomas both muscle-invasive and non-muscle-invasive urothelial carcinomas' indicating it has the potential to become an ideal target for bladder cancer therapy. However,

more gene amplification studies are required to be done in the cases showing positive expression (3+) of HER2 for choosing potential candidates for HER2- targeted therapy.

PS-26-013

Two cases of primary intratesticular rhabdomyosarcoma

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Background & objectives: Intratesticular Rhabdomyosarcoma is a rare malignant tumour showing skeletal muscle differentiation.
The importance of this paper is to emphasize the importance of macroscopic examination in confirming intratesticular location and to highlight the importance of Immunohistochemical study for the diagnosis.
Methods: 16 and 18 years old patients, with no medico-surgical or trauma history, consulted for painless scrotal mass gradually increasing in size. Scrotal ultrasound revealed, in both patients, suspect intratesticular mass. So, they underwent inguinal orchidectomy. Pathology results were consistent with the diagnosis of intratesticular embryonal rhabdomyosarcoma grade III of FNCLCC. Thereafter, the two patients received chemotherapy.
Results: Rhabdomyosarcoma is a malignant mesenchymal tumour showing skeletal muscle differentiation. Four types have been described in the 5th edition of WHO classifications of soft tissue and bone tumours. The most common histological subtype is Embryonnal-rhabdomyosarcoma. Primary intratesticular localization is very rare and must be differentiated from paratesticular locations. This distinction must be made during the per-operative period and while the macroscopic examination of the surgical specimen. The Immunohistochemical study is essential for diagnosis and to exclude other intratesticular spindle cell sarcomas and germ cell tumours. The optimal treatment is based on radical inguinal orchiectomy and adjuvant chemotherapy. Tumour size, age, histological type and lymph node involvement are important risk factors.
Conclusion: Rhabdomyosarcoma is a highly aggressive neoplasm occurring frequently in children and young adults. Intra-testicular localization remains exceptional and very few cases have been reported in the literature. Diagnosis of ITRMS is based on anatomopathological examination. Surgery and chemotherapy remain the mainstay of treatment. Radiotherapy is useful for local recurrence and metastasis.

PS-26-015

Intraductal carcinoma of the prostate in low-risk patients does not affect PSA failure and treatment decisions

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Background & objectives: Intraductal ductal carcinoma of the prostate (IDCP) is an independent poor prognostic factor for prostate cancer (PC) and known to be associated with adverse features. However, its significance in low-risk patients is poorly understood and was investigated in this study.
Methods: 866 cases of radical prostatectomy were performed between 2012 and 2021, of which 116 cases were low-risk PC preoperatively according to the EAU guidelines. Of these, 112 patients were enrolled, excluding 4 cases who received preoperative hormone therapy. Evaluation factors were clinicopathological characteristics of patients, and PSA free survival. The evaluation of IDCP and various pathological factors followed WHO.
Results: Of 112 patients, 12 (10.7%) had IDCP. PSA failure was observed in 4 of 112 patients (IDCP-: 3, IDCP+: 1). There were no significant differences in age, PSA and PSAD between patients with and without IDCP (age: p=0.432, PSA: p=0.7, PSAD: p=0.84). The occurrence of extraprostatic extension (EPE) and radial margin (RM), factors influencing treatment decisions, also did not differ between the two groups (EPE: p=0.172, RM: p=0.171). PSA free survival with and without IDCP demonstrated no significant differences (log-rank test: p=0.475).
Conclusion: Low-risk patients were found to have a better prognosis even when IDCP was detected in surgical specimens. In the low-risk group, IDCP may not affect PSA free survival. In addition, IDCP does not influence treatment decisions, as there is no difference in the incidence of EPE or RM with or without IDCP. These results also reaffirm the utility of active surveillance. The incidental finding of IDCP in low-risk patients is nothing to fear.

PS-26-016

Papillary renal cell carcinoma (PRCC): a single institution archive review of morphological variability in the light of the new WHO 2022 classification

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Background & objectives: The diagnostic approach to PRCC has changed substantially following the release of the new WHO Classification 2022 and the type 1 and 2 subtyping is no longer recommended. Herein, we map the variability of PRCC in a single institution archive.
Methods: We reviewed all reports of PRCC cases from a tertiary healthcare institution from a 10-year period [2012-2021], totalling 616 cases. Morphologic parameters, TNM stage, WHO/ISUP nuclear grade, immunohistochemical profile, and molecular study results were re-evaluated according to new WHO criteria. If available, patient's sex and age; tumour laterality, multifocality, size, presence of necrosis, and invasion of stage-defining structures were recorded.
Results: The most common subtype was PRCC NOS (39.9%), followed by classic PRCC (previously type 1) [35.9%], oncocytic (12.3%), biphasic squamoid (6.0%), mucin-producing (3.2%), solid (1.1%), reverse polarity (0.6%) and Warthin-like (0.8%). The mean patient age was 63 years and the male to female ratio was 2.6. Average tumour size was 49 mm. Overall, PRCC presented at an early stage in 79.3% of cases and out of the advanced stage cases, 77.6% were classified as PRCC NOS. Cytokeratin 7 was consistently expressed in most types, at times focally, with the exception of Oncocytic and NOS types which were negative in 29.4% and 44.2% of cases, respectively.
Conclusion: PRCC remains a highly heterogeneous group of renal tumours that will benefit from further studies aimed at subclassification and validation of clinical utility, as well as well-defined criteria. Just as important, PRCC's variability makes it a common mimic of other renal cell carcinomas (RCC), namely molecularly defined RCC (FH- or SDH-deficient and ALK- or TFE3-rearranged RCC), collecting duct carcinoma, oncocytic renal neoplasms and mucinous tubular and spindle cell carcinoma. Adequate immunohistochemical and/or molecular studies should resolve most diagnostic doubts.

PS-26-017

Pathological characterisation of Bosniak III and IV renal cysts

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Background & objectives: Complex renal cysts are a diagnostic challenge for radiologists and urologists. Bosniak classification uses imaging features to establish the malignant potential of these lesions. Our objective is to describe the pathological findings of Bosniak III and IV cysts.
Methods: We retrospectively reviewed the Bosniak III and IV lesions that were surgically resected at our institution between 2018 and 2021. Two genitourinary pathologists analysed the gross pictures and microscopic slides of the surgical specimens. We also searched our database to find the incidence of the different renal tumours in 2021 and compare it with the diagnosis of complex cysts.
Results: 27 lesions in 26 patients 14 males and 12 females, median age 60 years (41-77). Median size was 26 mm (12-70). 8(30%) were Bosniak III, 19(70%) Bosniak IV. 19 (70%) were malignant and 8 (30%) benign lesions. 79% of Bosniak IV and 50% of Bosniak III were malignant. 7(26%) lesions were solid, 14(52%) solid-cystic and 6(22%) cystic. 86% (6/7) of the solid and 17 % (1/6) of the cystic nodules were malignant. When <20mm, malignant lesions were encapsulated (5/5). 42% (8/19) were papillary carcinomas while these carcinomas represent 17% of our renal tumours. Benign lesions were 3 cystic nephromas, 2 simple cysts, 1 haemangioma, 1 pseudoinflammatory tumour and 1 oncocytoma.
Conclusion: Our results show a high incidence of papillary renal cell carcinoma in complex renal cysts compared to the incidence in overall malignant renal lesions. In lesions <20 mm the presence of a capsule is highly suspicious of malignancy. The Bosniak classification is useful to determine the malignancy probability of complex renal cysts. However, it still has numerous pitfalls, so we'll need more radio-pathological correlation studies in the future.

PS-26-018
P53 overexpression in prostate carcinoma
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Background & objectives: Somatic TP53 mutations are found in up to 20% of patients with localised prostate cancer and have been associated to disease aggressiveness and progression. The aim of this study was to assess p53 overexpression in prostate carcinoma.
Methods: We have retrospectively collected 24cases of prostate carcinoma diagnosed in our pathology department between 2012-2022.We have evaluated the archival formalin-fixed, paraffin-embedded cases to detect abnormal p53nuclear protein accumulation using immunohistochemistry. For each cases, we assessed the percentage of positive cells and the intensity of staining comparing with normal adjacent prostate tissue. A cut-off of 50% of positive tumour cells was considered for p53 overexpression.
Results: Mean age of patients was 70years old. The gleason score was 6 in 4cases,7 in 9cases,8 in 4cases,9 in 4cases and 10 in one case. ISUP grade was 1 in 4 cases,2 in 5 cases,3 in 4 cases,4 in 4cases and 5 in 5cases.Perineural invasion was described in 4 cases. Positive staining for p53 was found in 19 cases, however in 12 cases, less than 5% of cells were positive. Overexpression of p53 was found in 16,7. Gleason score was high (>=8) in 3 cases and ISUP grade was high (>=3) in 4cases. All patients with p53 overexpression developed resistance to hormonal therapy and 2 patients passed away because of distant metastasis.
Conclusion: In the present study, high protein p53 levels of expression was found in 16,7% and patients with p53 overexpression are more likely to develop hormone therapy resistance and poor outcome. However, p53 could be a potential marker for target therapy in the future mainly.

PS-26-019
The potential of tumour microenvironment markers in the onset and progression of prostate cancer
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Background & objectives: The aim of the study was to study the potential of a selected panel of prostate tumour micro-environment markers to define molecular subgroups of prostate cancer and to predict progression of prostate cancer.
Methods: We included 60 cases (prostate adenocarcinoma, benign prostatic hyperplasia and atypical lesions). Cases of adenocarcinoma showed a Gleason score ranging from 7 to 10, with a group grade of 3, 4 and 5. Three categories of immunohistochemically markers were used: for cancer activating fibroblasts (CAFs: CD34, Alpha SMA, Caveolin), vascular markers (CD31) and steroid hormone receptor markers (AR, PR, ER).
Results: Hormone markers were expressed, to varying degrees, nuclear, epithelial and stromal cells, progesterone became nuclear positive only in stromal cells, while the expression of alpha SMA, Caveolin and CD 34 was quantified stromal, cytoplasmic and membrane. Statistically significant results were obtained for CD31, CD34 and progesterone.
Conclusion: The research highlights a promising prognostic potential for some of the evaluated markers, with an important role in their subsequent validation as biomarkers, and in developing new therapies based on their stratification into risk groups.
Funding: This work was supported by the PROMETEU project, in the framework of Ovidius University of Constanta biomedical grant competition, contract no. 6 / 20.10.2021.

PS-26-020
Defining the most concordant basal and luminal urothelial markers using transcriptomic data
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Background & objectives: Transcriptome expression profiles allow for prognostically significant stratification of urothelial carcinomas into basal and luminal subtypes. In this study, we used NanoString mRNA data to correlate with CK20, GATA-3, CD44 and CK5/6 immunohistochemistry to identify the most appropriate basal/luminal immunomarkers.
Methods: A triplicate core tissue microarray of muscle invasive urothelial carcinomas was stained with known luminal (GATA3, CK20) and basal (CK5/6, CD44) markers. A subset were profiled for signature luminal and basal genes using a 23-gene NanoString chip. The area under the curve (AUC), sensitivity and specificity for each stain was calculated using SPSS.
Results: 243 chemotherapy naïve cases were stained and 91 (37%) had transcriptomic profiling performed. Hierarchical clustering of the Nanostring data segregated cases into a luminal or basal category. CD44 positivity was significantly higher in CK5/6 positive vs. negative cases (81.5% vs. 22.4%, $p<0.001$) and in basal vs luminal (89.8% vs. 43%, $p< 0.001$). CK20 positive cases were significantly more prevalent in GATA3 positive vs. negative cases (35.4% vs. 2.8%, $p<0.001$) as well as in luminal vs basal (35.2% vs. 0%, $p < 0.001$). There was a significant ($p<0.001$) correlation between the RNA expression levels and IHC measurements for

GATA3, CK5/6, CD44 and CK20 (AUC 0.951, 0.959, 0.871 and 0.938, respectively).
Conclusion: All markers significantly correlated with the respective subtype assigned by transcriptomic analysis and with each other. For luminal carcinomas, the AUC for CK20 was lower (0.816, sensitivity/specificity: 67%/87%) than GATA3 (0.965, sensitivity/specificity: 86%/96%). Similarly, CD44 had a lower AUC for basal carcinomas (0.617, sensitivity/specificity: 57%/69%) than CK5/6 (0.852, sensitivity/specificity: 91%/70%). While the markers may be complementary, CK5/6 and GATA-3 have the best AUC and should be considered as "first-line" in assigning a surrogate luminal or basal subtype.

PS-26-021
Clinicopathologic assessment of MTAP status in muscle invasive urothelial carcinoma
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Background & objectives: Methylthioadenosine phosphorylase (MTAP) deficiency correlates with 9p21 loss and susceptibility to antifolate therapy, is frequent in metastatic urothelial carcinoma, but underexplored in the primary muscle invasive setting. We determined MTAP status and associated clinicopathologic features in a cystectomy cohort.
Methods: A triplicate core tissue microarray with 302 muscle invasive carcinomas (T2= 50, T3=62, T4=90) was stained for MTAP (Abnova, clone 2G4). Staining was interpreted as negative when carcinoma was completely negative with appropriate internal controls. MTAP status was correlated with patient data, molecular subtype, stage, underlying mutation status, prior therapy, overall (OS) and relapse free (RFS) survival using SPSS.
Results: MTAP loss occurred in 87/302 (28.8%). There was no correlation with T-stage, nodal status, patient sex or age. MTAP was retained in 99% of luminal genomically unstable subtype, 65% of basal subtype and 50% of luminal- Uro type carcinomas ($p<0.001$). MTAP loss was strongly correlated with FGFR3 mutations, and MTAP retention with TP53 mutations ($p=0.0062$). Cases with MTAP loss had shorter OS (14.7 months vs 23.3 months MTAP retained) and RFS (11.2 months vs 18.2 months MTAP retained), $p>0.05$. Within the luminal-Uro group, loss of MTAP predicted for reduced RFS ($p=0.031$) but not OS. All analyses were also performed excluding cases with neoadjuvant chemotherapy (n= 59) with similar results.
Conclusion: Loss of MTAP occurs in <30% of primary muscle invasive urothelial carcinomas. It does not associate with stage suggesting loss is acquired early in the disease. There were no statistically significant association with outcome parameters or neoadjuvant chemotherapy status. MTAP loss was associated with FGFR3 mutations. Within the luminal-Uro molecular subtype, MTAP loss defined a group with shorter RFS and assessment of MTAP may be most beneficial in this cohort.
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PS-26-022
Neuroendocrine carcinomas of the urinary bladder: a large case series of a rare entity
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Background & objectives: Urinary bladder (UB) is the extra-pulmonary and extra-digestive organ with the highest frequency of neuroendocrine neoplasms (NENs). The recognition of UB-NENs and their distinction from high grade non-neuroendocrine (HG nonNE) UB carcinomas represent a challenge in diagnostic practice.
Methods: With the aim of clarifying the clinicopathological features of UB-NENs and of establishing differential diagnostic criteria for their distinction from HG nonNE carcinomas, we retrospectively reviewed a series of 78 cases collected from three Italian Institutions and originally diagnosed as UB-NENs or HG carcinomas with NE markers expression. The latest diagnostic criteria proposed for NENs by WHO/IARC were strictly applied.
Results: The histopathological review identified 51 UB-NENs, including 23 neuroendocrine carcinomas (NECs) and 28 mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs). Presence of neuroendocrine morphology (architectural and cytological), intense and diffuse expression of one/two neuroendocrine markers, and absence of urothelium-related markers were used to separate NECs from HG nonNE carcinomas. MiNENs were diagnosed when two separate components were morphologically identified and immunohistochemically confirmed. Small cell morphology was more frequent than large cell one, both in pure and mixed neoplasms. PDL-1 expression was lower in UB-NENs than in HG nonNE carcinomas. Clinically, patients were old males with smoking habits; NECs showed poorer prognosis than HG nonNE carcinomas, significantly improved by treatment with neoadjuvant chemotherapy.
Conclusion: With this study, we were able to identify true UB-NENs and to distinguish them from HG nonNE carcinomas of the same site, clarifying the clinicopathological features of these rare entities. We highlight the prognostic impact of UB-NENs diagnosis, also when mixed with a nonNE component, which confers a very poor outcome to patients, improved by the administration of neoadjuvant chemotherapy. Although very preliminary, data on PDL1 expression suggest a therapeutic chance with immune checkpoint blockage also in these rare malignancies.

PS-26-023
Retrospective report-based review of kidney biopsies and resections with a focus on oncocytoma
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Background & objectives: Synoptic reporting combined with the automated categorization of free text reports (ACFTR) and pathologist review allows insight to practice patterns. This project examined kidney biopsies for mass lesion and kidney resections, and matched specimens by an anonymized patient identifier (API).
Methods: All non-medical kidney biopsies with and without resections accessioned 2011-2020 were retrieved from one referral centre, matched by API and categorized by diagnosis and diagnostic group (DxGrp) (malignant (MAL)/suspicious (SUSP)/insufficient (INS)/benign (BEN)). All recent biopsy report categorizations were reviewed/classified by pathologists. APIs were categorized into biopsy only (BxOnly) and biopsy+surgery(Bx+Sx). Biopsies and surgeries were tabulated by the most recent pathology.
Results: The data set contained 948 patients; these were 641 BxOnly and 307 Bx+Sx. BxOnly by DxGrp 374(MAL)/3(SUSP)/58(INS)/206(BEN); Bx+Sx(by Sx diagnosis) was: 293(MAL)/0(SUSP)/ 0(INS)/14(BEN). 84 patients had two biopsies, 9 had three and two had four; the INS rate for the preceding biopsies was: 24.2%, 27.3% and 0%. Oncocytoma(ONC) was seen in 109/948 patients. Four patients had a prior ONC biopsy diagnosis linked to surgery; on resection: two were oncocytoma,

two were unclassified renal cell carcinoma (RCC). Four additional patients had incidental ONC on biopsy and biopsy-unrelated surgery: surgery for contralateral RCC (1 patient), ONC biopsy after prior surgery for ONC (1 patient), ONC biopsies after surgery for RCC (2 patients).
Conclusion: The approach used allows a large amount of data to be analysed with limited effort. Oncocytoma on biopsy rarely goes to surgery in our environment. The findings support an approach that includes kidney biopsy for the management of renal masses, and allows selected patients to avoid surgery. Reliable pathologic classifications, combined with follow-up data, are essential for safe conservative patient management strategies.

PS-26-024
Synaptophysin, CD117, and GATA3 as a diagnostic immunohistochemical panel for small cell neuroendocrine carcinoma of the urinary tract
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Background & objectives: Although the diagnosis of small cell neuroendocrine carcinoma (SCNEC) is based on its characteristic histology, immunohistochemistry (IHC) is commonly employed to confirm neuroendocrine differentiation (NED). The challenge is that SCNEC may yield negative results for traditional neuroendocrine markers.
Methods: To establish an IHC panel that could detect even traditional marker-negative SCNEC of the urinary tract, 17 neuronal, basal, and luminal markers were examined on 47 SCNEC cases as a discovery cohort. A decision tree algorithm was employed to analyse the immunoreactivity. An external cohort of eight SCNEC cases and transmission electron microscopy (TEM) were used to validate the model.
Results: Among the 17 markers, the decision tree diagnostic model selected 3 markers to classify NED with 98.4% accuracy. The extent of synaptophysin (>5%) was selected as the initial parameter, the extent of CD117 (> 20%) as the second, and then the intensity of GATA3 (negative or weak immunoreactivity) as the third for NED. The importance of each variable was 0.758, 0.213, and 0.029, respectively. In all cases with ≤5% of synaptophysin-immunoreactive area in the discovery and external cohorts showed > 20% of CD117 expression and their NED status was confirmed by the demonstration of electron dense neurosecretory granules of the tumour cells by the TEM.
Conclusion: We propose a decision tree-based IHC model consisting of two inclusion markers synaptophysin and CD117 and one exclusion marker GATA3 for the diagnosis of SCNEC of the urinary tract. Since SCNEC is an aggressive tumour type and requires therapeutic approaches that differ from those used for urothelial carcinoma, an accurate diagnosis of SCNEC is critical and this model may help pathologists accurately diagnose SCNEC in daily practice.

PS-26-025
Molecular correlates of somatic-type malignancies arising in male germ cell tumours
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Background & objectives: A subset of male germ cell tumours (GCTs) with aggressive clinical behaviour shows overgrowth of components resembling extra-testicular malignancies (e.g. sarcomas, carcinomas). The molecular mechanism of somatic-type tumour transformation in GCT is incompletely understood.
Methods: Following IRB approval, FFPE tumour material was retrieved from archives of participating institutions. Targeted NGS using a 447 gene panel was performed on 36 somatic-type malignancies (SMs), 10 matched conventional GCTs, and 20 SYSTs. A subset of 9 SM cases underwent fusion panel RNA sequencing. DNA methylation profiling was performed on 9 SYSTs, 15 SMs and 10 matched conventional GCTs.
Results: The median age at SM diagnosis was 34 years. The most common histotypes of SM were sarcoma, ENT/PNET, and carcinoma in 61%, 28%, and 6% of cases, respectively. KRAS and TP53 mutations were each identified in 28% of SM cases. Evidence of i(12p) was seen in 89% of cases. 97% of cases showed complex copy number profiles. MDM2 amplifications were detected in 15% of cases. Matched conventional GCTs and SMs harboured similar mutational and copy number profiles. Fusion panel RNA sequencing detected no oncogenic gene fusions. Irrespective of histotype, SMs had similar DNA methylation profiles that were different from profiles of matched conventional GCTs.
Conclusion: SMs in GCTs are molecularly unrelated to their true somatic counterparts. Instead, they are characterized by complex copy number profiles and mutations that are otherwise rare in GCT. Mutational profiles of SMs and matched conventional GCTs are almost identical. Different SM histotypes show similar mutational and DNA methylation profiles, indicating that identification of SM components of GCTs may be more important than precise sub-classification. DNA methylation profiling of additional tumour types (sarcomas, sarcomatoid/glandular YSTs, carcinomas) is ongoing.

PS-26-026
TFF3 in ERG/SPINK1 subsets of sporadic prostate cancer
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Background & objectives: TFF3 is a potential candidate for molecular prostate cancer subtyping, that could predict patients¢ clinical evolution. Our study focuses on TFF3 immunohistochemical expression in specific subsets of prostate adenocarcinoma defined by ERG/SPINK1 status, correlated with clinico-pathological parameters and biochemical recurrence.
Methods: The study group comprised 105 radical prostatectomy samples, immunohistochemically investigated using anti-TFF3, anti-ERG and anti-SPINK1 antibodies. TFF3 was semi-quantitatively assessed as low and high. Four subgroups were characterized based on positive and negative ERG/SPINK1 profile. For each subset, relationships between TFF3 immuno-expression and age, Gleason score, Gleason grade, tumour stage, capsular, perineural, lympho-vascular invasion, and biochemical recurrence were statistically analysed.
Results: In the predominant subset ERG+/SPINK1- (63 cases/59.04%), TFF3 over-expression was statistically correlated with Gleason score (p=0.02), Gleason grade and tumoral stage (p=0.00001). All 12 cases in ERG-/SPINK1+ subset (11.42%) over-expressed TFF3, with less favourable features: younger age of onset (75% under 65 years), higher Gleason grade (83.33%, >3), invasive tumour profile (91.66% capsular and perineural invasion). High-expression TFF3 indicated shorter time to biochemical recurrence in ERG-/SPINK1+ subset compared to low-expression TFF3, and all other ERG/SPINK1 subsets. ERG-/

SPINK1- subset (30 cases/28.57%) presented no significant correlation between low/high TFF3 expression, clinico-pathological parameters, and biochemical recurrence. ERG+/SPINK1+ subset included one case, with TFF3 over-expression; statistical analysis wasn't applicable in this situation.
Conclusion: Currently, the classification of prostate cancer in distinct molecular subclasses is still a "hot" debatable issue with exploring potential in modern pathology and oncology. The immuno-expression profile of TFF3 differs in subsets of sporadic prostatic adenocarcinoma outlined by ERG/SPINK1 status, its over-expression indicating a more aggressive biological and clinical behaviour. Further studies on bigger populations are required for a better understanding of the overlapping interactions between SPINK1, ERG and TFF3 in the progression and molecular stratification of this malignancy.

PS-26-027
Biomarkers implied in prostate cancer progression by flow cytometry analysis
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Background & objectives: Researchers need a greater understanding of prostate intratumoral heterogeneity and the cellular architecture of normal and diseased tissues to develop better treatments and more accurately predict disease progression.
Methods: The study presents flow cytometry determinations on prostate biopsies recovered from patients with adenocarcinomas (PCa, n=25), benign prostatic hyperplasia (BPH, n=25) reported to controls (C, n=25) to evaluate the DNA content, cell apoptosis, and CD biomarkers (CD34 Alexa Fluor 488/ CD61-PE stain for mesenchymal, endothelial cell proliferation and CD42b-PE stain for platelets aggregation to tumoral cells and endothelium).
Results: The results showed that 68% of BPH cases and 88% of patients with PCa presented aneuploidy. Relationships between the development of PCa, BPH with adhesion, migration, and cell proliferation were observed by Pearson correlations between G0/G1 phase of cell cycle and CD34+CD61+ glycoproteins ($r=-0.514$; $P<0.01$), and CD42b+ cell population ($r=-0.475$; $P<0.05$), between G2/M phase of cell cycle and CD34+CD61+ glycoproteins ($r=0.513$; $P<0.01$), and CD42b+ cell population ($r=0.446$; $P<0.05$), between S phase and CD61+ cell population ($r=-0.430$; $P<0.05$).
Conclusion: Combining the benefits of advanced high throughput flow cytometry and live-cell analysis offers the potential to gain additional insights into the mechanisms of cancer progression. It is concluded that DNA flow cytometry has much to tell us about the natural history and biological behaviour of prostate cancer and along with CD biomarkers provides additional information about the prognosis of the disease.
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PS-26-028
Correlation of GATA3, CK5/6 and p16 expression and overall survival in muscle-invasive bladder cancer
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Background & objectives: Muscle-invasive bladder cancer therapy choice could be influenced by the tumour molecular subtype. Currently well-defined subtypes are RNA based. Surrogate molecular subtypes based on immunohistochemistry are needed to make subtyping useful in routine work and facilitate future research.
Methods: A retrospective single centre series of 85 cases with localized disease was identified, and routine immunohistochemistry for GATA3, CK5/6 and p16 was performed on whole tissue blocks containing muscle-invasive disease. Surrogate molecular subtypes were defined. Patient information regarding treatment and survival was obtained from medical archives.
Results: The mean population age was 70 years (SD=8.7), and 73% were males. Conservative treatment (TUR with radiotherapy) was used in 45% of cases, while 47% underwent cystectomy with adjuvant chemotherapy. Only 7% underwent neoadjuvant chemotherapy or primary chemoradiotherapy. GATA3 and CK5/6 expression segregated cases into broad luminal and basal subtypes respectively, while p16 expression was used to subclassify luminal cases into luminal papillary and luminal unstable types. When subtyped this way, no difference in survival was observed overall and within therapy groups. GATA3 expression was strongly associated with better survival across all treatment groups, while CK5/6 was linked to worse survival. No effect of p16 on survival was observed.
Conclusion: No effect of p16 expression was observed on clinical outcome. When used together with GATA3 and CK5/6 in a combined immunohistochemical molecular subtype no difference in survival was observed. In our study GATA3 and CK5/6 expression was found to be an indicator of respectively improved and worse survival both overall and within conservatively treated and cystectomised patients.

PS-26-029
Dynamic sentinel node biopsies in penile cancer – the Edinburgh experience
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Background & objectives: The presence and extent of loco-regional lymph node metastasis is an important prognostic factor in penile cancer survival and therefore dynamic sentinel node biopsies of inguinal lymph nodes play an important role.
Methods: A retrospective review of all DSNB for penile cancer reported in our department over a 5-year period (2015-2019) was performed. This looked at initial diagnosis, reported macroscopic and histological features, use of immunohistochemistry and follow up including additional pathology. Locally all nodes are individually identified, serially sliced at 2 mm intervals and further ancillary tests done by request only.
Results: 67 cases were identified, with a total of 168 lymph nodes. Immunohistochemistry was performed in 11 cases. 14 nodes (7%) over 11 cases had metastatic tumour deposits. Two of these were micrometastasis (<2 mm) and both these patients had negative subsequent lymph node dissections. In patients with non-micrometastatic disease, there was an association of the size of the sentinel node deposit and the likelihood of further positive nodes in the node dissection.
In four of the cases with negative sentinel nodes initially, ipsilateral metastatic nodal disease was identified subsequently. These cases had further additional levels and cytokeratin immunohistochemistry performed but were true negatives.
Conclusion: Although our sample size is small, it raises the possibility that micrometatastic disease within DSNB may not be associated with further positive nodes in the node clearance and may benefit from further larger studies to see if clearance could be avoided for this subgroup of patients. We did not identify any false positive or false negative cases in our review.

PS-26-030

Next generation intraoperative margin assessment in nerve sparing radical prostatectomy, confocal laser microscopy versus frozen sections

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Background & objectives: Currently frozen section (NeuroSAFE) is the gold standard in intraoperative margin assessment at nerve sparing radical prostatectomy (RP), but does have drawbacks. It is time-consuming and laborious. Here we evaluate whether confocal laser microscopy (CLM) could replace NeuroSAFE.
Methods: 50 patients underwent a nerve sparing RP with intraoperative margin assessment by NeuroSAFE. Concurrently the margins were assessed using CLM by imaging both posterolateral sides using the SamanTree Histolog Scanner. Secondary resection of the nerve bundle was performed when a positive margin was identified by frozen section. Results were compared with final pathology.
Results: In total 14 out of 96 margins were positive in final pathology. 4 margins were excluded based on macroscopic visible cauterization or neoadjuvant therapy. 1 positive margin was only seen in the final pathology. CLM identified 15 positive margins, 12 of which were seen in the final pathology, for the other 3 deeper levels were necessary to verify that tumour on ink was present. NeuroSAFE identified 14 positive margins, 1 of these was not present in the final pathology. 6 out 14 secondary resections contained tumour, both intraoperative techniques identified these patients. CLM was significantly faster compared to NeuroSAFE (8 vs 50 minutes respectively, $p<0.001$).
Conclusion: This feasibility study demonstrates that surgical margin assessment by CLM at nerve sparing radical prostatectomy is a reliable method compared with the standard technique of intraoperative frozen sections and offers logistical advantages. Both techniques were equally good in identifying those patients that benefitted from resection of the neurovascular bundles.

PS-26-031

Rapid intraoperative surgical margin assessment in partial nephrectomy using confocal laser microscopy

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Background & objectives: Various techniques have been studied in intraoperative margin assessment of partial tumour nephrectomies varying from intraoperative ultrasound to frozen section. Here we present a series using a confocal laser microscope (CLM) to assess the surgical margins during robot-assisted partial nephrectomy.
Methods: Six patients underwent a partial nephrectomy. Peri-operative parameters were monitored. Once the tumour specimen was removed, it was examined by the pathologist in fresh state, making an assessment of the surgical margin using the Histolog Scanner by SamanTree Medical, Switzerland. The margin and/or the lamellae were scanned after immersion in a contrast agent. Results were compared with final pathology.
Results: A total of six tumour specimen from six individual patients were included. The cases contained a spectrum of diagnosis varying from angiomyolipoma (AML) to clear cell renal papillary renal cell carcinoma. In two cases final pathology showed a positive surgical margin, which was visible on the CLM images. Staining time with the contrast agent and image acquisition time was two minutes. The diagnosis of AML was suggested based on the CLM images. Differentiating normal tissue from renal cell carcinoma was possible, but separating various types of renal cell carcinoma was not possible.
Conclusion: Intraoperative confocal imaging using confocal laser microscopy is a feasible modality for the assessment of surgical margins from resected kidney tissue during robot assisted partial nephrectomy. Assessment of the surgical margin is easily applicable and fast. And potentially adds a diagnostic resolution to existing techniques such as intraoperative ultrasound or gross examination. Validation of the technique is necessary and its added value in clinical practice needs to be established.

PS-26-032

GRIN3A – a novel biomarker identifying a subtype of intraductal prostate cancer (IDC-P)

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Background & objectives: The molecular background contributing to the poorer prognosis of a cribriform pattern (invasive cribriform (ICC) and/or intraductal carcinoma (IDC-P)) in prostate cancer is still largely unexplored. Therefore, we aimed to identify molecular markers specific for a cribriform pattern.
Methods: Utilizing RNA-sequencing, we compared cribriform to non-cribriform Gleason pattern 4 (GP4; N=13), and genes with expression significantly associated with cribriform pattern were identified. Among these, *ACSM1*, *GRIN3A*, *PCDHB2* and *REG4* were selected for validation in a larger cohort (N=85) using RT-PCR. RNA *in situ* hybridization (RNAscope®) on tissue microarrays (N=479) was used to assess gene expression related to histopathology.
Results: Ten genes were significantly upregulated and 144 genes downregulated in cribriform pattern samples. Of the selected upregulated genes (*ACSM1*, *GRIN3A*, *PCDHB2* and *REG4*), only *GRIN3A* was significantly higher expressed in cribriform pattern samples when compared to non-cribriform GP4 samples in a larger cohort ($p=0.005$). In relation to histopathology, *GRIN3A* was more frequently identified in tissue cores with IDC-P (54%) followed by ICC (32%) and non-cribriform GP4 (29%) from tumours with a cribriform pattern compared to non-cribriform GP4 (20%) from tumours without any cribriform pattern (all $p<0.01$). *GRIN3A* was identified in benign tissue in 0.5% of samples.
Conclusion: In this relatively large prostate cancer patient series, *GRIN3A* was identified as an RNA-based biomarker for the presence of a cribriform pattern in prostate cancer and specifically a subtype of IDC-P. Furthermore, *GRIN3A* was idenitifed as a tumour marker, as it only rarely identified in benign tissue. Additional studies are needed to elucidate the functional role of *GRIN3A* in tumours with a cribriform pattern and whether it may be used in diagnostic setting.
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PS-26-033

Immunoreactivity of CK7 in clear cell renal cell carcinomas

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Background & objectives: There is inconsistent data on cytokeratin 7 (CK7) immunostaining patterns in clear cell renal cell carcinomas (CC-RCC). The aim of this study was to assess the CK7 expression pattern of CC-RCC.
Methods: We analysed 30 cases of CC-RCC from our institution, diagnosed between 2014 and 2022. CK7 immunostaining was performed. The tumours were divided into low-grade CC-RCC (LGCC-RCC) (WHO/ISUP grade I and II) and high grade CC-RCC (HGCC-RCC) (grade WHO/ISUP III and IV). Architectural pattern was also noted. The patterns of staining were divided into three groups: negative, focal and diffuse.
Results: The mean age at diagnosis was 62,5 years (33 - 83 years-old). 22 cases (73,3%) were classified as LGCC-RCCs and 8 cases (26,7%) as HGCC-RCCs. 14 cases (46.7%) showed CK7 immunoreactivity, with 3 cases displaying a diffuse expression pattern and 11 cases with focal staining. 13 cases of the LGCC-RCCs group (59,1%) and 1 case (12,5%) of the HGCC-RCC group showed expression of CK7. 10 out of 16 cases with macrocystic or microcystic architectures showed CK7 expression.
Conclusion: Our results showed that CK7 immunoreactivity in CC-RCCs can have a variable pattern and extent of expression. LGCC-RCCs revealed a higher rate of CK7 positivity regarding HGCC-RCCs, leading to a possible prognostic role of CK7 regarding these entities. Thus, the possibility of expression of CK7 by CC-RCC is an important characteristic that pathologists should keep in mind, particularly in the interpretation of small tissue samples.

PS-26-034
Morphological characterization of chromophobe renal cell carcinoma: review of 30 cases
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Background & objectives: Chromophobe renal cell carcinoma (ChRCC) is a renal neoplasm traditionally described by having sheets of large polygonal cells with pale to eosinophilic cytoplasm. The aim of this study was to document the histopathological features of ChRCC cases in our institution
Methods: We reviewed retrospectively the slides of cases diagnosed between 2014 to 2022. Immunohistochemistry for CK7, CD117 and CD15 were performed in all cases. 30 cases of ChRCC were identified from all 229 cases of renal neoplasms from our institution in this period.
Results: ChRCC represented 13% of all renal neoplasms. The mean age at diagnosis was 66.3 years old (47 – 87 years). 73.3 % of the patients were men and 26.7% women. The histological types were divided between solid sheet-like, tubulocystic and papillary patterns and the cytoplasm features were divided between pale cytoplasm versus eosinophilic cytoplasm. The architectural patterns were 18 cases (60%) of a predominant solid pattern, 11 cases (36.7%) with predominant tubulocystic areas, and 1 case (3.3%) with papillary architecture. 18 cases (60%) had abundant pale cytoplasm and 12 (40%) predominant eosinophilic cytoplasm. 56.7% had diffuse positivity for CK7, 96.7% showed CD117 expression and only 13.3% had CD15 focal positivity.
Conclusion: Our study demonstrated a similar distribution in age at diagnosis and gender in comparison to the existing literature, described the architectural diversity of this neoplasm and its immunohistochemical findings. To avoid misdiagnosis, this pathological heterogeneity of ChRCC is an important feature that pathologists should have in mind.

PS-26-035
Quantitative, rules-based grading for noninvasive papillary urothelial carcinoma
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Background & objectives: Noninvasive papillary urothelial carcinoma (NPUC) places great burdens on patients and healthcare systems. Histopathologic grading for NPUC guides management, yet subjective criteria and poor reliability limit its value. Here we develop an accurate, quantitative, and explainable NPUC grading algorithm.
Methods: Clinical data including recurrence and progression were collected for 201 NPUC patients presenting from 2008-2016. Image analysis was performed on 641 H&E stained tissue microarray (TMA) cores harvested from their transurethral resections. Histologic features extracted using Visiopharm software were analysed individually and in combination using regression and decision tree models. Survival analysis for Kaplan-Meier curves were calculated with log-rank statistics.
Results: Whole slide grade and stage were significantly associated with recurrence-free survival. TMA-based nuclear morphometry, cellular organization and automated mitotic figure counts differentiated low- from high-grade NPUC. As a single variable, variation in (standard deviation of) nuclear area distinguished between high- and low-grade with 82% accuracy. Multivariate models combining nuclear size and shape-related variables with mitotic activity increased balanced accuracy to 88%. To adapt these TMA-based findings to whole slide images, we are using deep learning to select and analyse hotspots that are enriched for high-grade features.
Conclusion: This work represents the first demonstration of explainable quantitative criteria for NPUC grading, and points to mitotic index and variation in nuclear size as key quantitative variables. Ongoing work will build a clinically-oriented user-friendly platform that works on whole slide images and optimizes the prognostic value of NPUC grading.
Funding: Ontario Molecular Pathology Network and Ontario Institute for Cancer Research

PS-26-036
Percutaneous renal biopsy of kidney tumours: what comes next?
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Background & objectives: Kidney tumours are frequently both diagnosed and treated through partial or radical nephrectomy after imagiological detection. Nevertheless, many are first approached by percutaneous needle biopsy. We aim to study and compare biopsy and surgical specimen diagnosis, grade and clinical outcomes.
Methods: We reviewed all cases of kidney tumour biopsy received in our department during the last 5 years (n=56). For each, we determined the biopsy diagnosis; the diagnosis in the nephrectomy specimens (if surgical treatment), patient management (surveillance, cryotherapy, surgical treatment, systemic treatment or palliative care), and clinical follow-up.
Results: In biopsy, clear cell renal cell carcinoma was the most frequent diagnosis (n=13;23%), followed by a differential diagnosis between oncocytoma and the eosinophilic variant of chromophobe renal cell carcinoma (n=7;13%). Regarding patient management, 16 (29%) were submitted to cryotherapy, in 14 (25%) was opted surveillance, 6 (11%) received palliative care and 3 (5%) systemic

treatment. In those submitted to surgical resection (11;20%), final diagnosis was concordant with biopsy diagnosis in 8 (73%) cases; and in 3 (27%) cases, it was included in the biopsy differential diagnosis. ISUP grade was upgraded from 2 to 4 in one case. Seventeen (30%) patients died, most (12;71%) from kidney cancer.
Conclusion: Kidney tumour biopsy is of paramount importance in patient management. Our series highlights the two main clinical settings leading to kidney tumour biopsy in our institution, with distinct diagnosis challenges – small tumours treated by crytotherapy or clinical follow-up, and aggressive tumours requiring histological subtype classification. It is also noteworthy the high concordance in the biopsy and surgical specimen diagnosis, as reported in the literature.

PS-26-037
Caveolin-1 expression in tissue and cfDNA methylation status in semen plasma of patients with benign prostate hyperplasia and prostate cancer
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Background & objectives: Prostate cancer (PCa) is the second most common malignancy and the fifth cause of death in male population. However, non- invasive and specific biomarker for distinguishing benign prostate hyperplasia (BPH) and prostate cancer is still not known.
Methods: Eighty tissue samples of patients (40 with PCa, 40 with BPH) were stained for HE and immunohistochemistry. Caveolin-1 (CAV1) expression in BPH and PCa was scored according to staining intensity and percentage of positive cells. Degree of cfDNA methylation as a potential biomarker for PCa was estimated in semen samples by pyrosequencing. Results were considered statistically significant when $p<0.05$.
Results: Statistically significant higher cytoplasmic CAV1 staining intensity score and staining proportion were observed in BPH stroma compared to PCa stroma. There was no epithelial reaction in both groups. Staining score did not correlate with Gleason grade group, nor with tPSA. In case of semen samples, cfDNA methylation mean of the first five CpGs was higher in BHP group while methylation of other CpGs and average methylation was similar in both groups. BHP cfDNA methylation median of 8 CpGs and average methylation was similar, difference between groups was $\leq 1\%$. Statistically significant degree of hypermetilated cfDNA for CAV1 only in CpG1 was observed in BPH patients compared to PCa patients.
Conclusion: Caveolin-1 is a protein important for caveolae formation in plasma membrane invaginations. It's functions include regulation of cell differentiation, apoptosis, cell proliferation, migration, angiogenesis, senescence, endocytosis and interaction with signalling molecules. The expression of this protein significantly differs in BPH and PCa tissue. As for cfDNA methylation, significant differences in DNA methylation of CpG1 between BPH and PCa were demonstrated. CAV1 is a potential non- invasive biomarker for distinguishing BPH and prostate cancer.

PS-26-038
Low grade oncocytic renal tumour (LOT): clinicopathological characterization of 9 cases from a single cancer centre
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Background & objectives: Oncocytic renal neoplasms are heterogeneous group of tumours that can pose diagnostic challenge. Recently, a subset of renal oncocytic neoplasms is described as LOT. In this study, we further investigate the histomorphological characteristics and clinical outcome of LOT, retrospectively.
Methods: Among 87 patients with low grade oncocytic renal neoplasms, 9 cases of LOT were identified from pathology archive between year 2005-2021. All cases were confirmed by immunostains for CK7, CD117 and other relevant markers. The clinicopathological characteristics features and follow up data were investigated.
Results: Median age of patients is 83 years old with male to female ratio of 1:7. Grossly, the tumours are heterogeneous solid masses (2 with cystic changes). The median size of tumour is 2.65 cm. Histologically, tumours show solid compact nested, focal tubular or trabecular patterns. Tumour cells are monomorphic bland with eosinophilic cytoplasm and uniformly round nuclei. Tumour nuclear grade is WHO/ISUP grade 2. All cases show strong CK7 positivity and negative for CD117, CAIX, CD10, AMACA and vimentin. All cases in our cohort demonstrate indolent behaviour and show no evidence of disease recurrence, progression or metastases during the follow-up period up to 82 months (median 13.5 months).
Conclusion: LOT is an emerging entity with incidence of 10% among low grade ORN. It has unique morphologic and immunohistochemical profiles that set them apart from oncocytoma and chromophobe renal cell carcinoma. LOT demonstrates indolent clinical behaviour. Future studies will be directed to understand molecular genetic profiles of LOT.

PS-26-039
Implications of correlation between PBRM1 and PD-L1 expression in renal cell carcinoma, clear cell type
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Background & objectives: Polybromo-1 (PBRM1) is the second most frequently altered gene after von Hippel-Lindau gene in clear cell renal cell carcinoma (ccRCC). PBRM1 alteration is reported as a significant barrier to immune checkpoint blockade response including anti-PD-L1target therapy.
Methods: To identify the correlation between PBRM1 and PD-L1 expression in ccRCC, we analysed the loss of PBRM1 (A301-591A; dilution: 1:250, Bethyl Laboratories, Montgomery, TX) expression and PD-L1 (22C3; pharmDx assay, Agilent, Santa Clara, CA) expression in a retrospective cohort of 526 surgically resected ccRCC in a single institute.
Results: Based on a cut-off of the combined positive score (CPS) $\geq 1\%$, positive staining for PD-L1 was found in 139 (26.4%) cases. Loss of PBRM1 expression was observed in 205 (39.0%) cases. PD-L1 expression was positively associated with loss of PBRM1 expression ($P<0.001$) in ccRCC. Notably, among the ccRCC cases which expressed the PD-L1, loss of PBRM1 was identified in more than 50% of cases. In addition, loss of PBRM1 expression showed correlations with aggressive clinicopathological features including higher ISUP/WHO grade, high pT stage, angiolymphatic invasion, venous invasion, and tumour necrosis ($P<0.05$). Kaplan–Meier analysis indicated that loss of PBRM1 expression and PD-L1 expression was positively correlated with tumour recurrence.
Conclusion: In ccRCC, previous clinical trials reported that there is no significant correlation between PD-L1 expression and anti-PD-L1 therapeutic effect. Our study showed that the loss

of PBRM1 is significantly correlated with PD-L1 expression in ccRCC. This result can suggest that the PD-L1 blockade may not be effective even though the PD-L1 was expressed in ccRCC due to the interference of PBRM1 alteration.
Funding: This research was funded by the Seoul National University Bundang Hospital Research Fund (grant number: 02-2018-015).

PS-26-040

Comparison of urinary cytology reported using the Paris System with follow-up biopsies: a single institutional experience

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Background & objectives: The Paris System (TPS) provided standardized cytomorphological criteria and terminology for the recognition of high-grade urothelial malignancies. The aim of this study was to evaluate the role of The Paris System by comparing urinary cytology with follow-up biopsies.
Methods: Urinary cytologies with follow-up biopsy up to 3 months from 2017 to 2021 were evaluated with TPS. The atypical urothelial cells category was also evaluated as positive. Inadequate urinary cytologies and samples submitted for decoy cell examination were excluded. Statistical analyses were performed by calculating sensitivity, specificity, positive and negative predictive value, diagnostic accuracy, and risk of high-grade malignancy (ROHM).
Results: A total of 203 samples were evaluated. 82.3% of the cases were categorized as negative, 7.4% AUC, 1.5% suspicious for high-grade urothelial carcinoma (SHGUC) and 8.9% high-grade urothelial carcinoma (HGUC). ROHM was 6.0% for the negative category, 40.0% for AUC, 100.0% for SHGUC, and 100.0% for HGUC. In the reporting of urinary cytology, the sensitivity of TPS was 72.0%, the specificity was 94.6%, the positive predictive value was 75.0%, the negative predictive value was 93.6%, and the diagnostic accuracy was 90.6%.
Conclusion: TPS has high specificity and negative predictive value for detecting high grade urothelial lesions. We found that ROHM increases gradually from negative category to HGUC. And we think that TPS has an important role in the detecting of high-grade lesions and reporting urinary cytology.

PS-26-041

Molecular characterization of the neuroendocrine variant of urothelial bladder carcinoma

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Background & objectives: Diagnosis of neuroendocrine (NE) bladder carcinoma (BC) remains challenging. Our aim was to compare consensus molecular subtyping and new immunohistochemical markers in a series of cases with morphology suggesting NE differentiation.
Methods: BC tumours with morphology suggesting NE differentiation were identified and stained using multiplex IHC (subtype markers CK5/6-GATA3), Ki67 and NE IHC markers (Chromogranin A, Synaptophysin, INSM1, TUBB2B). In tumours with adjacent non-NE morphology, the IHC expression of each area was individually assessed. Transcriptomic profiling was performed using 3'RNA-seq to determine consensus molecular subtype, including multiple samples in heterogeneous cases.
Results: We included 14 patients (9 men and 5 women) with a median age of 75 years. Ten cases were associated with area(s) of non-NE morphology.
Twenty-eight samples from 14 patients underwent 3'RNA-seq. Applying the consensus classifier, 9/14 cases (64.3%) had at least one neuroendocrine-like subtype area. Of the 6/9 NE-like cases with multiple sequenced areas, 4 harboured distinct subtypes (Basal/Squamous, Luminal Unstable and/or Stroma-rich).
NE-like tumours were characterized by negative or focal/weak CK5/6-GATA3 immunophenotype (quickscore <0.1 in 7/9). Six of 9 NE-like tumours showed INSM1 positivity, while non-NE-like tumours were all INSM1 negative. Further analysis of the other NE markers and their respective performance to identify NE-like subtype is ongoing.
Conclusion: Neuroendocrine bladder carcinoma is associated with intratumoral heterogeneity at the morphological, immunohistochemical and molecular levels. Preliminary results show that the majority of NE-like molecular subtype tumours are characterized by CK5/6-GATA3 double negative phenotype. Further analysis to determine the performance of NE markers (chromogranin A, synaptophysin, TUBB2B and INSM1) in identifying the aggressive NE-like consensus molecular subtype is ongoing.

PS-26-042

Alpha-methylacyl-CoA racemase in carcinoma in situ of the urinary bladder: a useful addition or not

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Background & objectives: Diagnosing carcinoma in situ (CIS) of urothelium may be challenging. CK20, p53 and Ki-67 are common immunohistochemical markers to differentiate CIS from reactive epithelial changes (REC). The value of AMACR is debatable. We evaluated AMACR immunoreactivity in CIS and REC.
Methods: Twenty-two CIS and 33 REC cases from our institution were included. All specimens were stained for previously mentioned IHC. Immunoreactivity for CK20, Ki-67 and AMACR was assessed as negative (≤1/3 of urothelial thickness) or positive (>1/3). AMACR was additionally quantified as <5% or ≥5% expression of the urothelium. P53 was evaluated as wild-type or aberrant-type.
Results: CK20 was positive in all 22 CIS and in 8/33 REC cases, in accordance with the highest sensitivity of 100% and a specificity of 75.8%. In 10/22 CIS and in 6/33 REC cases p53 showed an aberrant pattern (sensitivity: 45.5%, specificity: 81.8%). Ki-67 was positive in 22 CIS and in 6 REC cases (sensitivity: 90.9%, specificity: 81.8%). The first scoring method showed that AMACR was positive in 16/22 CIS and negative in REC cases, leading to a sensitivity of 72.7% and the highest specificity of 100%. Seventeen of 22 CIS and 2 REC cases showed AMACR expression in ≥5% of the urothelium (sensitivity: 77.3%, specificity: 93.9%).
Conclusion: According to these results the biomarker panel of CK20, Ki-67, AMACR and p53 appears to be useful for diagnoses of CIS in challenging cases giving the sensitivity and specificity. Also both scoring criteria for AMACR showed good correlation and similar sensitivity and specificity compared to each other and to the other IHC markers. Further study is necessary to evaluate the pitfalls and utility of AMACR in different settings.

PS-26-043

Reclassification of eosinophilic kidney tumours – a multi-institutional study of 318 cases

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Background & objectives: Eosinophilic/oncocytic renal neoplasms represent a heterogeneous group consisting of both well-known entities (oncocytoma and chromophobe renal cell carcinoma [chRCC]) and emerging/provisional tumours (eosinophilic vacuolated tumour (EVT), eosinophilic, solid and cystic (ESC) RCC, and low-grade oncocytic tumour [LOT]).
Methods: In this multi-institutional study, 318 renal tumours signed out as oncocytomas (n=164) or chRCCs (n=154) were reevaluated and reclassified according to current concepts. The revision was supported by immunohistochemistry of CK7, CK20, CD10, CD117, SDHB, FH, MelanA, and HMB45. Clinical data and pathological characteristics were obtained from the original histological reports.
Results: The revision resulted in 140 oncocytoma, 139 chRCC, 9 EVT, 8 LOT, 6 ESC RCC, 2 oncocytic papillary RCC, and 14 eosinophilic RCC not otherwise specified cases. Twenty-four oncocytomas and 15 chRCCs were reclassified as other tumours. Ten chRCC tumours were built-up of purely eosinophilic cells. The initial diagnosis was mainly oncocytoma for the EVT, LOT, and ESC RCC cases (20/23). The EVT and ESC RCC were primarily seen in women, while LOT affected older men (median age: 75.5; range: 51-83). The average tumour size for EVT, LOT, and ESC cases was 38.1 mm, 46.4 mm, and 38.2 mm, respectively. Progression and tumour-related death were registered exclusively in chRCC.
Conclusion: The diagnostic spectrum of eosinophilic renal tumours is evolving, and it may pose diagnostic difficulties. Caution should be raised when the diagnosis of oncocytoma is established, because a significant number of the cases may refer to emerging/provisional tumours. In our study, the frequency of EVT, LOT, and ESC RCC tumours was 12.16% among the eosinophilic renal tumours. In addition, 14 cases were left without a specific diagnosis and remained unclassified, indicating further research.
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PS-26-044

Evaluation of risk scoring systems for predicting inguinal lymph nodal metastasis in penile squamous cell carcinoma

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Background & objectives: Inguinal lymph nodal metastasis (ILNM) is the most important prognostic parameter in the outcomes of penile squamous cell carcinoma (PSCC). We compared two risk scoring systems to predict ILNM.
Methods: This is a retrospective study of 105 PSCC cases. Prognostic index score(PIS) was calculated by summing different points assigned to the following histological parameters- histologic grade(1-well,2-moderate,3-poor), anatomic level of deepest infiltration(1-lamina propria,2-corpus spongiosum,3-corpora cavernosa) and perineural invasion(PNI)(0-absent,1-present). In Histopathological risk score(HRS), pattern of tumour invasion(1-bulbous,2-cords,3-single cell) was used instead of PNI, the rest of the two parameters being the same.
Results: ILNM was present in 50 cases. PIS & HRS had a statistically significant association with ILNM ($p<0.001$). The composite score for PIS ranged from 2 to 7 & 3 to 9 for HRS. ILNM was noted in ≥50% of tumours with a PIS score ≥ 5 and HRS score ≥ 6. None of the tumours with PIS score ≤3 & HRS score ≤5 had ILNM. The Receiver operating characteristic curve analysis for PIS showed an area under the curve (AUC) of 0.751 ($p<0.001$ & CI-0.642-0.859) while for HRS, AUC= 0.737 ($p<0.001$ & CI-0.625-0.849), making them comparable in their utility to predict ILNM.
Conclusion: PIS and HRS risk scoring systems correlate with ILNM. The high-risk group of HRS (score ≥ 6) included all the cases with ILNM (100%) while PIS (score ≥5) had 90% cases. The risk scoring systems may aid in addressing the inguinal lymph node dissection in PSCC.

PS-26-045

The association between varicocele in adolescence and testicular cancer in young adulthood

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Background & objectives: Elevated intrascrotal temperature has been suggested as a risk factor for testicular cancer. Varicocele was linked to increased intrascrotal temperature, but whether it is associated with testicular cancer is unclear. We aimed to to explore their potential association.
Methods: This nationwide, population-based, historical cohort study includes 1,521,661 Israeli male adolecents (mean age 17.5 ± 0.4 years), who were screened for varicocele as part of their medical assessment prior to compulsory military service during the years 1967-2012. The diagnosis of testicular cancer was ascertained from linkage of records to the the Israeli National Cancer Registry. Logistic regression analysis was applied.
Results: In total, 53,210 adolescents were diagnosed with varicocele prior to military service. Of 1,988 (0.13% of the total cohort) men who were diagnosed with testicular cancer, 54 (0.1%) had varicocele prior to military service and 1934 were not exposed to the elevated intrascrotal temperature resulting from varicocele, $p=0.314$. The age at cancer diagnosis and the distribution of seminomas vs. non-seminomas did not differ significantly between those with and without varicocele in adolescence. Varicocele was also not associated with testicular cancer, in a multivariable analysis controlling for sociodemographic factors.
Conclusion: Varicocele in adolecents was not found to be associated with testicular cancer in young adults.

PS-26-047

Sarcomatoid carcinoma of the bladder. Histological, immunohistochemistry and molecular review of 20 cases of this rare entity with poor prognosis

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Background & objectives: Sarcomatoid carcinoma of the bladder is a rare entity considered a divergent differentiation from urothelial carcinoma (UC) as it accounts for less than 0.6% of bladder tumours. Our objective is to study the characteristics of these tumours and their survival.
Methods: We performed a retrospective review of urothelial tumours with sarcomatoid component (SC) diagnosed in our centre from 2010 to March 2022. We collected data of age, sample type,

biopsy stage, tumour type, immunohistochemistry studies, TERT promoter status and percentage of SC. From the clinical history, we obtained data of appearance and location at cystoscopy and survival.
Results: We identified 20 patients with a mean age of 79 years, 17 of them were diagnosed at transurethral resection (TUR). In cystoscopy 6 were located in the left lateral wall and 16 had a solid aspect. Thirteen patients had stage T2 in TUR. Cytokeratin was positive in all 20 cases. All the tumours that underwent TERT promoter were mutated (5 cases). Seven patients underwent cystectomy. Fourteen patients had mixed high-grade UC and SC (mean 63% of the tumour) and 6 patients had the entire sample with SC. Twelve patients died with a mean survival of 17 months. Five patients had previous radiotherapy with a mean of 13 years before diagnosis.
Conclusion: Sarcomatoid carcinoma of the bladder presents at an advanced age and has poor prognosis due to low survival. In our series, 70% SC had conventional urothelial carcinoma with sarcomatoid component, 65% were at least T2 at diagnosis. Cytokeratin was positive in all of our cases, and TERT promoter was mutated in the 5 cases studied. Of our patients, 25% had previous radiotherapy and 75% died because of the disease. Our findings are similar to those previously described in the literature.

PS-26-048
Gleason score before and after radical prostatectomy: a comparative study
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Background & objectives: The Gleason score (GS) places patients with prostate cancer in one of five categories (ISUP Grade Group). GS being the most important prognosis predictor, we investigated reliability and factors influencing a core needle biopsy (CNB) in predicting operative sample GS.
Methods: Retrospective study was conducted at the Center for Pathology and Histology of the University Clinical Center of Vojvodina. Querying patients' histories we identified 56 men who underwent CNB and radical prostatectomy (RP) at our institution in a two-year period (2018-2019). Preoperative and postoperative parameters were collected. Correlation and influence among the parameters were statistically analysed.
Results: Patients' average age was 66.75±4.24 years. The most common tumour was GS 3+4 (ISUP GG 2) - 37.5%, pT2 stage (60%). GS was upgraded on RP material in 50% of patients. All patients with CNB GS 3+3 (25%) had a higher GS on RP material. For 18 patients (32%) the score remained unchanged, while 10 patients (17.8%) had a lower GS postoperatively. Linear regression showed that with every year of the patients' age, GS and the number of positive biopsy samples increased (b=0.05, p=0.03; b=0.025, p=0.005 respectively). Spearman's test showed low statistically significant correlation between CNB GS and RP GS (r=0,2900).
Conclusion: Accurate defining of GS is of utmost significance for appropriate treatment of prostate cancer especially in elderly patients whose GS and number of positive biopsies tend to be higher. CNB is a modestly reliable method for defining GS/ISUP GG of prostate cancer, considering high number of upgraded GS on postoperative material. Therefore, postoperative assessment of RP specimen is mandatory for confirming GS defined on CNB and possible adjustment of treatment method.

PS-26-049
The impact of pathology review in a population-based cohort of 770 clinical stage I testicular germ cell cancer patients
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Background & objectives: Inaccurate pathology reporting may contribute to the ambiguous results on histopathological features as predictors of relapse in patients with clinical stage I testicular germ cell cancer (TGCC). This study compares the primary pathology reports with those obtained by pathology review.
Methods: We reviewed all histopathological slides from 770 patients who were diagnosed with stage 1 TGCC in Denmark between 2013 and 2018. We assessed tumour type, pathologic tumour (pT) stage according to the 8th edition of the AJCC TNM staging system, lymphovascular invasion (LVI) and invasion of stromal rete testis (RTI), hilar soft tissue (STI), epididymis, spermatic cord and tunica vaginalis.
Results: Following the pathology review, the tumour type was revised in 1% of the cases, including two spermatocytic tumours initially misclassified as pure seminomas. Overall, reporting of RTI was revised in 20% of the cases; of those initially called absent 24% were changed to present, and of those initially called present 11% were changed to absent. The reporting of LVI was revised in 16% of the cases. There was a discrepancy rate of 13% regarding the reporting of STI. The pathologic stage was revised in 23% of cases, mostly owing to the revised variables of LVI and STI in these cases. Epididymis status was revised in 3% of the cases.
Conclusion: Inaccurate histopathological interpretation of TGCC specimens is not uncommon and may lead to incorrect tumour classification and pathological staging. This study highlights significant reporting variability on histopathological features in testicular tumours. Therefore, the decision to give adjuvant therapy in clinical stage I TGCC patients based on the findings of decentralized pathologic assessment is problematic. Centralized pathology review is deemed necessary if the true prognostic value of histopathological features is to be determined.
Funding: The Danish Cancer Society

PS-26-050
Prostatic calculi supress the expression of VEGF in the prostate cancer
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Background & objectives: Prostatic calculi (PCa) are associated with the development of prostate cancer (PC) bone metastases. Nevertheless, their effect on angiogenesis remains unclear.
Objective:To study the effect of prostate calculi on the expression of Vascular Endothelial Growth Factor (VEGF).
Methods: For this study, we used 60 PC samples (30 PC samples with PCa and 30 samples without biomineralization). Initially, all samples were stained with hematoxylin-eosin. Immunohistochemistry was performed with antibodies against VEGF. Data sets were analysed by the Shapiro-Wilk test and Mann-Whitney's U-test.
Results: The presence of PCa in cancer tissue was associated with tissue damage, oedema, epithelium desquamation, inflammation and foci of necrosis. We detected significantly ($p < 0.05$) lower expression of VEGF by PC tissue with biomineralization. This provided evidences that PCa do not cause the intensification of

vascularization in the neoplastic tissue. It means that the angiogenesis in the PC tissue is not dependent and related to the presence of intraluminal concretions.
Conclusion: PCa causes mechanical injury of PC tissue and is associated with tissue remodelling and inflammation. At the same time, the VEGF expression by PC cells is lower in patients with PCa.

PS-26-051
PTOV1 is overexpressed in prostate adenocarcinoma and high-grade intraepithelial neoplasia
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Background & objectives: PTOV1 (prostate tumour overexpressed-1) was suggested as one of the most discriminants between normal and carcinomatous prostate, however, little has been investigated by immunohistochemical (IHC) analysis. We examined PTOV1 in normal, adenocarcinomas and high-grade prostate intraepithelial neoplasia (HPIN).
Methods: We examined, using IHC analysis, PTOV1 (cytoplasmic or nuclear), AMACR/P504S (cytoplasmic), and high-molecular-weight cytokeratin 34bE12, in 68 prostate acinar adenocarcinomas. Gleason combined score (2014 ISUP revised Gleason grading system) ranged from 6 to 9 in 41 radical prostatectomy and 27 needle biopsy specimens. HPIN coexisted in 31/41 cases from radical prostatectomies and in 20/27 cases from needle biopsies.
Results: Almost all the cases of adenocarcinoma (100% in cases from radical prostatectomies and 92.69% from needle core biopsies) and HPIN lesions (96.77% from radical prostatectomies and 100% from needle core biopsies) showed PTOV-1 moderate and strong cytoplasmic staining.
There was no obvious association between carcinoma differentiation (by Gleason score) and the level of PTOV-1 expression. PTOV-1 was negative or showed weak cytoplasmic staining in normal prostate glandular epithelial cells in cases obtained from cystoprostatectomy specimens for bladder tumours without prostate cancer. A significant correlation was found between moderate and strong PTOV-1 staining versus moderate and strong P504S staining ($p < 0.001$).
Conclusion: Our results indicate that PTOV-1 is a highly specific immunohistochemical marker for prostate malignancy.
PTOV-1 is a more sensitive immunohistochemical marker than P504S, for the diagnosis of HPIN.
The overexpression of PTOV-1 in isolated HPIN lesions in a prostate needle biopsy without concomitant cancer, could generate suspicion of undiagnosed cancer and indicate the need to repeat the biopsy.

PS-26-052
Does ductus deferens invasion matter in pT3b prostate cancer?
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Background & objectives: Seminal vesicle invasion(SVI) is a well-known prognostic factor in prostate cancer(PCa). Although few studies focused on ductus deferens invasion(DDI), it's prognostic contribution has not been clarified yet. We aimed to investigate the clinicopathological impact of DDI on PCa with SVI(pT3b).
Methods: Among 1259 radical prostatectomy(RP) specimens with PCa diagnosed at our institution between 2005-2022, all pT3b-PCa with DDI(n=43), and random pT3b-PCA without DDI(n=28) cases were included. Clinicopathological features (tumour volume, Gleason scores, ISUP-prognostic grades, positive surgical margins(PSM), extraprostatic-extension(EPE), intraductal carcinoma, lymphovascular/perineural invasion(LVI/PNI), lymph node metastasis(LNM), biochemical recurrence(BCR), time-to-BCR) were compared between two groups. Pearson chi-square, McNemar, Fischer's exact tests were performed.
Results: Among 1259 RPs with PCa, 46 cases(3.6%) had DDI, 136 cases(10.8%) had SVI, and 43 cases(3.4%) had both. Among 71 cases included in the study, 31 cases(43.6%) had BCR and median time to BCR was 117 months. Twenty-two cases(31%) had unilateral SVI. In 17(39.5%) cases DDI was unilateral, 26(60.4%) cases showed bilateral DDI. Two cases with unilateral DDI, showed contralateral SVI. Cases with bilateral SVI, showed higher rate of bilateral DDI (p=0.021). Cases with DDI, showed more EPE and PSM (p=0.021, p=0.02). In terms of BCR, time-to-BCR, LVI, PNI, LNM, Gleason scores, ISUP-prognostic grades, tumour volume, intraductal carcinoma, no statistical difference found between pT3b-PCa cases with and without DDI.
Conclusion: SVI is associated with adverse outcome for PCa. However prognostic significance of DDI is still controversial as there are a few studies focusing on DDI. To our results, DDI doesn't seem to be associated with BCR. However further analysis will be performed by adding cancer-specific survival analysis, as it's a better indicator for oncological outcome. Moreover, significantly frequent occurrence of EPE in the PCa with DDI suggests that the most common route of SVI is most probably EPE of PCa.

PS-26-053
Automated prostate cancer identification facilitates prognosis marker assessment in 11'845 prostate cancers using artificial intelligence and BLEACH&STAIN multiplex fluorescence immunohistochemistry
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Background & objectives: Although most prostate cancers behave in an indolent manner, a small proportion is highly aggressive. To evaluate the patient's risk, several prognosis parameters, that can be accompanied by a high interobserver variability has been established. A reproducible prognostic evaluation is lacking.
Methods: To enable automated prognosis marker quantification, we have developed and validated a framework for automated prostate cancer detection that comprises three different artificial intelligence analysis steps and an algorithm for cell-distance analysis of BLEACH&STAIN immunohistochemistry. We have used the analysis framework to measure PSA, PSMA, INSM1, AR, Ki-67, CD56, Chromogranin A, Synaptophysin, CD8 in a cohort of 11'845 prostate cancers.
Results: The Ki-67 labelling index provided the strongest prognostic information among all analysed prognosis marker in 11'845 successfully analysed prostate cancers ($p<0.001$ each). The combined analysis of the Ki67-LI and Gleason grades obtained on identical tissue spots showed that the Ki67-LI added significant additional prognostic information in case of classical ISUP grades (AUC:0.82 [p=0.002]) and quantitative Gleason grades (AUC:0.83 [p=0.018]). Several combinations of these 8 prognosis markers were combined to prognosis scores and used for unsupervised clustering to identify

a proportion of prostate cancers with a particularly poor prognosis ($p<0.001$ each).
Conclusion: Automated prostate cancer identification enables fully automated prognosis marker assessment in routine clinical practice using deep learning and BLEACH&STAIN mfIHC.
Funding: The PSA, INSM1, Ki-67, Chromogranin A, Synaptophysin, CD8, AE13, p53 antibody clones were provided by MS Validated Antibodies GmbH (owned by a family member of GS)

PS-26-054
Rare localisations of metastatic renal clear cell carcinoma – twenty years of experience of two institutions
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Background & objectives: Clear cell carcinoma is the most common type of renal malignancy, accounting for over 70%of all renal carcinomas. Tumours can arise in any area of the renal cortex, with the deletion of the 3p chromosome being a common chromosomal aberration.
Methods: This study comprised 266 patients with confirmed clear cell renal carcinoma, using data collected from two medical facilities (University Hospital Ostrava, CGB Laboratory) between 2000 and 2020. After that, parameters such as gender, age, and location were examined. All of the statistics were collected in March 2022, over the course of three weeks of rigorous work.
Results: There were 167 males (62.8%) and 99 women (37.2%) among the 266 patients, with a mean age of 64.2 years (median 65). The tumour spread through the lymphatic system to the lymph nodes was seen in 13.4%. Hematogenous metastases, on the other hand, predominated, with the following examples: lungs 59 (19.8%), bones 37 (12.4%), spine 24 (9,02%), adrenal glands 26 (8.7%), skin 13 (4.4%), peritoneum 12 (4%), fallopian tube and brain 9 (both 3%), vagina and liver 8 (both 2.7%), breast and mediastinum 7 (2.3%), pancreas and small intestine 6 (2.3%). Bronchus, parotid, thyroid, and stomach are among the most uncommon and underrepresented sites of metastasis, according to the study.
Conclusion: The goal of this statistical research is to show that clear cell renal carcinoma can spread hematogenously. When we consider the vascular system's architecture, we can see that the most common locations of metastases (lungs, spine, and adrenal glands) are all extremely close to the kidney basin, putting these structures at a higher risk of metastatic clear cell carcinoma.

PS-26-055
Immunohistochemical expression of the ERG oncoprotein in prostatic cancer and its relationship with pathological parameters
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Background & objectives: The fusion of transmembrane protease serine 2 with E26 transformation-specific family genes, particularly ERG, is the most widespread genetic alteration in prostatic adenocarcinoma. In this study,we investigated the ERG overexpression in prostate adenocarcinoma and its association with pathological prognostic parameters.
Methods: The study was conducted at Rabta hospital incorporating 25 specimens of radical prostatectomies sent to histopathology department. Different pathological findings were re-evaluated by reviewing histopathologic slides. ERG immunohistochemistry was performed using ERG antibody (clone EPR3864). Comparative analysis was done for ERG(+) and ERG(-) groups based on age ;WHO grade group; perineural invasion; vascular invasion; extraprostatic extension; pTNM classification 8th edition.
Results: ERG expression was positive in 32%(8 cases) and negative in 68%(17 cases). In ERG(-) group, mean age was 64.7 years. Perineural invasion was seen in 11 cases. Lymphovascular invasion, extraprostatic extension and seminal vesicle invasion were noted in 6, 7, and 2 cases respectively.10 cases were pT2 stage and 6 cases were pT3 with significant association to WHO grade group 2. In ERG(+) group, mean age was 66.4 years, showing perineural invasion in 7 cases, Lymphovascular invasion in 2 cases, extraprostatic extension and seminal vesicle invasion in 7 cases. Tumours were staged pT2 in 4 cases and pT3 in 4 cases. WHO grade group 1 was seen in 5 cases.
Conclusion: The ERG overexpression seems to be an early molecular event harbouring in prostatic adenocarcinoma with lower WHO grade group in patients older than 66 years.

PS-26-056
Molecular classification of urothelial bladder carcinomas: input of the immunohistochemistry
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Background & objectives: Urothelial carcinomas are characterized by Distinct molecular subtypes with different evolutive and therapeutic features. this study aimed to analyse the expression of the antibodies anti-CD44;anti-GATA3; anti-CK5/6;anti-CK20 and anti-FGFR3 in the urothelial bladder carcinomas and to classify them into molecular subtypes.
Methods: This was a retrospective study of 36 cases of urothelial bladder carcinoma. The immunohistochemical analysis was carried out using the antibodies anti-CK5/6,anti-CD44,anti-CK20,anti-GATA3 and anti-FGFR3. Subsequently, the tumours were classified into luminal or basal subtype depending in the immunohistochemical profile. The expression of these antibodies and the molecular subtypes were analysed according to epidemiological and prognostic factors of urothelial bladder carcinoma.
Results: The average age was 61.24 years. Tumours were unifocal in 75%, low grade in 44% and high grade in 56% of cases. These tumours infiltrated the vesical muscle in 36% of cases. The tumours expressed CK5/6 in 17%, CD44 in 20%, CK20 in 42%, GATA3 in 86% and FGFR3 in 70% of cases. 88% of cases were classified into luminal subtype and 12% into basal subtype. The expression of CD44 was correlated with the grade while CK20 was associated with tumour localization. The expression of FGFR3 was associated with the grade and the infiltration of the lamina propria. The molecular subtype was correlated with the infiltration of the bladder muscle.
Conclusion: The molecular classification of urothelial bladder carcinomas appears to be the future of the pathology of the bladder. However, microscopic analysis still play an important part in rapid diagnosis but a comparison of these two molecular and histologic aspects is crucial.

PS-26-058

Plasmacytoid urothelial carcinoma of the bladder: histological and clinical features of 14 cases

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Background & objectives: The plasmacytoid urothelial carcinoma (PUC) of the bladder is a rare and aggressive subtype of urothelial carcinoma (UC) with delayed presentation, infiltrative spread, and poor prognosis. In this study, we report clinicopathological and prognosis outcomes on patients with bladder PUC.
Methods: 14 cases with pathologically proven PUC were identified among 566 bladder UC between 2001 and 2021. Archived H&E-stained slides were reviewed for pathologic analysis, including histologic features, tumour grade, association with UC, lymphovascular invasion, metastasis to lymph nodes and other organs, and cancer TNM stage. Clinical data, including age, clinical presentation, treatment, and outcomes were retrieved from patients medical records.
Results: 2.47% of invasive UC of the urinary bladder show plasmocytoid phenotype. Mean age was 68 years. 80% of patients presented with haematuria. All 14 patients underwent cystoprostatectomy with urinary diversion. Histologically, all tumours were high grade carcinomas. Pure plasmacytoid features were seen in 4 cases, while in the others 10 cases, the plasmacytoid phenotype was mixed with conventional UC. Lymphovascular invasion and metastasis to lymph nodes were seen in 71.42% and 64.28% of cases respectively. 57.14% Cases were PT2 stage, 28.57% cases were PT3 stage and 14.28% cases were PT4 stage. The 3 year survival rate was ranged from 64.2% without locoregional recurrence to 57.1% without distant recurrence.
Conclusion: Accurate identification of UC histological subtypes is an important part of risk stratification,as these variants exhibit malignant biological characteristics. Bladder PUC presents a distinctive clinicopathological outcome represented by high aggressiveness and poor survival rate.

PS-26-059

Prognostic value of keratins and desmosomal proteins in muscle-invasive urothelial carcinoma

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Background & objectives: Keratins (CK) and desmosomal proteins like desmoglein (DSG) and desmocollin (DSC) have diagnostic and prognostic value in many tumour entities. We investigated their prognostic value in primary tumour (PT) and matched lymph node metastases (LNM) from muscle-invasive bladder cancer (MIBC).
Methods: Tissue micro arrays (TMA) were generated for PT and corresponding LNM. Samples were immunohistochemical stained for keratins (CK8, CK18, CK7, CK19, CK20, CK10, CK13, CK5, CK14, CK17) and desmosomal proteins (DSG3, DSC3, DSG2). Evaluation was done using the H-Score and correlation between PT and LMN followed by survival analysis using Cox proportional-hazard model.
Results: The study cohort consisted of 232 cases of which 66 cases (28%) had LNM. We noted significant ($p<0.05$) and positive ($r>0,60$) correlations in the expression of CK7, CK8, CK19 ,CK20 and CK5 in PT and LMN. In the multivariable Cox regression analysis, we found that CK10 levels in PT were independently associated with worse outcomes – hazard ratio (HR) 1.08 (95% confidence interval [CI]: 1.03-1.13) for overall survival (OS) and HR 1.12 (95%CI:1.05-1.18) for relapse-free survival (RFS).
Conclusion: Our results of a two-centre cohort show that the immunohistochemical expressions of CK and desmosomal protein have different concordance in PT and matched LMN in MIBC. While the simple and luminal proteins, respectively, tend to show correlative expression, basal proteins like CK10, DSG3, DSC3 (except CK5) had no or little correlation in their expression pattern of PT and LMN. A high CK10 expression in PT is significantly associated with worse outcomes, both RFS and OS.
Funding: Doctoral Scholarship University Hospital Magdeburg

PS-26-060

SHH pathway tissue expression depends on histological type of germ cell tumours

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Background & objectives: Sonic hedgehog (SHH) pathway affects embryological cell migration, morphogenesis, gonadal formation, and sexual differentiation. SHH signalling is activated in many aspects of cancerogenesis, including the biology of paediatric germ cell tumours (GCTs)- a heterogeneous group of neoplasms.
Methods: 98 GCTs (46 girls, 52 boys; 1m-18yrs) examined: 7 embryonal carcinomas (EC), 19 seminomatous tumours (SEM), 18 yolk sac tumours (YOL), 33 immature teratomas, 6 mature teratomas, 15 mixed-type tumours. The clinical presentation, tumour localization, stage varied. SHH pathway elements: SHH, PTCH-1, SMO, SUFU, GLI-1, GLI-2, GLI-3 were evaluated immunohistochemically on FFPE sections (TMAs, full sections) with own semi-quantitative scale.
Results: In immunohistochemical analysis EC, SEM, YOL tumours (homogenous cases and components of mixed tumours) were strongly positive for GLI-1 (nuclear), SHH (membranous and cytoplasmic), and PTCH-1 (nuclear). In parallel, GLI-2 (nuclear) and SUFU (nuclear) were varied in expression, while GLI-3 (nuclear) and SMO (cytoplasmic and nuclear) were mostly negative/ weak. Protein expression in teratomas was variable in intensity and localization, dependent on constituent tissue type, with heterogeneous presentation between tumours and even individual slides. Primitive neuroectoderm revealed high SHH expression. The stroma of GCTs was also positive for pathway proteins in the majority of cases, although rarely showed full concordance to the staining of tumour cells.
Conclusion: GCTs show heterogeneous SHH pathway proteins tissue expression, related to their histological type. SHH expression in tumour cells and tumour stroma suggests its auto- and paracrine role in their biology. No significant difference was found between protein expression in monomorphic tumours and corresponding components in mixed tumours.
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PS-26-061

TFE3 is related with PI3K/Akt pathway in renal cell carcinoma

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Background & objectives: PI3K/Akt pathway in renal cell carcinoma progression, metastasis, resistance to therapies has not been investigated clearly. TFE3 expression is related to worse prognosis in renal cell carcinoma in several studies. We tried to find relation between TFE3 and PI3K/Akt pathway.
Methods: Human renal cell carcinoma cell lines UOK146, Caki-1, and Caki-2 were maintained in DMEM supplemented with 10% foetal bovine serum. TFE3 down regulation was done by small interfering RNA transient transfection in UOK 146 cells. TFE3 overexpression was don by transient transfection in Caki-1 and Caki-2 cells. Western blot analysis was done for TFE3 and phospho-Akt, and Akt.
Results: The PI3K/Akt signalling pathway serves an important role in renal cell carcinoma for the regulation of cell proliferation, differentiation and survival. When TFE3 was down regulated with TFE3 specific siRNA, phospho Akt was decreased, significantly ($p<0.001$). When TFE3 was upregulated with TFE3 transfection, phosphor Akt was increased, significantly ($p<0.001$).
Conclusion: TFE3 was related with PI3K/ AKT pathway in renal cell carcinoma. Our result suggest an important role for PI3K/Akt inhibitors as a potentially useful treatment for patients with renal cell carcinoma.

PS-MD-01 | Poster Session Molecular Diagnostics Pathology Symposium

PS-MD-01-001
EIF1AX mutations in thyroid nodules: analysis of a series of 1095 consecutive cases

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Background & objectives: EIF1AX, on X chromosome (Xp22.12) encodes an essential eukaryotic translation initiation factor (eIF1A). EIF1AX mutations are RAS-like genetic changes found in a minority of thyroid nodules. Little is known about their prevalence and correlation with thyroid pathology in Europe.
Methods: Between February 2019 and December 2021 we analysed 1095 samples (709 cytology and 386 FFPE histology specimens) using a NGS panel including 330 genomic regions and comprising EIF1AX (exons 1, 2, and chrX intronic region g.20148634–20148745).
Results: Amplifiable DNA was obtained in 1029 of 1095 samples (cytology: 654/709, 92.24%; FFPE histology 375/386, 97.15%). EIF1AX mutations were found in 15/1029 cases (1.46%). Mutated cytology specimens: 1/48 (2.08%) BETHESDA-I (histology: hyperplastic nodule); 2/125 (1.60%) BETHESDA-II (histology: one follicular adenoma, one hyperplastic nodule); 4/234 (1.71%) BETHESDA-III (all without histology follow-up); 1/100 (1.00%) BETHESDA-IV (histology: hyperplastic nodule); 1/61 (1.64%) BETHESDA-VI (histology: undifferentiated thyroid carcinoma; PIK3CA and TERT promoter were also mutated). Mutated histology specimens: 1/38 (2.63%) hyperplastic nodules; 5/79 (6.33%) follicular adenomas. In addition to the undifferentiated carcinoma, EIF1AX mutations co-existed with additional mutations (NRAS-p.Q61R: two cases; HRAS-p.Q61K, GNAS-p.A201H, TSHR-p.F631L: one case each) in 5/1029 (0.48%) cases, all with benign diagnoses.
Conclusion: EIF1AX mutations are RAS-like alterations found in benign follicular-patterned thyroid nodules (hyperplastic nodules and follicular adenomas) where, in a small minority of cases, they may co-exist with other RAS-like mutations. No EIF1AX mutations were found in 172 papillary, 14 follicular, 12 oncocytic, 10 medullary carcinomas. The only malignant tumour with EIF1AX mutation in the series was an undifferentiated carcinoma with co-mutated highly pathogenic alterations (PIK3CA and TERT promoter). Isolated EIF1AX mutations are not a marker of malignancy in thyroid nodules.

PS-MD-01-003
First steps in molecular classification in endometrial carcinoma: experience in a low income country

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Background & objectives: The Cancer Genome Atlas (CGA) categorized endometrial cancer into four genomic groups combining POLE mutational analysis with immunohistochemical analysis of p53 and mismatch repair (MMR) proteins.
We aimed to evaluate feasability of this new classification of endometrial carcinoma in routine.
Methods: Searching POLE mutations in exons 9 to 14 was performed by SANGER sequencing on frozen tumoral material. Mismatch repair genes deficiency (MSH2, MSH6, MLH1, PMS2) was assessed by either immunohistochemistry and/or MSI statement using the PCR real-time based molecular idyllaTM system testing, on formalin fixed and paraffin embedded (FFPE) tumoral tissue. P53 was evaluated by immunohistochemistry on FFPE.
Results: We achieved molecular classification in twenty endometrial carcinoma cases.
Our first results revealed 3 new silent mutations in exons 9 and 10 and a novel stop mutation at exon 13 of POLE gene: One patient carries two silent mutations in respectively exon 9 and 10 with and MSS status and a normal expression of P53; a second patient with a silent mutation at exon 9, is deficient in MLH1 and PMS2 protein and normal expression of P53; the functional mutation at exon 13 concerned a woman with proficient MMR protein and a focal immunostaining of P53. 50% of patients without any mutation in POLE gene were MSI and P53+.
Conclusion: Our first step in molecular classification of endometrial cancer highlighted new mutations in POLE gene. Our experience showed that molecular classification is quite complex in routine. Pole mutation is somewhat tedious because of the need of frozen tissue and the technique is long. Immunohistochemistry needs good practice in pre-analytical step and idylla technique could be an alternative solution.

PS-MD-01-004
Genomic landscape of 63 samples of 29 Hungarian breast cancer patients

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Background & objectives: Incidence of breast cancer (BC) in Hungary is similar to neighboring Central European countries, however, BC mortality is much higher. It is of importance to characterize commonly affected genes in specific patient populations in order to efficiently aid targeted therapies.
Methods: We performed whole genome sequencing of 63 samples of 29 Hungarian BC patients using the Illumina NovaSeq

6000 instrument. Short genomic variants (both germline and somatic) and copy-number alterations were detected using standard bioinformatical protocols. Comparison of the germline mutation allele frequencies with the 1000 genomes project and the non-Finnish European population of the gnomAD database was performed.
Results: Canonical BC-associated genes with pathogenic germline mutations were CHEK2 and ATM. Most of the detected somatic short variants were SNPs and on average only 8% and 6% of them were deletions or insertions. The ratio of tumours harbouring pathogenic somatic variants in the most affected genes were: KMT2C (31%), MUC4 (34%), PIK3CA (18%) and TP53 (34%). Among the cancer-related genes, copy-number alterations were most common in NBN, RAD51C, BRIP1 and CDH1. COSMIC mutational signature analysis showed domination of the mutational processes associated with homologous recombination defect (specifically SBS3 was present in 59% of the patients with a weight of 8% or larger), APOBEC-related processes and general aging-related, clock-like signatures.
Conclusion: Most of the observed germline mutations are approximately as frequent in the Hungarian BC cohort as in independent European populations. We foresee that more accurate and reproducible detection of pathogenic SNPs and mutations will generate a more complete picture of the landscape of breast carcinomas. Additional investigation of the genes presented above with pathogenic germline mutations and harbouring pathogenic somatic variants and associated pathways could delineate biological susceptibilities and improve treatment options in different breast carcinoma subtypes.

PS-MD-01-005
Learnings from two years of external quality assessment (EQA) for BRCA1/BRCA2 testing in metastatic castration-resistant prostate cancer (mCRPC)
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Background & objectives: Prostate cancer is the second most common cancer diagnosis in men. PARP inhibitors were approved for treatment of mCRPC patients with *BRCA1/BRCA2* gene variants in 2020. We share findings from EQA schemes in which up to 100 laboratories participated globally.
Methods: EMQN CIC and GenQA provided three formalin fixed paraffin embedded (FFPE) samples to participating laboratories for *BRCA1/BRCA2* testing; the laboratories were asked to use their routine test methodologies. The anonymised results were assessed and peer reviewed. Individual laboratory and overall summary scheme reports were produced to help laboratories improve their performance and to enable benchmarking of results and reporting.
Results: Two pilot EQA schemes for *BRCA1/BRCA2* testing in Prostate cancer ran in 2020 (32 laboratories) and 2021 (100 laboratories). The overall analytical (genotyping) error rate in 2021 was 9%, with errors reported for all three cases, probable causes for these errors will be discussed. Additionally, there were several common themes identified where improvements could be made to the reporting of the clinical interpretation of the results.
Conclusion: The results demonstrate the benefit of participation in EQA to proactively identify sources of error in *BRCA1/BRCA2* genotyping and to improve the quality of interpretation and reporting of results in order to help ensure correct access to treatment and appropriate follow up for mCRPC patients.

E-Posters

E-PS-01 | E-Posters Autopsy Pathology

E-PS-01-001
Ultrasound-guided minimally invasive autopsy as an alternative to conventional autopsy in selected patients: a case report
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Background & objectives: Ultrasound-guided Minimally Invasive Autopsy (US-MIA) has been made in the context of COVID-19 pandemic to reduce the risk of infection during the procedure, but this technique could be used in other autopsies for different purposes.
Methods: We report a case of an 85-year-old woman with solid lesions in right-orbital region and both parotids, as well as multiple cervical lymphadenopathies. A previous diagnosis of an aggressive marginal B-lymphoma was made; but the scarce tissue received, did not allow the performance of complementary studies in view of certain clinical discrepancies. Patient died and an autopsy study was requested.
Results: Ultrasound Guided Fine Needle Aspiration (US-FNA) and core needle biopsy (CNB) of orbital and parotid lesions were performed with subsequent Rapid On-Site Evaluation -ROSE- of tissue to ensure an adequate specimen and preserve the anatomical appearance. US-MIA made by trained pathologist is a good method to obtain representative tissue samples as an alternative to a conventional autopsy in some patients. In this case, dissection of both parotids would have been a disfiguring and difficult procedure, even unnecessary. This method allowed us to evaluate the specimen on site to guarantee enough material for additional studies and postmortem diagnosis.
Conclusion: US-MIA, US-FNA and CNB are safety and easy methods of obtaining tissue samples that can be performed by a trained pathologist. These procedures could be applied in our daily work as an alternative to complete diagnostic autopsies, not only in procedures with elevated risk of infection.

E-PS-01-002
Sudden cardiac death in pancreatic acinar-neuroendocrine carcinoma
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Background & objectives: Pancreatic acinar-neuroendocrine carcinoma is a tumour that often remains undiagnosed during life. We present a case of pancreatic acinar-neuroendocrine carcinoma, which was a histological finding in a patient who died from massive myocardial necrosis.
Methods: Patient N. (80 years of age) was admitted to the emergency hospital with severe chest pain, which was relieved by drugs. Based on clinical signs and the results of laboratory and instrumental studies, doctors diagnosed infarction of the lateral wall of the left ventricle. The patient died 3 days after admission to the emergency hospital.
Results: Autopsy revealed: 1) necrosis in the myocardium, similar to an anterior transmural infarction with involvement of the septal wall; 2) intact coronary artery; 3) myocardial hypertrophy (where LV wall thickness constituted 1.8 cm), thickening of the interventricular septum thickness (1.7 cm).

Microscopic examination revealed undifferentiated pancreatic carcinoma with irregular tumour glands with cribriform components embedded in the desmoplastic stroma. Changes in the myocardium included necrosis with prominent neutrophilic infiltration, indicating an acute state of secondary myofiber necrosis (4-5 days).
Conclusion: Features of this case include undifferentiated pancreatic carcinoma undiagnosed during life; no visible changes in the pancreas during the autopsy; lesions in the myocardium, that are considered secondary to necrosis.

E-PS-01-003
Incidental multilocular cystic nephroma in forensic pathology
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Background & objectives: Multilocular cystic nephroma is a rare cystic tumour without a grossly appreciable solid component, which mainly occurs in adult women. The aim of our study is to report five cases of multilocular cystic nephroma incidentally discovered in the necroptic examination.
Methods: The reports from autopsies performed in the last five years in our department have been reviewed and five cases of multilocular cystic nephroma, with age range between 50 to 80 years old (four females vs. one male), have been selected. The necroptic examination has been associated to collection of tissue specimens for microscopy, followed by paraffin-embedding and routine staining.
Results: The gross findings were that of multiple well-circumscribed, multilocular cystic renal masses, with variable size, ranging between approximately 4-7.5mm diameter, filled with serous to serosanguinous fluid, eccentrically-located, and pushing the renal pelvis. The microscopic examination revealed numerous cysts lined by a single layer of cells with various morphology (flat, cuboidal, and hobnail type), with minimal cytological atypia, and no evident mitoses. The cysts have been characteristically associated with fibroblastic stroma, containing hemosiderin-laden macrophages and focal chronic inflammation. Polycystic renal disease has been excluded in all cases.
Conclusion: Despite their rare occurrence, multilocular cystic nephromas should be considered in the differential diagnosis of cystic renal cancers or benign tumours, such as mixed epithelial and stromal tumour (MEST), angiomyolipoma with epithelial cysts, partially differentiated cystic nephroblastoma (CPDN), and tubulocystic renal cell carcinoma. They may be incidentally discovered during necropsy and microscopic examination may certify the diagnosis.

E-PS-01-004
Fatalities in environmental heat exposure
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Background & objectives: Death from hyperthermia may occur when the core body temperature is higher than 40 degrees Celsius. The aim of our study is to report the microscopical and immunohistochemical features of hyperthermia from our files, in the appropriate environmental conditions.
Methods: The autopsy reports of our department, from the last 12 years, have been reviewed, and four cases of hyperthermia have been selected, in men with an age range between 31-49 years old. Routine hematoxylin and eosin staining, along with Periodic Acid-Schiff (PAS) and immunohistochemistry using Sirtuin1 (SIRT1), Ubiquitin (Ub), Heat shock protein 70 (Hsp70), and Aquaporin-1 (AQP-1) have been performed.
Results: The gross findings showed pulmonary and cerebral oedema, along with pleural, epicardial, and peritoneal haemorrhagic petechiae (3 cases), along with myocardial fibrosis and hepatic steatosis (2 cases). Microscopy revealed alveolar and cerebral oedema, pleural and epicardial microhaemorrhages. AQP-1 immunopositivity was observed in lung endothelial cells, while neurons showed a positive expression of Hsp70. Cardiomyocytes showed vacuolar degeneration and contraction bands, along with SIRT1 weak immunoreactivity and its focal positivity loss in areas associated with contraction bands. Amorphous intra-tubular and intra-capsular space material, renal corpuscle basal lamina thickening, and Ub intense positive expression in distal convoluted tubules epithelium and in the outer layer of the Bowman's capsule have been also identified.
Conclusion: Death from environmental-induced hyperthermia is a rare condition in legal medicine, which occurs when the thermoregulatory mechanisms are no longer capable of effectively dissipate the heat. The microscopic examination and immunohistochemistry may add valuable information for diagnosis in these cases.

E-PS-01-005
Capnocytophaga canimorsus septicaemia diagnosed post-mortem - a case report
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Background & objectives: Capnocytophaga canimorsus is a gram negative bacteria which is a constituent of the oral flora of dogs. Infection in humans is uncommon, however predisposing factors include alcoholism, asplenia, and immunosuppression. A case of fatal C.canimorsus infection diagnosed post-mortem is described.
Methods: A 60 year old male patient presented to the emergency department with a history of epigastric pain and a low-grade temperature, on a background of recent heavy alcohol consumption. The initial impression was acute pancreatitis, however the patient rapidly deteriorated, developing respiratory failure within an hour of presentation. He subsequently had a cardiopulmonary arrest which was not amenable to resuscitation.
Results: A post-mortem examination carried out demonstrated severe coronary artery atheroma and biventricular hypertrophy. Of note, there were no findings suggestive of recent animal-inflicted trauma. The initial patient history did not enquire about animal exposure or dog bites or scratches, however subsequent history from the family revealed the patient had been a dog-owner and had a history of alcohol abuse. C.canimorsus was isolated on ante-mortem blood cultures after a prolonged incubation period.
Conclusion: C.canimorsus infection is associated with a mortality of between 25 to 30%. The diagnosis is often difficult due to the variable presentation, and the elusiveness of diagnosis can lead to adverse outcomes. A high level of suspicion in patients presenting with sepsis in the presence of risk factors is important. The rapid deterioration of the patient in this case highlights the importance of considering C.canimorsus in the differential diagnosis, and in initiating antimicrobial therapy promptly.

E-PS-01-006

Spontaneous coronary artery dissection in a pregnant woman with COVID-19

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Background & objectives: Spontaneous coronary artery dissection (SCAD) is a rare condition with life-threatening maternal complication. We describe a case of a 35-year-old pregnant woman, who died with an acute myocardial infarction (AMI) and try to highlight the possible association with COVID-19.
Methods: During the third trimester of pregnancy, the patient presented with chest pain and was diagnosed with AMI caused by SCAD on the left anterior descending (LAD) coronary artery. Stenting of the LAD was performed. Concomitantly, the patient was tested positive for COVID-19. Due to life threatening cardiac instability, an emergency caesarean section was performed, and she died shortly after.
Results: The autopsy was performed at the Institute of Forensic Medicine of Targu Mures and revealed an extensive anterior AMI of the left ventricle. A permeable stent on the LAD with an important subintimal haemorrhage was seen. On microscopic view, the transmural AMI was confirmed. LAD examination revealed a discontinuous intimal area and a massive haemorrhage into the subjacent media. Based on elastica van Gieson staining the fibro-muscular dysplasia diagnosis was infirmed. Massive acute pulmonary oedema was also seen, but without pathological changes suggestive for COVID-19 pulmonary involvement.
Conclusion: SCAD is a rare event, and its causes are still debated. The association of COVID-19 with some other known risk factors (age >30 years and smoking) could have aggravated the underlying condition and lead to the occurrence of this SCAD.
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E-PS-01-008

An unusual case of infrarenal pheochromocytoma developed on ectopic adrenal tissue

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Background & objectives: Pheochromocytomas are catecholamine-secreting tumours arising from the chromaffin cells of the adrenal medulla. Ectopic adrenal tissue is usually formed by cortex only. We describe an unusual case of pheochromocytoma located in the infrarenal area associated with bilateral adrenal hyperplasia.
Methods: A 70-year-old patient was admitted for syncope, diaphoresis, and high blood pressure. Computed tomography showed a 73x70x72 mm mass of the left infrarenal/paraaortic area. High levels of metanephrine and noradrenaline were found in the urine. Tumour resection was performed. After surgery, the blood pressure suddenly decreased and could not be restored. A few days after the surgery the patient died.
Results: Histopathological examination of the surgical specimen revealed a proliferation of tumoural monotonous cells, with eosinophilic cytoplasm, round nuclei with prominent nucleoli arranged in clusters. Among them, there were highly pleomorphic areas composed of large, atypical cells, with abundant, eosinophilic cytoplasm and irregular, hyperchromatic nuclei. Large areas of haemorrhage were observed, same as vascular invasion. Immunohistochemically (IHC), the neoplastic cells were positive for Synaptophysin and Chromogranin, showed a Ki67 index over 80% and did not express Inhibin A and S100. At the autopsy, both adrenal glands proved to show hyperplasia but unrelated to the tumour mass. The histological aspect, location, and immunophenotype indicated an ectopic infrarenal pheochromocytoma.
Conclusion: In patients with pheochromocytoma developed on ectopic adrenal tissue clinical management might be difficult and diagnosis can be sometimes established only based on post-mortem histopathological examination. Autopsy can be extremely useful in such cases with unexplained evolution.

E-PS-01-009

Covid-19 and granulomatosis with polyangiitis. Autopsy report

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Background & objectives: Granulomatosis with polyangiitis is a rare type of autoimmune necrotizing vasculitis typically associated with antineutrophil cytoplasmic antibodies (ANCA). This disease affects small and medium vessel with a perivascular granulomatous inflammation. The renal and pulmonary vessels are predominantly involved in process.
Methods: We present an autopsy case of 36-years old man with COVID-19 and previously diagnosed untreated granulomatosis with polyangiitis. The patient in a critical condition was transported to the intensive care unit of a hospital where he died within 5 hours despite all the resuscitation treatment. Autopsy examination was performed.
Results: An autopsy revealed multiple petechial haemorrhages in the brain with a cerebral oedema. The pleura and the pericardium are covered with fibrin deposits. Serous fibrinous effusion in pleural cavity is also revealed. Lungs are oedematous with a foam fluid and blood. The surface of the kidneys was with regenerated infarctions.
Histopathological examination of the lungs revealed perivascular and peribronchial sclerosis. Alveoli was with intraalveolar hyaline membranes formations. Interstitium is infiltrated by lymphocytes. Histopathological examination of the kidneys showed emerged necrotizing glomerulonephritis has led to massive glomerulosclerosis. There was also lymphocytic infiltrate in interstitium of kidneys. Microcirculatory vessels of lungs and kidneys was thrombosed and affected by granulomatous inflammation.
Conclusion: In this article we have presented a rare case of a COVID-19 occurring against the background of active phase of untreated granulematosis with poliangiitis. This combination of severe vasculitis of different aetiologies led to multiply damage of highly vascularized organs such as lungs and kidneys.

E-PS-01-010

A fatal case of fibrinous pericarditis in a uremic patient – a case report

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Background & objectives: Fibrinous pericarditis is an often-difficult diagnosis, important for its potential complications. Hemopericardium and subsequent cardiac tamponade are life-threatening conditions and

must be readily identified, for which the aetiology of the pericarditis invests itself of a greater significance in the prognosis.
Methods: A 67-year-old male patient with non-dilated ethanolic cardiomyopathy and chronic kidney disease presented to the emergency department with intense abdominal pain and hypotension. The echocardiogram revealed a pericardial effusion of 3 cm extent with hemodynamic failure. A pericardiocentesis to drain the effusion was initiated, but the patient suffered a cardiorespiratory arrest and died.
Results: During the post-mortem, while opening the pericardial cavity, we found a large quantity of blood and clots, totalling a volume of approximately 750 mL. We also observed an epicardium with abundant fibrinous adhesions, which warranted a fibrinous pericarditis diagnosis. In our case, several aetiologies were proposed and investigated, having favoured the uremic cause, in the context of the patient's chronic kidney disease, now acutely worsened by the clinical picture. In fact, the patient presented with very high levels of creatinine (4,03 mg/dL, reference values between 0,72 – 1,25) and urea (260 mg/dL, reference values between 18,0 – 55,0), as well as an estimated glomerular filtration rate of 14 mL/min/m2.
Conclusion: Fibrinous pericarditis is caused by several factors, and in patients with chronic kidney disease, the uremic aetiology has to be considered. The accumulation of metabolites in the blood leads to an inflammatory response in the pericardium and the platelet dysfunction can further complicate this with hemopericardium. A careful autopsy examination, showing a dry, granular heart surface, covered in fibrinous exsudate, is typical. Our case shows how the post-mortem and its correlation with clinical findings enables a precise etiological diagnosis.

E-PS-01-011
The histological effects of colchicine in the setting of Behcet's disease: an autopsy case report
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Background & objectives: Colchicine is a drug with antimitotic effects used in the treatment of a variety of medical conditions such as Behcet's disease. It has a narrow therapeutic window, and its toxicity can result in multiorgan failure and death.
Methods: We present the case of a 64-year-old female with hypertension, depressive disorder and Behcet's disease. She was medicated with 1mg of Colchicine daily. The patient presented to the emergency department with a three-day history of abdominal pain, diarrhoea and vomiting, which culminated in her death. Clinical autopsy was requested.
Results: The autopsy revealed extensive ecchymoses in both arms, generalized atherosclerosis, and hardened white pleural plaques in the apex of both lungs, among other changes. There were no mucosal ulcers or macroscopic changes to the myocardium. Histological analysis showed an early stage myocardial ischemic event with associated neutrophils, precirrhotic alcoholic steatohepatitis, renal hypertensive changes and pulmonary "apical caps". In addition, histopathological study of the oesophagus, vagina and bladder showed epithelial pseudostratification, loss of polarity and multiple "ring" (metaphase) mitosis in their mucosas. There were no specific changes attributed to Behcet's disease. No toxicological analyses of colchicine levels in blood or urine were available and no samples were collected.
Conclusion: This case highlights the striking histopathological manifestations of colchicine, which only occur at toxic levels. They can therefore serve as a surrogate for toxicological analysis in cases such as this with clinical symptoms of toxicity. Despite not being always present, these signs should be recognized by the pathologist with great care not to misdiagnose them as dysplastic or neoplastic alterations.

E-PS-01-012
Unexpected cause of a blunt vertebral artery injury with a lethal outcome and contributing factors
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Background & objectives: The majority of vertebral artery injuries are due to blunt trauma from motor vehicle crashes while other causes are less common. Closed injuries of vertebral arteries are induced by hyperextension coupled with lateral flexion or rotation of the head.
Methods: 43-year-old woman complained of the neck pain and shortness of breath lasting three days. MSCT angiography revealed a bleeding from the right vertebral artery with hematoma involving the neck, the mediastinum and the right hemithorax. The patient denies the injury, but states that she had a dental intervention seven days before the first symptoms.
Results: The patient was urgently referred for vascular surgical procedure, but the lethal outcome occurred during the surgery. An autopsy confirmed transection of right vertebral artery in the neck, 2 cm away from origin, with the formation of hematoma in the neck and mediastinum, and severe right haemothorax (3000 ml blood). Further detailed examination revealed that the woman was suffering from hypertension (hypertensive heart, kidney and brain diseases), induced by incidentally found pheochromocytoma of the right adrenal gland. Furthermore, an external examination revealed several soft subcutaneous nodules of upper and lower extremities which histologically corresponded to neurofibromas, altogether indicating possible inherited diseases such as NF1 or MEN2.
Conclusion: Bleeding from the vertebral artery in the neck is extremely rare consequence of blunt injury, usually caused by neck hyperextension, but not frequently associated with common procedures such as dental interventions. Mild but prolonged neck hyperextension causes a vertebral artery compression at the entry into the vertebral column, producing a focal vessel injury with a higher possibility of dissection/transection in hypertensive patients. In this case, hypertension induced by pheochromocytoma was contributing factor to fatal vertebral artery bleeding.
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E-PS-01-013
Amyloiosis: report autopsy in a patient with suspected sepsis
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Background & objectives: Amyloidosis is a syndrome characterized by a group of diseases which have in common extracellular protein deposits called amyloid fibrils.
Methods: Autopsy report of a 53-year-old woman with abdominal discomfort, inappetence and asthenia, evolving with progressive worsening and severe hepatic and renal dysfunction requiring dialysis, deep vein thrombosis and suspected sepsis.
Results: At autopsy, yellowish meninges; congested brain; voluminous bilateral pleural effusion; pericardial effusion; enlarged heart,

yellowish myocardium, myocardial hypertrophy; wine-coloured lungs with subpleural petechiae and mild oedema and congestion; ascitic fluid with a citrine appearance; liver with a micronodular appearance, firm consistency and yellowish coloration on cuts, with a diffusely hardened and yellowish parenchyma; yellow kidneys with a finely granular surface and on cuts there is medullary congestion with a yellowish cortical zone. The histopathological study shows liver, heart and kidneys with diffuse extracellular deposition of amorphous, hyaline and eosinophilic material refracting to polarized light with Congo Red staining. Microscopic findings of deposits are consistent with amyloidosis.
Conclusion: How there is no clinical and morphological evidence of active inflammatory or infectious disease, inferring this is primary amyloidosis that justifies and explains the clinical picture and the Outcome otherwise, the clinical suspected septicemia was not set by the anatomo-pathological findings.

E-PS-01-014
A clinical case of acute myocardial infarction with myomalacia in COVID-19 in a man with hypertension
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Background & objectives: The COVID-19 pandemic is a serious health threat. In addition to pulmonary complications, cardiovascular consequences are common. Purpose - to describe a case of infection with the SARS-CoV-2 virus with the development of acute myocardial infarction and myomalacia.
Methods: According to the autopsy - the corpse of a man, 50 years old, a history of hypertension for 15 years. According to computed tomography - 75% lung damage. PCR test for covid-19 positive. The electrocardiogram showed signs of acute anterolateral myocardial infarction with myomalacia. Clinical and morphological analysis, virological method, staining of histological sections with hematoxylin-eosin were carried out.
Results: Autopsy in the lungs revealed alternation of moderately airy alveoli with areas of dystelectasis. In the lumen of the alveoli, oedematous fluid, focally desquamated alveolocytes, macrophages, erythrocytes, and hyaline membranes along the contour of the alveoli were diffusely determined. In the heart - muscle fibres were fragmented, focally wave-like curved. There were fields of non-nuclear necrotic cardiomyocytes with perifocal neutrophilic infiltration. Electron microscopic examination in the foci of myomalacia revealed damage to organelles, contractures of myofibrils, myocytolysis and disintegration of muscle cells with the formation of fine granular detritus. Plasmatization of the vascular wall, erythrocyte stasis with sludge phenomenon and precapillary fibrosis were determined.
Conclusion: In this case, against the background of covid pneumonia, an acute myocardial infarction of the anterolateral wall of the left ventricle was determined, which was not extensive. Significant changes were revealed in non-infarction zones: plasmatization of the vascular wall, erythrocyte stasis with sludge phenomenon and precapillary fibrosis. The stromal vessels were filled with blood to varying degrees, signs of endotheliitis were detected. Early onset of myomalacia was noted, obviously associated with the severity of the process and hemodynamic instability.

E-PS-02 | E-Posters Breast Pathology

E-PS-02-001
Primary mucoepidermoid carcinoma of the breast - case report
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Background & objectives: In comparison to its counterpart in the salivary gland, primary mucoepidermoid carcinoma (MEC) of breast is a very rare entity, accounting for 0.2-0.3% of all breast carcinomas. There are only 41 cases described up to date in the English literature.
Methods: We present a case of a 60-years old female patient with palpable lump in the upper lateral quadrant of her left breast. Ultrasonographic examination showed solid, malignant appearing lesion, 2.6 centimetres in greatest dimension and an adjacent area of clustered microcalcifications with diameter 2 centimetres. Core biopsy was performed, which was interpreted as a poorly differentiated triple-negative ductal carcinoma.
Results: The patient underwent quadrantectomy with axillary lymph node dissection. Grossly, well-circumscribed lesion, 23 millimetres in diameter, with solid and cystic areas was found. Microscopically the tumour was composed of different proportions of mucinous, epidermoid and intermediate cells, arranged in solid sheets and cystic spaces, filled with mucoid material. Tumour cells exhibited immunonegativity for oestrogen, progesterone and HER-2 protein, but appeared to be positive for CK7, CK5/6, p63 and EMA. Additionally, 30% of the cells were positive for Ki-67. Based on the specific morphologic and immunohistochemical characteristics the lesion was histologically classified as mucoepidermoid carcinoma of intermediate grade.
Conclusion: In conclusion, primary breast MEC is extremely rare, causing diagnostic and therapeutic challenges in the everyday practice. Although being triple-negative, it has favourable prognosis, especially for the low-grade histologic variants, with low risk for metastasis or recurrence. Reporting MEC cases is essential for better understanding of its clinical and biological behaviour and for establishing standard treatment strategies by the multidisciplinary team.

E-PS-02-002
Neuroendocrine tumour of the breast showing invasive micropapillary features and multiple lymph node metastases
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Background & objectives: The WHO classifies neuroendocrine neoplasms (NENs) as a special tumour entity, representing <1% of invasive breast carcinomas (IBCs), and recognises two subtypes: neuroendocrine tumour (NET) and neuroendocrine carcinoma. Herein, we present the first case with an invasive micropapillary mammary NET.
Methods: A 65-year-old woman had become aware of a tumour in her right breast 11 months prior to presentation at our hospital. Ultrasonography revealed a huge, cystic right breast tumour with enlarged regional nodes. No other lesions were identified by either systemic CT or bone scintigraphy. The patient underwent fine-needle aspiration of the mammary lesion, and the cytological diagnosis was carcinoma.
Results: A well-demarcated, multinodular, red-brown tumour, which measured 15x15x15 cm, was found in the mastectomy specimen. Histopathologically, this solid and cystic lesion consisted of medullary growth of carcinoma cells accompanied by a highly developed vascular stroma. Carcinoma cell nests displayed a retraction artifact and antipolarity. Carcinoma cells were polygonal and possessed fine-granular cytoplasm

and nuclei. Macrometastases, up to 13x8 mm, were present in 3 of 15 dissected axillary nodes. Immunohistochemically, primary and metastatic carcinoma cells were diffusely positive for chromogranin A and the oestrogen receptor. HER2 was negative, and the MIB-1 index was 36.2%. Band-like expressions of MUC1 and EMA were noted on the stroma-facing surface of the carcinoma cell clusters.
Conclusion: Some investigators recently reported that NEN is a distinctive type of aggressive IBC. Multivariate analyses have revealed that, in patients with mammary NENs, overall survival can be predicted by tumour size, nodal status, and the MIB-1 proliferation rate. Our present patient with an unusual breast cancer showing both invasive micropapillary and neuroendocrine features developed plural lymphoglandular metastases as well as having a tumour with a large diameter and luminal B-like immuno-profile. Accordingly, meticulous clinical follow-up is essential for this case.
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E-PS-02-003
Morphologic and immunohistochemical features of triple negative breast cancers: a tissue – microarray study
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Background & objectives: Triple negative breast cancers (TNBC) are the most aggressive breast cancer subtypes according to the Sain Gallen classification. The aim of the present study was to evaluate the immunohistochemical features of TNBC in relation with their histopathological characteristics.
Methods: Consecutive invasive breast cancer cases diagnosed from 2005 through 2013 were included. All tumours were re-examined and classified in accordance with the Saint Gallen classification criteria. Immunostaining with tissue micro-array was performed in all TNBC with Ventana BenchMark Ultra system with antibodies for E-cadherin, Ki67, Cytokeratin 17, Cytokeratin 14, Cytokeratin 5/6, MUC1, Androgen receptors, IgF1R, p53, Claudin, VEGF, and PD-L1.
Results: Globally, 2572 cases with a mean age of 59 years were examined, and among them 199 (8%) were identified as TNBC; 4 were excluded because they were not Sardinians. Therefore, 195 TNBC patients were analysed. At the time of diagnosis, most of them had a ductal NOS breast carcinoma (DBC, 109, 55.8%), 112 (57.4%) had a T2 or greater disease stage, but 108 (52.8%) had no axillary lymph node involvement. The grade of the disease was G3 in 146 (74.8%) cases. Considering the expression of the biomarkers analysed, seven TNBC subtypes were identified: cytokeratin negative DBC, basal-like DBC, apocrine cancers, medullary cancers, pleomorphic lobular cancers, anaplastic cancers, and metaplastic tumours.
Conclusion: TNBC show a wide range of specific morphological and immunohistochemical features, which characterize subgroups with different biological and clinical behaviour. Knowledge of these features are essential for correct diagnosis and treatment of patients with TNBC.

E-PS-02-004
Mammary Paget's disease mimicking in-situ melanoma – a case report and review of literature
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Background & objectives: Mammary Paget's disease (MPD), in-situ breast carcinoma, a scarce histological condition, accounting for 1-4% of female breast cancers, may appear either independently, or in conjunction with an invasive carcinoma (~90%). The immunophenotype generally comprises, among others, positivity for HER2.
Methods: We report the case of a 44-year-old female patient, presented with a rash of the nipple accompanied by a right mammary mass, previously identified on digital mammography. The microscopical examination and immunohistochemical profile were consistent with MPD associated with invasive breast carcinoma (NST), the former particularized by an infrequent negative reaction for HER2, while oestrogen receptor was positive.
Results: Herein, the histopathological and immunohistochemical approach derived from the exigency of excluding the possibility of synchronous tumours: a mammary invasive carcinoma, accompanied by another component with MPD phenotypic mimicry. The unexpected negative HER2 reaction conducted to a primary focus on excluding a malignant melanoma in situ. The absence of MelanA and S100 expression, lack of pigmentation and clinical aspects infirmed it. Bowen's disease was invalidated by its rare presentation in the breast cutaneous tissue and the absence of individual risk factors suggestive of a pre-existent immunosuppressive status. In case of similar morpho-immunohistochemical aspects, high expression of Ki-67 signals MPD, an immunoreactivity that helped distinguish the cellular population from Toker cells.
Conclusion: MPD's global pattern may provoke to diagnostic pitfalls, due to the occasionally polymorphic immunoreactions and its ambiguous clinical presentation. The current case highlights an unusual biomarker profile of MPD – overexpression of oestrogen receptor and HER2 negativity, an association only encountered in 6% of the cases. Thus, the utmost importance of immunohistochemistry is reflected in its ability to segregate between different lesional entities and in its prognostic significance, being geared towards extending the therapeutic arsenal.

E-PS-02-005
Malignant solitary fibrous tumour of the breast: a rare tumour in a rare location
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Background & objectives: Solitary fibrous tumour (SFT) is an uncommon mesenchymal neoplasm most often found in the pleura. Breast malignant SFTs are extremely rare, being this case the third reported so far.
Methods: We present a case of a 79 year-old woman with a 2 cm tumour on the upper quadrants of the left breast (BI-RADS-4C). The core biopsy revealed a CD34+ mesenchymal tumour of low malignant potential (EWGBP-B3). The patient refused surgery. After four years, the size of the breast mass was 8 cm and was adherent to deep soft tissue.

Results: A new core biopsy was performed revealing an extrapleural solitary fibrous tumour (CD34+, STAT6 +) with features suspicious of malignancy (EWGBP-B4).The patient was submitted to total mastectomy and partial excision of the pectoralis muscle, and the histological diagnosis was a breast malignant solitary fibrous tumour. According to Demicco et al's refined stratification model, this case fitted into the high risk class for distant metastasis. Despite a suboptimal excision margin, considering patient performance status, the sarcoma's multidisciplinary team proposed local and systemic vigilance. Four months later, clinical status quickly deteriorated, liver and lung metastization was detected, and the patient died within a month.
Conclusion: SFT has an indolent course with relatively infrequent metastasis (5-25%), aside those cases with sarcomatous transformation. There are few cases of breast SFT and most of them are benign and limited to the female gender. This is the third case of a breast malignant SFT so far and in this case with a fatal outcome.

E-PS-02-006
Metaplastic breast carcinoma: a case report
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Background & objectives: Metaplastic breast carcinoma is a morphologically diverse cancer type which shows differentiation of malignant epithelium into squamous or mesenchymal elements and accounts for 1% of breast cancers. The mesenchymal elements are usually composed of osteoid, chondroid and areas of carcinoma.
Methods: We present the case of an 84 year old lady presenting with a rapidly enlarging left breast mass over 6 months. Past medical history was significant for ischaemic heart disease. A wide local excision revealed a 60mm, calcified lesion.
Results: This was a well-circumscribed tumour composed of atypical mononuclear epithelioid and spindled cells. There were areas of bone and cartilage formation with osteoclast-like giant cells. There were focal areas of malignant squamous and chondroid differentiation. Mitotic activity and necrosis was noted. The atypical epithelial cells were strongly positive for AE1/3, p63, and focally positive for CK5/6 and SMA. They were negative for CD34, desmin, EMA, ER, PR, Her2, GATA3, LCA and S100. SATB2 was positive in the malignant osteoid component. As such, this lady was diagnosed with a metaplastic carcinoma with osteosarcomatous differentiation.
Conclusion: Metaplastic breast carcinoma is a rare malignancy and thorough sampling is crucial. When mesenchymal elements are present, the other main differentials are a primary breast osteosarcoma and malignant phyllodes tumour. Metaplastic carcinoma will stain for cytokeratins. Staging is dependent on tumour size as per the UICC/ATCC 8th editions. Diagnosis depends on the degree of heterologous elements present – those with a bland spindled morphology often do well while those with mesenchymal differentiation tend to be aggressive.

E-PS-02-007
Tall cell carcinoma with reversed polarity of the breast
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Background & objectives: Tall cell carcinoma with reverse polarity (TCCRP) is an uncommon breast carcinoma, recently recognized as a separate entity in the 5th edition of the WHO classification of breast tumours. Herein, we report the first case of TCCRP in South Tunisia.
Methods: We report a case of a 34-year-old woman diagnosed with TCCRP and we review histological and immunohistochemical features of this rare entity.
Results: Our patient presented with a palpable mass located in the superomedial quadrant of the right breast. Echomammography revealed an atypical mass classified ACR4a. The trucut biopsy specimen reported an atypical papillary proliferation. The patient underwent lumpectomy. Histological examination showed circumscribed nests of epithelial cells with delicate fibrovascular cores resembling papillary structures. Fibrovascular cores contained sometimes foamy histiocytes and were lined by columnar cells with abundant eosinophilic cytoplasm and apical nuclei showing some grooves. On immunohistochemistry, tumour cells were diffusely positive for CK5/6, Calretinin and were negative for oestrogen, progesterone, HER-2, TTF1, and p63 (this antibody indicated the absence of myoepithelial cells within and around the nests).
Conclusion: Few cases of TCCRP have been reported in the literature. It resembles tall cell variant of papillary thyroid carcinoma but has a distinct morphological, immunohistochemical, and molecular profile (IDH2 mutation). Its pathological diagnosis can be challenging and difficult to establish. The treatment is mainly based on surgery. No clear indications exist for lymph node dissection, radiotherapy, and chemotherapy. TCCRP has an excellent prognosis with low metastatic potential.

E-PS-02-008
Digital radiography for histopathologic examination of breast cancer after neoadjuvant chemotherapy
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Background & objectives: Pathologists have various and difficult problems related to sampling for histologic examination specimens of breast cancer after neoadjuvant chemotherapy. The aim of this study was to optimize the pathologic assessment for residual disease in breast cancer after neoadjuvant chemotherapy.
Methods: The analysis were patients who underwent radical surgical treatment for invasive carcinoma of the breast after neoadjuvant chemotherapy. All patients had a good clinical response to treatment. It was performed using a pathology specimen digital radiography the Faxitron® Path system (digital X-ray). Specimens radiography reports were compared to the histopathologic evaluation.
Results: The study comprised 32 subjects, average age of the patients was 52.5 (9.4). Macroscopic assessment of the primary tumour was not probable, the tumour bed was not palpable. Accuracy of macroscopic determination of calcinates in relation to digital radiography was 93.8% (79.2–99.2). Tumour bed sizes determined macroscopically (mean maximal size 6.1 (3.3) cm, median 5.2 (3.4–8.0) cm) and using digital X-ray (mean maximal size 4.8 (2.6) cm, median 4.1 (2.7–6.2) cm) had statistically significant differences ($p < 0.0001$). In most cases (31/32 (96.9%)), clear dimensions of the tumour bed were determined by digital X-ray, whereas macroscopy in 25/32 (78.1%) cases determined fuzzy dimensions ($p < 0.0001$).
Conclusion: Using digital X-ray facilitated the morphological identification of metal markers implanted into the tumour bed, microcalcifications, altered foci, improved tumour bed visibility, which is important for further objective status assessment of the resection margins and residual cancer burden class. The number of repeated incisions decreased which reduced the number of histological cassettes and study time. Without specimen radiography, important pathological areas may be easily missed. The results

obtained indicate that specimen radiography provides perfect documentation of the residual breast cancer.

E-PS-02-009

The rare and the hidden – twin challenges posed by malignancy in microglandular adenosis of the breast. Metaplastic matrix producing triple negative and multifocal luminal type invasive carcinomas

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Background & objectives: Triple negative metaplastic carcinoma(TNMC) and luminal type invasive ductal carcinoma(LTIDC) arising in microglandular adenosis(MGA) emphasized the spectrum of malignancy developing from MGA is wider. Management and prognosis of these malignancies are different from TNMC and IDC not arising from MGA.
Methods: Here we report on two cases of invasive malignancy arising from MGA. Neither of them could be recognized from the pre-operative core biopsy. This report discusses the results of the retrospective analysis of the previous core biopsies, it reviews the literature for similar cases and considers the implications of this rare tumour type on patient management.
Results: One case, core biopsy reported as B4, suspicious of malignancy. As a result diagnostic surgical excision was performed instead of WLE and SLN biopsy. Following diagnosis of triple negative matrix producing metaplastic carcinoma arising in a background of MGA, WLE and SLN biopsy was recommended but the patient opted for a mastectomy which showed residual foci of MGA with atypia and no lymph node metastasis on SLN biopsy. The other patient had a core biopsy of LTIDC(ER & PR were 8/8 and Her2 were negative), B5b without suggestions of background MGA. Subsequent WLE specimen revealed multifocal LTIDC. The background MGA was only recognized after specialist review of the case.
Conclusion: Despite the rarity of MGA, we have recently encountered two cases where the histological subtyping were not typical. In one instance the complicating invasive carcinoma was triple negative but had a matrix producing metaplastic carcinoma component. In the other instance luminal type and multifocal IDC. Our examples suggest that: MGA is usually not recognized on core biopsy and MGA can be associated with metaplastic carcinoma as well as luminal NST IDC.

E-PS-02-010

Extramammary metastases to the breast: a retrospective analysis of 15 cases in a Tunisian institution

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Background & objectives: Extramammary metastases to the breast (EMMB) are uncommon. Distinguishing these tumours from primary breast cancer is crucial as it affects clinical management and treatment. The aim of this work is to review clinico-pathological and therapeutic features of this rare entity.
Methods: In a retrospective study, we collected 15 patients who were diagnosed, in our department of pathology, with EMMB between 1992 and 2020 (29 years). These tumours represented 0.25% of the total number of breast cancer cases during the period of study (5892 cases). An analysis of clinical, imaging, pathological and therapeutic features was carried out in all cases.
Results: The mean age of our patients (1 male-14 females) was 38.42 years (13-62 years). All patients presented with a mammary mass which was more frequently unilateral, left-sided and located in the superolateral quadrant of the breast. Metastases were synchronous with primary tumours in 9 cases and metachronous in 6 cases (average onset time: 44.4 months). Sources of EMMB were carcinomas of the lung, ovary, stomach (each 2cases), nasopharynx and rectum (each 1case). Other sources were lymphoma (3cases), melanoma, neuroblastoma, leiomyosarcoma and choriocarcinoma (each 1case). Immunohistochemistry was used in 12 cases. Therapeutic management was based on chemotherapy or radiochemotherapy. Six of our patients were dead (average delay of 12.83 months).
Conclusion: The diagnosis of metastasis in the breast of extramammary origin is often difficult. A confrontation of clinical and pathological data with immunohistochemical study is recommended. Immunohistochemistry is very helpful in the absence of medical history. The most common sources are lymphomas and melanomas. In this study, there was a high incidence of carcinomas. The prognosis of this entity is poor. The death rate is about 80% during the first year following the discovery of the breast metastasis.

E-PS-02-012

Metastatic NET of the cranial orbit: a case report of unknown origin

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Background & objectives: Metastatic neoplasms of unknown primary location often present difficulty in diagnosis. The intracranial spread of tumours is a common site and clinical findings can point to the origin of the neoplasm.
Methods: A 50-year-old female presented with right exophthalmos, complete vision loss and ocular pain. Cerebral MRI showed a right cranial orbit mass, with intracranial extension, most likely consistent of meningioma or a metastasis. Further findings discovered, a previously unknown breast lesion with invasive characteristics. Representative sections of the orbital mass were examined under H&E and immunohistochemical stains.
Results: Microscopic examination demonstrated a tumour of epithelioid differentiation (AE1/AE3 positive), predominantly insular and nested pattern of growth (almost 100%). Neoplastic cells display eosinophilic, granular cytoplasm with a bland eccentric placed nuclei and were diffusely positive for oestrogen and progesterone receptors, E-cadherin, GATA3, Synaptophysin and Chromogranin A. Common mammary markers such as CK7, EMA, GCDFP-15, ERBB2 (HER2) and Mammaglobin, were negative along with S100 and transcription factors such as CDX-2 and TTF-1. Cell Proliferation index Ki67 (MiB-1) was estimated at 25%. Taking all the above histologic and imaging findings into consideration, a diagnosis of metastatic NET G2 most likely of breast origin was made.
Conclusion: Breast NETs are extremely rare neoplasms (<1% of primary breast neoplasms), by definition are invasive tumours and may present with a metastasis. Due to the rarity of these neoplasms, diagnosis of metastasis is possible through exclusion and consideration of clinical findings. Further studying of these tumours may

present more diagnostic criteria, but also prognostic and therapeutic meaningful data.

E-PS-02-013

Breast malakoplakia mimicking malignancy: a case report

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Background & objectives: Malakoplakia is an uncommon inflammatory disease. Breast is extremely rare as a site of occurrence. By this case, we aim to discuss clinicopathological characteristics of this entity and challenges in the diagnosis.
Methods: We present a case of breast malakoplakia (BM) in a 35-year-old woman, that mimicked a malignant tumour.
Results: A 35-year-old patient, with no medical history, presented to the emergency department with fever and respiratory distress. Rapid SARS-coV-19 testing was negative. The patient underwent a chest-tomography-scan. It showed no signs of SARS-coV-19 pneumopathy. However, it revealed an 8mm mass in the inner upper quadrant of the right breast. A mammography was undertaken and showed round opacities, with spiculated contours and architectural distortions (ACR4), mimicking malignancy. Biopsy revealed a well limited lesion composed of abundant foamy histiocytes and basophilic targetoid intracytoplasmic structures (Michaelis-Gutmann bodies) that were PAS positive. The diagnosis of BM was established. The patient received antibiotherapy with good outcome.
Conclusion: Malakoplakia is a very rare inflammatory condition. It results from an acquired defect in the phagocytic bactericidal activity of macrophages. Its occurrence in breast is extremely uncommon with four reported cases in the literature. Clinical presentation of BM is non specific. In the case we presented, it did not result in any symptoms and was discovered incidentally. However, it can mimic carcinomatous lesion and be challenging for the diagnosis. Only histologic examination can confirm the diagnosis and rule out malignancy.

E-PS-02-014

Mammary-like carcinoma in an extramammary site: vulvar adenocarcinoma arising from specialized anogenital mammary-like gland. Thinking outside the box. Case report and summary of the literature

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Background & objectives: The 68-year-old patient presented with an ulcerous vulvar lesion in 2014 that persisted for 8 months. A highly differentiated endometrium adenocarcinoma without ovarian involvement (FIGO1A) was diagnosed in her hysterectomy/bilateral salpingo-oophorectomy specimen 8 years prior to her vulvar lesion.
Methods: An invasive adenocarcinoma with DCIS grade 3 was diagnosed in the vulvar excision. Mammography detected no breast carcinoma. The patient received aromatase inhibitor (Exemestane) for 5 years. Irradiation was given locally in the vulvar region (30 x 2 Gray) and regionally for both inguinal region (25 x 2 Gray). No recurrence 8 years after the vulvar operation.
Results: Histopathological and immunohistochemical (IHC) examination revealed an invasive adenocarcinoma with breast cancer features which was positive for GATA3, ER, PR, AR, CK7, MUC1, but negative for HER2, WT-1, TTF-1, GCDFP-15 and CK20. For differential diagnosis the following alternatives were considered 1. metastasis/regional recurrence from endometrium adenocarcinoma, 2. breast cancer metastasis, 3. carcinoma arising from ectopic breast tissue, 4. carcinoma arising from local apocrine sweat glands. The histological findings together with the IHC results were mostly suggestive for a primary vulvar adenocarcinoma arising from anogenital mammary-like glands. Only tumour tissue was detected in the lesion without ectopic breast tissue or apocrine sweat glands (mucoapocrin marker GCDFP-15 was negative in the tumour).
Conclusion: Vulvar adenocarcinoma of mammary gland type is a rare tumour arising from specialized anogenital mammary-like glands. Mammography excluded primary breast carcinoma. Differential diagnosis is challenging: 1. Absence of uroplakin II, but ER+, mammaglobin+ can confirm breast origin. 2.Metastatic breast carcinoma may mimic GATA3+ invasive urothelial carcinoma. 3.Metastatic lobular carcinoma may mimic plasmocytoid bladder carcinoma. The current case with DCIS component was suggestive of a primary carcinoma. Diagnosing a breast carcinoma like tumour outside the breast requires to "think outside the box".

E-PS-02-015

Pleomorphic adenoma-like tumour of the breast: an unusual entity

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Background & objectives: "Pleomorphic adenoma-like tumour of the breast" is a term that has been recently proposed to describe breast lesions with overlapping histopathologic features between pleomorphic adenomas (PAs) of the salivary glands (SGs) and matrix-producing metaplastic breast carcinomas (MBCs).
Methods: Here we describe a case of a PA-like tumour of the breast, in an 87-year-old female, who presented with a 6-cm lump in the right breast, near the nipple. No lymphadenopathy was evident. The patient underwent modified radical mastectomy. Hematoxylin-eosin and immunohistochemical stained sections from the tumour were examined.
Results: Microscopic examination revealed a well-circumscribed tumour, consisting of an epithelial component within myxoid or chondroid stroma with focal osseous metaplasia. The epithelial component was characterised by atypical tubular and cribriform structures, and scattered individual cells. Moderate atypia was focally detected, without significant mitotic activity. On immunohistochemical evaluation, neoplastic cells were positive for CK5/6, AE1/AE3, and S100, whereas immunostains for ER, PR, HER2, p53, and p63 were negative. Few cells were immunoreactive to SMA, GFAP, and CD117 antibodies. The Ki67 proliferative index was <5%. Taking into account the overall indolent histological features and the focal atypia, the diagnosis of PA-like tumour of the breast was set. The patient remains disease-free.
Conclusion: PA-like tumour of the breast is an unusual entity with diagnostic challenges. There are no strict diagnostic criteria discriminating it from MBC. The majority of the cases have an indolent behaviour, although cases of local recurrence or carcinoma development have also been reported. Considering the rarity of this entity, multicentre studies are warranted to accurately determine its biological nature and behaviour, as well as the best therapeutic approach.

E-PS-02-016

Primary malignant melanoma of the breast. A rare case report

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Background & objectives: Primary melanoma of the breast is classificated into cutaneous and non-cutaneous forms. Despite the fact that both forms of the tumour arise from melanocytes, they differ significantly. In the breast, non-cutaneous melanomas are extremely rare (<5% of all malignant melanomas)
Methods: We present a case of primary non-cutaneous melanoma of the breast. A 60-year-old woman was admitted with complaints of a slowly growing pain-less mass in the left breast. A needle biopsy was performed (according to the results of which melanoma was suspected), followed by a total mastectomy with lymph node dissection and a wide histological (hematoxylin/eosin stain) and IHC study.
Results: Gross examination showed multiple round whitish nodules in the breast parenchyma with extension into the mammary fatty tissue. Histological examination revealed many atypical spindle and round melanocytes against the background of desmoplastic stroma. Tumour cells expressed S-100, Sox-10, HMB-45, Melan A. There was a complete absence of expression of Her-2, ER, PR. A diagnosis of primary non-cutaneous parenchymal melanoma of the breast was established.
Conclusion: Primary non-cutaneous breast melanoma is rare and presents a diagnostic challenge for both the histopathologist and the clinician. Thanks to the presented case, we have expanded our understanding of the nature of these tumours.

E-PS-02-017

Pure signet-ring cell carcinoma of the breast – two case reports of a rare entity

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Background & objectives: Primary signet-ring cell carcinoma (PSRCC) of the breast is a very rare entity. To date, few cases have been reported in the literature. We present two case reports of pure PSRCC of the breast and discuss the available literature.
Methods: We searched the archives of the Department of Surgical Pathology, Centro Hospitalar Lisboa Ocidental (CHLO), between 2010 and 2021. From the breast invasive carcinomas diagnosed in that period, we retrieved the pure PSRCC from the database. Clinical information was collected from the medical records, and the pathological material was reviewed according to the current WHO guidelines.
Results: Of the total of 576 cases of invasive carcinoma diagnosed in surgical specimen only 2 cases showed dominant signet-ring cells (in at least 90% of the tumour) and were diagnosed as pure PSRCC. The age of the patients was 30 and 74 years-old. One of the cases was of histologic grade 2 and the other grade 3. Neither of the cases had axillary lymph node (LN) metastasis nor distant metastasis were present. One of the cases had family history of breast carcinoma. Both patients underwent adjuvant chemotherapy, radiotherapy and hormonal treatment.
Conclusion: Pure PSRCC of the breast is uncommon and rarely mentioned in the English literature. It has been associated with an aggressive clinical course, with greater frequency of LN involvement, poorer prognosis and higher mortality rate, compared with other forms of breast cancer. Because of its rarity, there is no clear understanding of the oncogenesis, treatment and clinical follow-up of these patients. Once there are no established treatment guidelines we believe that sharing is important for better comprehension of this entity.

E-PS-02-018

To explore the changes of 21 gene detection in the 2022 version of the breast cancer NCCN guidelines and the interpretation of the 21 gene in breast cancer in the 2017 version of the guidelines

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Background & objectives: To compare the changes of 21 gene detection in the 2022 version of the breast cancer NCCN guidelines and the 2017 version of the breast cancer 21 gene interpretation.
Methods: The invasive breast cancer was screened, with negative lymph nodes/1-3 ipsilateral axillary lymph nodes, HER-2 negative and infiltrating. The clinicopathological data of 207 patients with foci >0.5cm were collected. To study the differences in the 21 gene detection guidelines of the 2022 version of the NCCN Guidelines, compare the clinical significance of the two versions of the guidelines.
Results: A total of 207 IBC patients were collected, including 1 male and 206 females, aged 35-71 years. Interpretation results of the 2017 edition: 124 patients with low recurrence risk, 70 patients with moderate recurrence risk, and 13 patients with high recurrence risk. Interpretation results of the updated guidelines: 92 patients with low risk of recurrence, 95 patients with moderate risk of recurrence, and 20 patients with high risk of recurrence. There were significant differences in the interpretation results of the two versions of the guidelines ($P<0.05$).
Conclusion: The updated 2022 version of breast cancer NCCN guidelines 21 gene detection can effectively distinguish the RS interpretation results of breast cancer patients before and after menopause in clinical practice. For patients with early-stage invasive breast cancer, accurate determination of 21-gene status is critical to ensuring that patients most likely to benefit receive targeted therapy.

E-PS-02-019

Association between protein expression of KISS1 and KISS1R and receptor status in invasive breast carcinoma

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Background & objectives: KISS1 and KISS1R act as metastasis suppressors, in breast cancer their function is altered with the exact mechanism being still unknown. Here we present the association between protein expression of KISS1 and KISS1R with receptor status in invasive breast carcinomas.
Methods: Immunohistochemistry was used to detect protein expression of KISS1, KISS1R, ER, PR and HER2. The Allred scoring system was used for ER and RP and a four-tier scoring system was used for HER2. KISS1 and KISS1R immunostaining was assessed using ImageJ software by measuring mean grey value and calculating reciprocal intensity that is directly proportional to the amount of chromogen.
Results: A total of 54 cases of invasive ductal carcinomas were examined. For ER and PR scores of 0-2 were considered receptor-negative and scores of 3-8 were considered receptor-positive. For HER2, scores of 0 and 1+ were considered HER2-negative and scores of 3+ were considered HER2-positive. Equivocal scores of 2+ were resolved by DISH. Examined cases included 12

ER-negative, 42 ER-positive, 21 PR-negative, 33 PR-positive, 47 HER2-negative and 7 HER2-positive carcinomas. No difference was found between receptor-negative and receptor-positive cases with respect to ER and PR for both KISS1 and KISS1R and with respect to HER2 for KISS1, however KISS1R expression levels were significantly higher in HER2-negative compared to HER2-positive carcinomas.
Conclusion: Software-based assessment of immunostaining is a more objective way of quantifying staining intensity when studying potential new markers for which no standardized assessment systems are developed. Taking into account receptor status is important when studying the altered function of KISS1/KISS1R system in the context of breast carcinomas. Higher expression of KISS1R in HER 2-negative carcinomas might indicate an alternative pathway for stimulating proliferation of tumour cells when HER2 expression is low.
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E-PS-02-020
Primary neuroendocrine breast carcinoma or metastatic lung cancer? The role of a careful interpretation of GATA-3
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Background & objectives: Primary small cell neuroendocrine carcinomas (SCNECs) of the breast are extremely rare. Here we report the case of a 61-year-old woman with a palpable mass developed in the upper-outer quadrant of the left breast.
Methods: Biopsy specimens were fixed in 10% formalin and paraffin embedded. Serial sections were stained with H&E. Histology revealed a pattern compatible with infiltrating small cell neuroendocrine carcinoma of the breast. Immunohistochemical analyses were performed using the following antibodies: Cytokeratin AE1/AE3, p63, GATA-3, Cytokeratin 7, Cytokeratin 20, Chromogranin A, Synaptophysin, CD 56, Estrogen Receptor, Progesteron Receptor, Her2-neu and TTF-1.
Results: Microscopically, tumour cells were arranged in solid nests and cords with nuclear pleomorphism, high nuclear-cytoplasmatic ratio and scattered areas of intratumoural necrosis. Immunohistochemical analyses revealed negativity for Cytokeratin 20, Chromogranin A, Estrogen and Progesterone Receptors, HER2-NEU and p63. Cytokeratin AE1/AE3, Cytokeratin 7 and the neuroendocrine markers CD 56 and Synaptophysin were positive. TTF-1 was strongly positive and GATA-3 was focally positive. On these bases the diagnosis of primary small cell neuroendocrine carcinoma (SCNEC) of the breast was made.
Conclusion: The tumour here described showed a strong and diffuse positivity to TTF-1 in the absence of ductal carcinoma in situ or areas of conventional-type mammary carcinoma. Thanks to the presence of a positive, albeit focal, GATA-3 stain of the tumour cells, it was possible to make a diagnosis of primary small cell neuroendocrine carcinoma (SCNEC) of the breast. Our diagnosis was subsequently confirmed by a PET-scan performed by the patient in another facility.

E-PS-02-021
Challenging diagnosis in breast undifferentiated sarcoma - a case report
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Background & objectives: Primary breast sarcomas are rare entities with aggressive behaviour and poor prognosis. Undifferentiated pleomorphic sarcoma is even rarer in non-irradiated patients. It is important to corelate the clinical features, histology and immunohistochemistry in order to make this diagnosis.
Methods: We present the case of a 36-year-old woman who presented in January 2022 to our clinic because of a fast growing, giant tumour of the right breast. Mammography showed a 23 cm nodule with increased radio-intensity and with homogenous texture, occupying almost the entire breast.
Results: A core needle biopsy was performed and it showed a mesenchymal proliferation with desmin(+) and vimentin(+), focal positivity for actin, caldesmon, cytokeratin and ki-67 30%, suggestive of a Phyllodes tumour without the epithelial component on biopsy or a sarcoma.
The right mastectomy showed a multinodular, relatively well-delineated, non-encapsulated tumour. On cut surface there was a heterogenous lesion with solid, cystic or translucid areas with extensive necrosis and haemorrhage and a thin rim of breast tissue at the periphery of 0.5cm.
Histology showed a proliferation of spindle and epithelioid cells with a storiform pattern, frequent giant cells, marked pleomorphism, areas of tumour necrosis and frequent mitotic figures. No leaf-like epithelial pattern.
Conclusion: This case was signed out as a right breast undifferentiated pleomorphic sarcoma, grade 3 FNCLCC, pT4, and immunohistochemistry was recommended for confirmation.
Primary undifferentiated pleomorphic sarcoma of the breast is a rare entity with an aggressive behaviour. This case shows the classic clinical features of a breast sarcoma as a fast-growing giant tumour with interesting morphologic features. Immunohistochemistry is very important to differentiate it from other sarcomas, metaplastic breast carcinoma or from a malignant phyllodes tumour.

E-PS-02-022
Incidental invasive lobular carcinoma arising in a fibroepithelial lesion
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Background & objectives: Malignant transformation of the epithelial component of fibroepithelial lesions is rare, and when identified, is most often either an in-situ malignancy or invasive ductal carcinoma. We report an exceedingly rare case of invasive lobular carcinoma, discovered in a fibroepithelial lesion.
Methods: A 41-year-old patient presented to the breast clinic with a lump of 2 months duration. On examination this was felt to be benign, however mammogram and ultrasound were performed and the decision was made to excise the lesion.
Results: Microscopically the lesion was a well-circumscribed multinodular tumour, composed of some areas resembling a fibroadenoma, but with other areas displaying mild stromal hypercellularity, periductal condensation and nuclear pleomorphism. The tumour was mitotically low, and appearances were consistent with a borderline phyllodes. Within the lesion, however, individual atypical cells were noted, displaying mild nuclear pleomorphism and prominent nucleoli. Immunohistochemistry revealed these atypical cells to express AE 1/3 and ER but to be negative for e-cadherin and CK5. The appearances were consistent with a focus of classical grade 2 invasive lobular carcinoma

within an otherwise borderline phyllodes tumour. The patient underwent further axillary sampling, and remains well.
Conclusion: Although the occurrence of invasive carcinomas within phyllodes tumours is rare, their existence must be considered by the pathologist. Due to its rarity, there is limited clinical outcome data specifically regarding disease progression and patient prognosis in invasive lobular carcinoma within phyllodes tumours. It is therefore important to highlight these rare cases and build on the volume of data in the literature.

E-PS-02-023
Subtleties of early breast implant-associated anaplastic large cell lymphoma – a potential for missed-diagnosis
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Background & objectives: Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a rare and significant complication of breast augmentation surgeries. Early diagnosis depends on the cytology of the peri-implant effusion, as histologically it can resemble post-implant changes, posing a diagnostic challenge for pathologists.
Methods: We present a case of a 57-year-old lady with a 12-year history of bilateral breast augmentation, presenting with a sudden unilateral breast enlargement. On examination, asymmetrical enlargement of the right and a palpable nodularity of the left breasts were noted. Ultrasound revealed 310ml of right-sided fluid collection and a peri-implant well-circumscribed mass. Fine-needle aspiration and core needle biopsy were performed.
Results: Fluid examination showed only a few CD68-negative, CD30-positive atypical lymphoid cells. Core biopsy of the left-sided nodularity showed benign reactive synovial metaplasia. Further radiological examination with MRI and CT-PET also demonstrated peri-implant effusion with very faint metabolic activity. Patient underwent en-bloc removal of bilateral implants and peri-implant capsulectomy. Entire capsules were sampled as no abnormality was seen macroscopically or on initial microscopy. On further sampling, scattered hallmark cells were identified with a CD30+, IRF4+ and ALK- immunophenotype, seen mostly as singletons and a few small aggregates, that were confined to the luminal aspect of the right capsule, confirming the diagnosis of BI-ALCL. Molecular analyses revealed no DUPSP22 or TP63 rearrangement.
Conclusion: Early-stage BI-ALCL has an indolent course, hence, early diagnosis is of paramount importance(1). Early findings may be inconspicuous, with scarce hallmark cells, and capsule changes that may resemble post-implant changes only, a real potential for misdiagnosis. Extensive sampling and a low-threshold for immunohistochemistry can aid the diagnosis. Absence of DUPSP22-IRF4/TP63 rearrangements in BI-ALCL distinguishes it from ALK-negative ALCL(2). When suspected, the first fluid aspirate has the best diagnostic value as the dilutional effect of subsequent effusions can delay the diagnosis(3).

E-PS-02-024
A rare, unusual case of eosinophilic mastitis: case report
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Background & objectives: Eosinophilic mastitis is a rare, benign breast entity and very few cases have been documented worldwide. We document a recent and rare case of eosinophilic mastitis, with a clinical differential diagnosis of malignancy or chronic granulomatous mastitis (CGM).
Methods: A 50-year-old lady presented with a palpable right breast lesion at 12 o'clock, with architectural distortion, tenderness and lymphadenopathy. Grossly, multiple thin cores of greyish yellow tissue, ranging from 8mm to 14mm in length were received. Entire tissue was submitted in one block. Routine H&E was performed, and the histological features were reported digitally using Aperio Image Scope.
Results: Multiple linear core biopsies of right breast lesion showed scattered normal appearing breast glands, a few cystically dilated, surrounded by striking distribution of abundant eosinophils, along with very occasional polymorphs and lymphocytes. Peri lobular concentration and aggregation of eosinophils and stromal infiltration by eosinophils was seen throughout in all the core biopsies studied. Occasional 'eosinophilic islands' were present. There was also formation of eosinophilic emboli within a few of the dilated glands. No atypia or necrosis or features of lobular mastitis were seen.
Conclusion: Isolated eosinophilic mastitis is extremely rare in occurrence and can be clinically mistaken for malignancy or chronic granulomatous mastitis (CGM). It can be associated with systemic involvement or occur without peripheral eosinophilia. The management of such cases is extremely different when compared to conventional ductal carcinoma or lobular mastitis. This benign entity reemphasizes the need for histopathological diagnosis of breast lesions prior to treatment.

E-PS-02-025
Acquired lymphangiectasia following surgery and radiotherapy of breast cancer: report of two cases
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Background & objectives: Acquired lymphangiectasia (AL) is a dilatation of lymphatic vessels that can result as a complication of surgical intervention and radiation therapy for malignancy. We describe two new cases of AL and discuss their clinical and pathological features.
Methods: Two patients aged of 40 and 56 years old were presented to the department of dermatology with vesicles and bullae in the chest evolving for two and one year. The patients had undergone radical mastectomy with axillary lymphadenectomy for breast carcinoma 4 and 7 years ago respectively. They also had received a complementary radiotherapy and hormone therapy after surgery.
Results: On examination, multiple grouped vesicles and bullae were spread over the left anterior and lateral wall of the chest for the first patient and in the right lateral wall of the chest for the second patient without evidence of lymphedema in the two cases. Few of the vesicles were purple in colour, pedunculated and hypertrophic. A biopsy was taken from lesions. Histopathological examination revealed numerous dilated lymphatics in the superficial and papillary dermis lined by flattened endothelial cells, with mild hyperkeratosis consistent with diagnosis of lymphangiectasia. The lesions were managed with sclerotherapy. No recurrences were notified.
Conclusion: Clinically, AL manifests as translucent vesicles in a chronic lymphedematous area arising after many years following surgery with or without radiotherapy. The combination of surgery and irradiation increase their appearance comparing to surgery or irradiation alone and reduce the time of occurrence of AL. Treatment modalities include electrodessication, surgical excision and sclerotherapy. These two new cases has demonstrated the importance of keeping lymphangiectasia in mind as a rare and late complication of radiotherapy and surgical procedures.

E-PS-02-026

Cystic neutrophilic granulomatous mastitis - case report

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Background & objectives: Cystic neutrophilic granulomatous mastitis is a rare type of infectious, granulomatous mastitis, usually occurring in parous or currently pregnant women.
Methods: We present the case of a 30-year-old breastfeeding secundigesta secundipara, reaching the surgery department, one month after emphirical antibiotic treatment, for a poorly delineated, palpable breast mass, measuring 7/7/5 cm (ultrasound confirmed).
Results: In the pathology department, we received a 5.5/4.5/3 cm sectorectomy specimen. The piece was entirely occupied by a whitish-pearly lesion, with an irregular, polylobate contour that extended focally to the level of the resection margin. Microscopically, the area consisted of multiple inflammatory foci, with a tendency to fuse, composed of neutrophils, lymphocytes, collections of histiocytes and giant multinucleated cells, with the destruction of lobes and ducts of the breast parenchyma and the formation of microabscesses. Pseudocystic spaces were detected, containing isolated pale-basophilic, linear structures (histological aspect suggestive of bacilli). The pseudocystic spaces were delineated by a crown of neutrophils and numerous epithelioid cells arranged radially in the periphery.
Conclusion: The pathological changes were highly suggestive of cystic neutrophilic granulomatous mastitis. A Gram stain was performed to support our diagnosis. Typically presenting as a palpable mass, CNGM may mimic breast carcinoma. Early diagnosis is essential for the proper management of these patients. In medical literature these cases are uncommon, almost all being reported after childbirth.

E-PS-02-027

Decreases discrepancies between frozen and final diagnosis in the evaluation of breast sentinel lymph node

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Background & objectives: Frozen section of breast sentinel lymph nodes is an extremely useful tool to reduce morbidity associated with unnecessary axillary dissection. We aimed to evaluate discordances rates between frozen section diagnosis and final diagnosis of BSLN at our institution.
Methods: We evaluated at least 2 serial sections at 2mm of BSLN with Frozen. Final evaluation after formalin fixation was done by a second pathologist with breast expertise, and was considered as the gold standard. Comparison of discordance rate and aetiology of discordant cases was performed to cases that were retrospectively identified from the two-years prior.
Results: Seventy specimens retrospectively collected from 2019- 2021. Discordances were observed in 8 cases (11,4%). Four causes of discordance were identified: gross sampling (2cases), block sampling (1 case), micro-metastasis/isolated tumour cells (3 cases) and misdiagnosis (2 cases) (metastases from lobular carcinoma).
Conclusion: The rate of observed discrepancies was relatively high. We think that the implementation of a standardized BSLN grossing protocol can decrease the rate of discordance between frozen section and final diagnosis.

E-PS-02-028

Synchronous bilateral primary breast angiosarcoma after reduction mammoplasty: an extremely rare case and literature review

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Background & objectives: Primary angiosarcoma of the breast is extremely rare. Since its radiological features are nonspecific, diagnosis can be challenging. Its aetiology is unclear due to its rarity.
Methods: A 31-year-old female who is breastfeeding presented with rapidly growing masses in both breasts. She had bilateral reduction mammoplasty 3 years ago. She had no history of radiotherapy. Her first ultrasonographic examination was evaluated as postlactational mastitis. Tru-cut biopsy performed due to the progression of the masses was reported as angiosarcoma. Bilateral simple mastectomy was performed.
Results: A 10 cm mass in the right breast and four masses in the left breast, the largest of which is 4 cm, were observed on gross examination. The tumoural lesions had irregular borders and contained small haemorrhagic cystic spaces. All lesions had similar morphology. On microscopic examination, the tumours consisted of pleomorphic cells with spindle/oval nuclei and vascular structures anastomosing with papillary formations in their lumens. The tumour cells expressed CD34, CD31, ERG, and FLI-1. Ki-67 proliferation index was 15-20%. C-myc and D2-40 staining were not observed. It was reported as grade III angiosarcoma due to necrosis, frequent mitosis (>50/10 HPF), blood lakes, endothelial tufting, and solid areas.
Conclusion: Primary angiosarcoma of the breast accounts for less than 0.04% of all malignant breast tumours. It is known to be unrelated to radiation, but its aetiology remains unclear. In this article, we present a unique case of bilateral primary angiosarcoma, initially confused with postlactational mastitis, with a history of reduction mammoplasty 3 years ago.

E-PS-02-029

Primary osteosarcoma of the breast – diagnosis of exclusion with metaplastic carcinoma and malignant phyllodes tumour

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Background & objectives: Primary osteosarcoma of the breast (BOS) accounts for <0.125% of all breast malignancies and 12.5% of mammary sarcomas. BOS has an inferior prognosis with 5-year overall survival below 40%. The common presentation is a progressively enlarging mass with coarse calcifications.
Methods: We present a 53-year-old female with a tumour 7cm diameter localized in the left breast. The patient had no medical history of breast or preceding fibroadenoma or phyllodes tumour. In January 2022 patient underwent a core biopsy, and in March 2022, a mastectomy. An extended histopathological examination was performed.
Results: Microscopically, the neoplasm was highly cellular, composed of spindle cells with moderate to high atypia and high mitotic activity, necrosis and multiple haemorrhages, and numerous multinucleated giant cells. The large osteoid formation, lace-like ossification fields, and chondroid islets were seen in the stroma. Immunohistochemically, the tumour cells were: SATB2(+) strongly positive, p53(+/-), CKAE1/AE3(-), CAM5.2(-), CK5/6(-), p63(-), CD10(-), ER(-). PRG(-), HER2(-), SMA(-), Desmin(-), Caldesmon(-), CD34(-), S100(-), MDM2(-), H3F3A(-), H3F3B(-), CD163(-). The tumour was examined in several sections and did not show cytokeratin expression or malignant tumour phyllodes (MTP)

architecture. Our patient was in clinical staging cT3N0M0 and was qualified for postoperative radiotherapy (total dose 54/60Gy).
Conclusion: In conclusion, BOS is an exceptional diagnosis and up-to-date, only a few cases have been reported. The differential diagnosis with MC (if lacking invasive/in-situ carcinoma the immunohistochemical confirmation of epithelial differentiation is needed) and MTP requires extended sampling and immunohistochemical assessment. Treatment should include complete surgical removal of the tumour with R0 margins; adjuvant chemotherapy (methotrexate and bleomycin, cyclophosphamide, CDDP, doxorubicin, and ifosfamide) seems to be effective, however, no standard regimen has been established for extraskeletal osteosarcoma yet.

E-PS-02-030
Heterogeneity of breast cancer surrogate subtype of primary tumour and local metastases
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Background & objectives: Patterns of surrogate subtype change in breast cancer (BC) metastases stay unclear. This heterogeneity may be the reason of treatment effect decrease. Objective: to describe changes of surrogate subtype of breast cancer in regional metastases compared with primary tumour (PT).
Methods: Postoperative specimens of primary and metastatic tumours taken from 104 patients were examined using immunohistochemistry (ER, PR, Her2/neu, Ki67) and SISH (HER2). Allred, ASCO/CAP 2013 and percentage of stained tumour cell nuclei systems were used. Surrogate subtypes of primary tumour and metastasis were assessed according to St Gallen 2015 recommendations. Frequencies of subtype change in BC metastasizing were analysed.
Results: Primary tumour and metastasis subtypes were the same in 73 cases (70,2%, 95% CI 60,3-78,6%), discordant in 31 cases (29,8%, 95% CI 21,4-39,7%) ($p<0,05$, Fischer's exact probability test). Among 52 cases with PT luminal A subtype metastasis had another subtype in 10 cases (19,2%, 95% CI 10,1-33,0%); among 16 cases with luminal B subtype – in 11 cases (68,7%, 95% CI 41,5-87,9%); among 8 cases with HR+ Her2+ subtype – in 3 cases (37,5%, 95% CI 10,2-74,1%); among 8 cases with HR- Her2+ subtype – in 4 cases (50,0%, 95% CI 17,4-82,6%); among 20 cases with triple negative subtype – in 3 cases (15,0%, 95% CI 4,0-38,9%).
Conclusion: Breast cancer primary and metastatic tumour surrogate subtype is concordant in the majority of cases in the whole sample. Subtype heterogeneity of metastatic and primary tumour has the highest frequency among cases with luminal B primary tumour subtype. Triple negative subtype is the most stable during regional metastasizing of breast cancer.

E-PS-02-031
Two cases for a rare association; mixed tumour of the breast which contains acinic cell carcinoma and metaplastic carcinoma components
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Background & objectives: Acinic cell carcinoma is a rare form of salivary gland-type breast cancer that shows indolent behaviour, in contrast to other triple-negative cancers. Metaplastic carcinoma is a term for breast cancers characterized by neoplastic cells differentiating into squamous or mesenchymal-looking components.
Methods: Case 1: 42 years-old female patient presented with a mass in the right breast. Trucut biopsy revealed metaplastic carcinoma. After chemotherapy, she underwent nipple sparing mastectomy. In the resected specimen, tumour characterized by two distinct components was observed. In the one component, tumour was growing in infiltrative pattern with small acinar structures. Case 2: 83 years-old female patient presented with a mass in the right breast. Trucut biopsy specimen revealed invasive carcinoma characterized by acinar structures. Tumour cells were characterized with granular and eosinophilic cytoplasm some of which contain zymogen granules.
Results: Tumour cells were characterized with monotonous round cells with granular and eosinophilic cytoplasm some of which contain zymogen granules. Immunohistochemically, neoplastic cells were positive for lysozyme and S100. In the other component, pleomorphic and discohesive tumour cells scattered in chondromyxoid matrix was observed. The case was reported as metaplastic carcinoma with acinic cell carcinoma. In NGS TP53(c.818G>A) and KRAS(c.351A>C) mutations were observed.
Immunohistochemically, neoplastic cells were positive for lysozyme, antichymotrypsin and S100. The case was reported as acinic cell carcinoma. In the resected specimen, acinic cell carcinoma was accompanied by large areas of metaplastic carcinoma with discohesive cells. In NGS TP53(c.488A>G) and PTEN(c.166_167del) mutations were observed.
Conclusion: Acinic cell carcinomas are usually seen in pure form, but in rare cases, they may be associated with high-grade triple-negative carcinoma component, such as metaplastic carcinoma.

E-PS-02-032
A relapsing breast abscess – about a case
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Background & objectives: Cystic neutrophilic granulomatous mastitis (CNGM) is a rare subtype of granulomatous mastitis with a highly distinct histological pattern often associated with Corynebacterium species, although evidence of corynebacterial infection can be difficult to prove.
Methods: A parous 29-year-old woman, an immigrant from Nepal living in Portugal for a year, presented in the emergency department with a painful tumefaction in right breast. Radiological investigation revealed an abscess and she was discharged with antibiotic therapy. Three days later she was submitted to abscess drainage and Corynebacterium species were isolated. During follow-up, a core needle biopsy was performed.
Results: Microscopically, the biopsy revealed breast parenchyma with an exuberant chronic granulomatous process, constituted by an inflammatory infiltrate of lymphocytes, plasma cells, neutrophils, Langhans giant multinucleated cells, and well-formed granulomas with occasional central cystic spaces surrounded by neutrophils. In Gram stain rare bacillary structures were observed. PAS, Grocott and Ziehl-Neelsen were negative. Due to the relapsing nature of the abscess, she completed several antibiotic cycles and was posteriorly started on corticosteroids. Currently, she is asymptomatic.
Conclusion: The diagnosis of CNGM is often missed or delayed due to its rarity and many potential mimickers. Invasive carcinoma is the most important entity to consider in differential diagnosis, as both clinical presentation and radiological features can mimic

malignancy. A high index of suspicion is needed based on the recognition of characteristic histological features, to pursue fungal, mycobacterial, and bacterial organisms - especially gram-positive bacilli - within lipid vacuoles by using ancillary studies, such as Gram stains, and microbiological studies.

E-PS-02-033

The impact of increased p53 expression on the clinical outcome in hormone receptor positive breast cancer: a new useful biomarker?

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Background & objectives: Predicting the prognosis of breast cancer depends on interactions of various biological factors, one of which is p53. In this study, we aim to elucidate the relationship between p53 and survival outcomes in oestrogen receptor-positive/HER2-negative breast cancer.
Methods: Slides obtained from tissue microarrays constructed using 3-mm cores of breast tumours from 122 patients were stained for p53. All tumours were scored by multiplying the percentage of p53 positive neoplastic cells with the staining intensity (weak:1 moderate: 2 strong: 3) and the final scores were correlated with the clinical follow-up data to predict biological behaviour.
Results: The patient demographics were as follows: The mean age: 42 (range 22-92). Clinical stage of the patients: Stage I; 11 (9.2%) Stage II: 53 (43.8%) and Stage III: 58 (47%). All of the patients received hormone receptor directed therapy, additionally 108 patients received chemotherapy. The median follow-up time of the patients was approximately 50 months. The p53 scores ranged between 0 - 285. Twenty-seven of patients (22%) had a score of 0. Patients with a score of 60 or less (n=91) had a significantly better disease free and overall survival compared to the patients with a score higher than 60 (n=31) ($p < 0.001$).
Conclusion: A variety of methods/tests are used to predict prognosis in breast cancer. However, in a world-wide perspective, most of them are not easily affordable. In exchange, surrogate markers, such as ki-67 etc., are more widely used for prognosis prediction. The expression of p53, evaluated by immunohistochemistry, could be a potential surrogate marker to predict clinical outcome in oestrogen receptor-positive/HER2-negative breast cancer.

E-PS-02-034

Distant metastases from phyllodes tumours: a retrospective review from a single institution

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Background & objectives: Phyllodes tumours (PTs) are rare fibroepithelial breast neoplasms. Distant metastases occur in about 2%, almost exclusively in malignant PTs (MPTs). We aim to provide an overview of metastases from PTs with emphasis in achieving an accurate diagnosis.
Methods: Retrospective analysis of all patients diagnosed with distant metastases from PTs in our institution between 2010 and 2022. Evaluation of clinicopathologic features of both primary and metastatic tumours, including age at diagnosis, interval between primary and metastatic disease, site of metastasis, morphological features, immunohistochemical profile and interval between metastatic disease and death.
Results: From a total of 265 PTs, nine women with distant metastases were identified. All had a MPT diagnosis, three after local recurrence of borderline PT. Mean age at metastasis diagnosis was 58 years and mean interval between primary and metastatic disease was 21.5 months (range 6.0-50.9). Sites of distant metastases included lung (5), bone (2) and soft tissues (2). Metastases presented spindle cell (4), mixed (3), epitheliod (1) and pleomorphic (1) morphology. Heterologous elements were identified in two cases. Epithelial component was absent in all. No immunohistochemical marker was helpful for differential diagnosis. Six patients died and mean interval between metastatic disease and death was 11.6 months (range 0.9-39.4).
Conclusion: Distant metastasis of PTs are extremely rare and preclude a dismal outcome. Diagnosis can be challenging given the absence of a specific morphological pattern and useful immunohistochemical markers. Morphological comparison between primary and metastatic lesions remains the most reliable tool for an accurate diagnosis.

E-PS-02-035

Rare localizations of metastatic lobular carcinoma – twenty years of experience of two institutions

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Background & objectives: Lymphatic tissues, breast and skin are the sites most likely to cause metastases of lobular breast cancer. This retrospective observational study focuses on the assessment of rare metastases, which are a significant burden in terms of prognosis.
Methods: For the period 2000-2020, those metastatic lobular carcinomas that metastasized into uncommon areas were selected from the databases of two medical facilities (University Hospital Ostrava, CGB Laboratory) in Moravian-Silesian region. The work with the databases was preformed in the CGB laboratories during March 2022, followed by a statistical analysis of a total of 485 patients.
Results: The average age of the 485 patients, all of whom were women, was 62.5 years, while the median was 63 years. There was no significant age difference between the cohorts of usual and rare metastases. 70 of all metastases (14.4%) were located out of the lymphatic tissue, breast or skin. The most frequent localizations were following: stomach (1.65%), peritoneum, liver and bones (all 1.44%), ovaria (1.24%), omentum (0.82%) and fallopian tube (0.62%). Out of the other unique metastatic localizations can be mentioned for instance cerebellum, orbit, bronchus or adrenal gland.
Conclusion: Although the majority of lobular carcinomas metastasize to the lymphatic system, skin, or breast, nearly every sixth metastatic location is unusual and may adversely affect the condition of patients. As a result, these areas should be considered in ordinary clinical practice.

E-PS-02-036

Extracellular matrix analysis in breast cancer. Study of 5 cases

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Background & objectives: To understand the morphogenesis of breast cancers and non-malignant breast diseases, it is necessary to analyse the reorganization of two structurally and functionally interconnected tissue components such as parenchyma and stroma.
Methods: We present an analysis of the tumour extracellular matrix of 5 cases of invasive ductal carcinoma of no special type (IDC NST). The subject of the study was postoperative samples of 5 breasts obtained from sectoral resection with lymph node dissection, for IDC NST. Histological study, IHC-study and transmission electrone microscopy was carried out.
Results: As a result of the study, it was found that the extracellular matrix of the IDC NST stroma contains a large number of thin and thick collagen fibrils concentrated in the perivascular tissue and in the foci of the desmoplastic reaction. Quite often, basement membranes are adjacent to the cytoplasm of carcinoma cells. In some foci, we found striated collagen fibres, as well as microfibrils shaped like an electron-dense rod. In most cases, the perivascular tissue resembled connective tissue containing sparse collagen fibres with fragments of proliferating vessels, areas of necrosis, and cells that can be regarded as fibroblasts and macrophages. Interesting that we didn't find pericytes in the capillaries.
Conclusion: Changes in the stroma during tumour progression consist in a decrease in the total amount of the non-fibrillar matrix in the background of increase in the amount of collagen and elastic fibres, and the appearance of lymphoplasmacytic infiltrates. Changes in the histoarchitectonics of the microcirculation are an integral part of tumour progression. Extracellular matrix is characterized by an increase in the number of pericyteless capillaries localized mainly in the periphery of the tumour and directed outward from the tumour.

E-PS-02-037
Axillary region nodule: an unusual finding
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Background & objectives: Ectopic breast tissue in the axillary region can give rise to tumoral conditions which are challenging to diagnose. This study aims to present a case of fibroadenoma (FA)of the axillary region revealing an ectopic breast tissue, mimicking an adnexal gland tumour clinically.
Methods: A 25-year-old female without past medical history presented with a mass in her left axilla evolving for 4 years. On clinical examination, the mass was firm, freely mobile, and completely isolated from the left breast. Ultrasound showed a solid, oval, heterogeneous, hypoechoic node measuring 2*1cm. The ultrasound-mammogram was normal. The mass was excised and addressed for a histopathology examination
Results: On gross examination, the mass was firm with the bosselated surface, whitish. The serial sectioning was homogeneous. Histological examination showed that the mass was composed of 2 components: epithelial and mesenchymal. The mesenchymal component is made of hyaline connective tissue with uniform cellularity. The epithelial component is made of stretched ducts lined by a double cellular layer without atypia. The diagnosis of fibroadenoma in the axillary accessory breast was retained.
Conclusion: A mass of the axillary region is a common clinical presentation. The most frequent diagnoses are lymph node malignancy followed by sweat gland tumours. FA in the axillary region is a rare disorder representing a diagnostic dilemma. confused with other benign or malignant pathologies. It most commonly affects adult women aged in the 3rd and 4th decade of life. Imaging is not contributive. Pathological examination is mandatory to rule out another differential diagnosis, especially malignancies.

E-PS-02-038
A rare case of metaplastic carcinoma with neuroendocrine differentiation
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Background & objectives: Metaplastic breast carcinomas represent a heterogeneous group of carcinomas with epithelial and mesenchymal components. Primary neuroendocrine breast carcinoma is an exceedingly rare entity. Here we describe the first reported case of metaplastic breast carcinoma with neuroendocrine differentiation.
Methods: A 60-year-old lady was found to have a suspicious nodule in her left breast, measuring 19mm on radiology. Following the core biopsy, a diagnosis of malignancy was made, and she proceeded to have a wide local excision and sentinel lymph node biopsy.
Results: Histological examination of the specimen showed an infiltrative solid tumour, composed of predominantly tightly packed small basophilic cells, with stippled nuclear chromatin, inconspicuous nucleoli growing in sheets, with large areas of necrosis and apoptotic debris. Admixed with these undifferentiated neoplastic blue cells were small clusters of epithelioid groups showing squamous differentiation. The undifferentiated blue cells showed a neuroendocrine carcinoma phenotype with AE1/3, CK7, CD56 and synaptophysin positivity as well as basal marker positivity (CK5/6, p63 and CK14). The epithelioid component was also AE1/3, CK7 and CAM5.2 positive with no neuroendocrine differentiation. Based on the immunomorphological features a diagnosis of triple-negative metaplastic carcinoma with neuroendocrine differentiation was made.
Conclusion: Metaplastic carcinomas have monomorphic or biphasic epithelial and mesenchymal components. Identifying in-situ components can aid the diagnosis, as in this case. Primary neuroendocrine tumour of the breast is an extremely rare entity, that requires clinicoradiological correlation to exclude metastasis, and in view of this case, may also require exclusion of metaplastic carcinoma with neuroendocrine differentiation.

E-PS-03 | E-Posters Cardiovascular Pathology

E-PS-03-002
New perspectives in cardiac surgery: electrical DC tensions implements morphologic patterning in chick heart embryo model
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Background & objectives: Cell polarity and electrotaxis play an important role in cardiac embryogenesis and on genes expression to specific phenotypes. Chemical and physical electrodynamic laws direct the bioelectric endogenous fields. (Faraday 1831, Henry 1832, Maxwell 1865, Wolpert 2015, Levin 2017).
Methods: We designed devices A and B:
A- A passive two terminal condenser storing an uniform 800 mV / mm electric field. Inside we accommodated 30 fertilized eggs for 52 hours after laying (gastrulation, looping, septation) inverting the polarity.
B- A second device /same Electrical Field, to treat 7 fertilized cockerels during the egg passage in the oviduct (germinal disk, blastula, gastrula).
Results: In group A we observed 4 giant Omphaloceles (18 %). Overall mortality 13.6% (Capuani et al Virchows 2020). In group

B, 42.8 % of eggs did not progress with an overall mortality of 57 % suggesting a very high interference of the applied EF on the embryogenetic process (genes expression in primary heart tube and other organs lateralization - rotation process).
Conclusion: 1- Dc electrical forces of 800 mV / mm affect the endogenous fields during the overall chick embryogenesis. 2-It is possible, applying external Electrical Fields, to interfere on the heart embryogenetic process, what we refer as Molecular Cardiac Surgery. We present devices and procedures.

E-PS-03-003
Cardial intimal sarcoma
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Background & objectives: Intimal sarcoma (IS) is exceptionally rare primary mesenchymal neoplasm arising from the intima of great vessels, most commonly pulmonary artery and thoracic aorta, while heart is secondary involved. Heart chambers, as the primary site of IS origin, are extremely rare.
Methods: Comparative histopathological and immunohistochemical analysis of antemortem removed left atrium (LA) tumour, and postmortem sampled periadventially invaded right upper pulmonary vein.
Results: We present a case of a 42-year-old male who was admitted to the Clinic for cardiovascular surgery due to LA tumour clinically assessed as myxoma, and died a day after surgery due to acute myocardial infarction. Intraoperatively, tumour showed infiltrative growth, with invasion and destruction of mitral valve which was removed. Autopsy revealed invasion of upper right pulmonary vein, as well as deposits around distal branches. Histopathological analysis showed hypercellular highly pleomorphic spindle-cell neoplasm with fascicular and storiform growth pattern, necrosis, and vascular invasion. Tumour expressed diffuse vimentin and MDM2 positivity, single cells expressed CD31, CD34, ERG and Desmin, while cytokeratin AE1/AE3 expression was absent, corresponding to IS immunophenotype.
Conclusion: Primary cardial IS are extremely rare tumours, thus their initial unspecific clinical and radiological presentation could be confused with other cardiac tumours which are more common and benigan, like myxomas. Since IS is aggressive and invasive neoplasm, a complete surgical excision is usually impossible, and having in mind that radio- and chemotherapy modalities are of low success, the prognosis of IS at the moment of diagnosis remains poor.

E-PS-03-004
Early myocardial infarction recognition by CD15 and C9 expression
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Background & objectives: Early macroscopic diagnosis (12-24 hours) of Myocardial Infarction (MI) is challenging to Pathologists and macroscopic/microscopic observation in necropsies depends on the interval time between acute ischaemic onset and death. Biomarkers expression was searched in two MI evolutional phases.
Methods: 43 MI samples retrieved from autopsies (IAP-PM/INM-LCF archives) were evaluated by two Pathologists. The following panel CD15, C9, C5b9, IL-15, Gal-3, and Fibronectin global expression was registered and submitted to statistical analysis - SPSSv27 and Mann-Whitney/Kruskal-Wallis tests to score different MI phases; ROC curves determined the best cut-off value for differentiating early (<3 days) from old (≥ 3 days) MI.
Results: Neutrophils were considered grosso modo as MI classifier dating over three days since the clinical ischaemic coagulation necrosis onset. Two study groups were registered. CD15 (U=41,500; p<0,001; N=43) and complement fraction C9 (U=42,000; p<0,001; N=43) demonstrated significantly higher global expression (intensity of expression x percentage of positivity) in early MIs (<3 days) cases. Global expression cut-off of 105 for CD15 and 85 for C9 associated with Se and Sp of 0,875/0,818 and 0,875/0,600, respectively, for distinguishing old MI (>3 days) from early MIs. The other biomarkers were irrelevant due to similar expression in considered old and early MI.
Conclusion: MI keeps being one of leading causes of death worldwide and Clinicians claim correct dating for therapy adjustment knowledge. The cut-off values determined, with high Se and Sp, demonstrated CD15 and C9 expression of high value aiding the Pathologist in evolutional MIs phase dating. CD15 and C9 different global expression can be used to distinguish between early (<3 days) and older (>3 days) MIs.
Keywords: Myocardial Infarction; CD15; C9

E-PS-03-005
Inflammation, media degeneration and atherosclerosis during ascending aortitis
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Background & objectives: Aortitis may be present during ascending aortic dilatation and dissection. Histologically, the aortic wall reveals inflammation, media degeneration and atherosclerosis. We quantified aortic wall histology in surgically treated patients with ascending aortitis.
Methods: Ascending aortic wall inflammation, media degeneration and atherosclerosis were graded according to the AECVP-SCVP guidelines in 42 patients (25 males:17 females, mean age 68 years, range 58-75 years). At least six samples from each aorta were evaluated using Haematoxylin-Eosin, Alcian Blue-Periodic Acid-Schiff, Verhoef-van Gieson stained sections and CD3, CD68, CD20, CD38 and SMA immunohistochemistry.
Results: Inflammatory infiltrate was lympho-plasmacytic in 32 (74%) cases. Mixed inflammatory pattern was diagnosed in five (12%) cases, granulomatous pattern in four (9%) and suppurative in two (5%). IgG/IgG4 disease was detected in two (6%) cases together with lympho-plasmacytic infiltrate. Overall degeneration was mild in three (7%), moderate in 16 (37%) and severe in 24 (56%) cases. Various degree of atherosclerosis encompassed all specimens. Severe atherosclerosis was most common (n=19 (44%)), of which three included plaque disruptions and eight calcified plaques. There were ten (23%) cases of mild atherosclerosis and 14 (33%) moderate atherosclerosis.
Conclusion: Various degree of aortic wall inflammation, media degeneration and atherosclerosis were often present during surgically treated aortitis. Notably, a lympho-plasmacytic inflammatory pattern occurred in three quarters of the patients with aortitis,

while severe aortic wall media degeneration and severe atherosclerosis were present in almost half of the patients.
Funding: VTR grants from Pirkanmaa Hospital District

E-PS-03-006
A rare case of heart metastasis of chondrosarcoma
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Background & objectives: Chondrosarcomas are malignant mesenchymal tumours which account for 20% of malignant bone tumours. Local recurrences and metastases are often encountered. Through this case, we aim to present an unusual case of chondrosarcoma metastasis in the heart.
Methods: We, hereby, present a case of cardiac metastasis of a chondrosarcoma.
Results: A 58 year old female patient operated on for left iliac chondrosarcoma few days earlier, presented with chest pain and dyspnea. A Chest-Tomography-Scan was performed and revealed not only pulmonary lesions but also an intra-cardiac mass. The decision was to remove the cardiac mass surgically. Gross examination showed a myxoid arborescent lesion. Histopathological examination showed a malignant cartilaginous proliferation. It was arranged in diffuse sheets of dense cartilaginous tissue with areas of necrosis. The tumour cells had atypical, hyperchromatic and enlarged nuclei. Some cells were binucleated. The diagnosis was consistent with cardiac metastasis of a chondrosarcoma.
Conclusion: Chondrosarcoma is a malignant bone tumour with often an indolent course. The prognosis is favourable after complete surgical resection. However, hematogenous spread, most commonly to the lungs has a poor prognosis. Chondrosarcoma's cardiac metastasis is extremely rare. The diagnosis is challenging and requires multimodality approach guided by clinical context. The diagnosis of certainty is based on hispathologic examination.

E-PS-03-007
A rare cardiac neoplasm: case report of a cardiac angiosarcoma, review of literature
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Background & objectives: Primary cardiac malignancies are rare. Although angiosarcomas are rare soft tissue tumours, they are the most common primary cardiac malignancy.
Methods: In this study, we present a case of primary cardiac angiosarcoma in a 24-year-old female patient. The patient presented with complaints of chest pain and shortness of breath. Following clinical and radiological evaluation, primary cardiac mass was surgically removed.
Results: Pathological examination revealed a mesenchymal tumour with areas of haemorrhage and necrosis, solid and vessel-like areas, composed of atypical cells. Immunohistochemical examination showed diffuse and strong staining with CD31, ERG and FLI1. With these findings, it was diagnosed as angiosarcoma. Although our case was limited to the heart during surgery, lung and pleural metastases were arisen in the postoperatively 5th month despite chemotherapy. Currently she is in the postoperatively 10th month and her follow-up is continued.
Conclusion: Cardiac angiosarcomas have a poor prognosis and a fatal course, because they are metastatic at the time of diagnosis and show rapid progression. Early diagnosis and surgical resection can improve the survival.

E-PS-03-008
New method of an assessment of thrombogenic complications caused by SARS-CoV-2 virus. Anatomical research
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Background & objectives: COVID-19 is a new respiratory viral disease caused by a Sars-Cov-2 virus. According to recent research massive vasculitis leading to thrombosis is a typical feature of COVID-19. Blood clots can be found in different parts of the vasculature.
Methods: We present a new method consisting of assessment of thrombosed vessels of upper and lower limbs. This method applied on 4 upper and 5 lower limbs that were amputated due to critical ischemia caused by thrombosis associated with Sars-CoV-2 virus. Non-fixated material was frozen with the temperature -15°C and cutted in steps of 5 cm by band saw machine JWBS-10S.
Results: During the research, accurate cuts of the upper and lower limbs with a thickness of 5 cm were obtained. Usage of a band saw machine allows us to observe exactly thrombogenic complications on every limb. On each of them, sections of vessels filled with thrombotic masses were doubtlessly visible. Such pathomorphological changes caused extensive critical ischemia. Multiple areas of necrotic muscle tissue were also revealed.
Conclusion: In this article we have presented a new method of an assessment of thrombogenic complications caused by Sars-Cov-2 virus. This approach can expand pathomorphological practice and may substitute the method of layer-by-layer study of muscles, fascia and vessels. Acute thrombosis may lead to severe ischimization of any limb that provokes its necrosis. Gross anatomy observation of thrombotic masses based on N.I. Pirogov's cutting method allows to estimate thrombosis on different locuses of upper and lower limbs more precisely.

E-PS-03-009
Universal model for advanced macroscopic assessment of acute myocardial injuries
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Background & objectives: Currently existing laboratory models lack a clear algorithm for selecting a myocardial tissue site for histological and/or immunohistochemical examination to detect tissue reactions and obtain a result linked with prevalence and their ratios in the various areas of myocardium tissue.
Methods: The experiments were carried out on 15 white male rats. Three groups of 5 animals were formed. In animals of 1 group, myocardial contusion was reproduced. In the second group, the mechanical occlusion of the coronary was reproduced by ligating the anterior intraventricular artery. In the third group, the ischemic imbalance was reproduced by administration of isoprenaline.
Results: Nitro blue tetrazolium chloride confidently differentiated the damage zones of myocardium in animals of all groups, which allowed to calculate its total area. In the first group of animals, the myocardial damage zone within 24 hours of the myocardial contusion simulation captured the intraventricular septum and the anterior walls of the left and right ventricles equally, which was

largely consistent with the projection of the impact. In the second group of animals, the damage area was located in the region of the disturbed coronary blood flow. In the third group of animals, the damage sites were diffused in the myocardium of both ventricles and ventricular septum.
Conclusion: The approach helps to identify areas of myocardial damage regardless of their nature (traumatic, ischemic-hypoxic, secondary-metabolic). Since the proposed model for identifying sites of myocardial injury is universal, it can be successfully used to identify candidate zones for morphological examination, including for immunohistochemical studies to assess severity, localization and ratio of tissue autophagy and apoptosis reactions in altered myocardium. The model allows the selection of heart tissue fragments for examination in the alteration zone and adjacent areas of intact myocardium.

E-PS-04 | E-Posters Cytopathology

E-PS-04-002
Strongyloides stercoralis: a rare case diagnosed with oesophageal swab sample

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Background & objectives: Strongyloides stercoralis (S.s.) is an intestinal nematode which might involve different systems. Although the infection caused by S.s. is usually asymptomatic, in immunocompromised host it could be severe and fatal. We presented a case that diagnosed with oesophageal swab sample.
Methods: A 70 year old man with pneumoconiosis, applied to hospital with oral intake disorder. Endoscopic examination was performed. Because of diffuse ulcers on oesophagus only one swab sample could be obtained. On this sample larvae and soils were observed. It was reported to clinic that may correspond to S. stercoralis, then another esophagogastroduodenoscopy was performed. Many biopsies were conducted on.
Results: This samples exhibited chronic inflammation and distortions of gland architecture. In crypt lumens, eggs as aggregations with basophilic granular appearance and typical larva structure with sharply ended tails were seen. Concurrent fresh sampling from gastric and oesophageal fluid studied by spreading between slides was examined with biopsies. The biopsy and swab samples were evaluated as compatible with S. s.
Conclusion: Infected individuals with S.s. are usually asymptomatic. However, it may cause a hyperinfection syndrome in immunocompromised hosts. Furthermore, this scenario may be severe and has a high mortality risk. It can be prevented by detecting infection in asymptomatic individuals. Particularly in risk groups that have history of travel endemic zones or begin using immunosuppressive agents can be scanned.

E-PS-04-003
Metastatic malignant mixed germ cell tumour of the epigastrium as a primary incidental finding: a rare case presentation

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Background & objectives: Germ cell tumours (GCTs) constitute a rare and diverse group of neoplastic entities. They affect mainly young people and arise from primordial germ cells. We present a rare case of metastatic malignant GCT to the epigastrium, diagnosed by EUS-FNA cytology.
Methods: A 57-year-old male, with a history of weight loss and abdominal pain, presents with a 16-cm lymph node block in the epigastric region, accompanied by enlarged mediastinal and peripancreatic lymph nodes, and a 2-cm mass in the body of pancreas, as detected on CT scans. His laboratory tests were normal, except for elevated LDH levels.
Results: With the clinical impression of lymphoma, an EUS-FNA of the mass was performed. FNA smears revealed highly atypical pleomorphic cells, lying singly or in loose clusters in a haemorrhagic and necrotic background with many lymphocytes. Immunocytochemical evaluation showed strong and diffuse positivity of malignant cells for SALL-4, PLAP, OCT-4, a-FP, focal positivity for AE1/AE3 and CK7, and Ki67 index > 80%. The final diagnosis of a metastatic malignant germ cell tumour was rendered. Since there was no known history of testicular tumour, a thorough evaluation of the gonads was advised, for identification of the primary lesion.
Conclusion: GCTs are an uncommon group of heterogeneous tumours including both benign and malignant neoplasms. They are categorized into germinomatous and non-germinomatous types, affecting mainly the gonads of young patients. The uncommon mixed GCTs are constituted of two or more types of malignant primitive or germ cell components, accounting for approximately 8% of all malignant GCTs.

E-PS-04-004
Pancreatic metastasis of multiple myeloma diagnosed by EUS-FNA: report of a rare case

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Background & objectives: Multiple myeloma (MM) metastases to pancreas, as a secondary extramedullary disease (EMD), is a rare occurrence with less than 300 cases reported in the literature, and only 2,3% in autopsies.
Methods: A 68-year-old female, with a past history of MM 5 years ago, presented to our hospital with obstructive jaundice. Abdominal contrasted CT scan detected a non-homogenous mass in the head of the pancreas (2,5 cm), fat stranding, peripancreatic fluid collection and swelling of the regional lymph nodes (<1cm).
Results: An ultrasound-guided fine needle aspiration (EUS-FNA) of the pancreatic mass revealed infiltration by a population of monotonous neoplastic plasma cells with characteristic eccentrically placed nuclei and abundant cytoplasm, mainly arranged in compact nests. Immunocytochemistry was performed taking into consideration patient's history. The neoplastic cells were positive for CD138, MUM-1, CD79a and kappa light chain and negative for CD3, CD20 and lambda light chain. Morphology and immunocytochemistry profile lead to a diagnosis consistent with metastasis of MM to the pancreas.
Conclusion: Pancreatic metastasis from MM are rare but despite their rarity they should be considered in the differential diagnosis of obstructive jaundice and primary pancreatic neoplasms. Therefore, a detailed medical history in combination with immunocytochemical findings are paramount for the diagnosis. Extramedullary involvement is one of the indicators of poor prognosis. There is no consensus in treatment options and their efficacy.

E-PS-04-005

Immunocytochemistry-assisted diagnosis of solid pseudopapillary neoplasm of the pancreas in a young man

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Background & objectives: Solid Pseudopapillary Neoplasm (SPN) of the pancreas represents a very rare, low-malignant potential tumour that usually occurs in young females. Cytological diagnosis of SPN is straight-forward in typical cases but immunocytochemistry is required in material with unusual cytological features.
Methods: A 38-year-old man presented with a partially cystic pancreatic mass measuring 1,6cm on maximum dimension and localized in the uncinate process, an incidental finding on abdominal MRI. Endoscopic Ultrasound Fine Needle Aspiration (EUS-FNA) was performed to obtain material from the lesion. ThinPrep prepared slides and hematoxylin-eosin stained cell block sections were examined. Additionally, immunocytochemistry was performed on cell block sections.
Results: The neoplastic cells were uniform and bland, with nuclei with granular chromatin and inconspicuous nucleoli. They were arranged in loose clusters without forming papillary structures. Hyaline globules were not identified. The morphological features did not allow the challenging differential diagnosis between SPN and well-differentiated neuroendocrine tumour (NET). Immunocytochemical analysis revealed that neoplastic cells were strongly positive for vimentin, PR, synaptophysin, CD56, CD10 and LEF-1 whereas the expression of pan-cytokeratin AE1/AE3 was weak and focal. Importantly, the tumour cells displayed nuclear immunopositivity to β-catenin and were negative for chromogranin expression. Additionally, the proliferation marker Ki-67 was extremely low. The immunoprofile complemented the cytomorphologic findings and established the confident diagnosis of SPN.
Conclusion: This challenging case illustrates the difficulty in diagnosing pancreatic SPN with atypical features. Patient's gender and the tumour location (head instead of body or tail of pancreas) were not suggestive of SPN. Given that the typical cytological features of SPN were not present and the morphological overlap between SPN and NET, a broad immunohistochemical panel was required for correct diagnosis. The patient underwent the Whipple surgical procedure and histological examination of the resected specimen confirmed the diagnosis of SPN.

E-PS-04-006

Cytomorphological and clinical features of desmoplastic small round cell tumour in peritoneal effusion

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Background & objectives: Desmoplastic small round cell tumour (DSRCT) is a rare lethal malignant tumour which affects predominantly young males. The majority of cases arise in the abdominopelvic region. Here a case of DSRCT infiltration in peritoneal effusion was presented.
Methods: A 41-year-old male patient presented complaining of abdominal pain - swelling, and losing weight for a while. Peritoneal fluid and 22 cm sized mass were detected in abdominopelvic region. The sampling was made from the free fluid and mass (trucut biopsy). A PAP staining slide and a cell block obtained from peritoneal fluid by prepared with liquid-based cytology (Surepath, BD®).
Results: Cytologic examination of the peritoneal fluid demonstrated a very hypercellular lesion which consist of small round tumour cells with scant cytoplasm, round or kidney or hearth shaped nuclei and inconspicuous nucleoli. Nuclear molding was usually present. Mitotic figures, numerous crushed nuclei, and apoptosis were frequently seen. In the immunohistochemical examination of cell block tumour cells were positive for Vimentin, PanCK, Desmin, WT1 and negative for BerEp4, CD45, CD99, CDK4, Calretinin. Ki67 proliferation index was %75-80 in tumour cells. The microscopic examination of trucut biopsy showed similar features. With these findings the case was reported as "DSRCT infiltration in peritoneal effusion".
Conclusion: Cytologic diagnosis of DSRCT infiltration to the effusions is a rare entity. In differential diagnosis other small round cell tumours such as rhabdomyosarcoma, Ewing sarcoma/PNET, neuroblastoma, also lymphoma should be considered. The immunohistochemical studies on cell blocks helps in the differential diagnosis.

E-PS-04-007

Comprehensive comparative assessment of the whole slide images of cytologic samples for quality assurance program in Korea

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Background & objectives: The Korean Society for Cytopathology first introduced a digital proficiency test in 2021. However, there are still many doubtful opinions whether digitally scanned images can present subtle differences of nuclear features and chromatin patterns of cytologic samples satisfactorily or not.
Methods: We performed a comprehensive comparative assessment of the whole slide images of 12 various cytologic slides using five different scanners with various scanning conditions. The scanner specification such as capacity, z-stacking, file formats, size, scan time, and error rate were assessed. Four cytopathologists assessed the image quality using the questionnaire on focus, colour balance, nuclear/cytoplasmic/chromatin features, etc.
Results: 3DHistech Panoramic 250 Flash was the best in terms of image quality, feature presentation, and error rate for most cytologic samples. Hamamatsu NanoZoomer 360 was the best in terms of scanning speed and weekly capacity. Both 3DHistech and Hamamatsu models provide extended focus function that saves storage and server capacity. Although Leica AT-2 showed comparable performance in image quality to 3DHistech Panoramic 250 Flash, the scanning speed and error rate were relatively poor. As Roche and Philips models do not provide a z-stacking function, it is least recommended for cytologic samples.
Conclusion: As 3-dimensional clusters are common and nuclear/chromatin features are critical for cytologic interpretation, careful selection of scanners and optimal conditions are mandatory in cytologic practice.
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E-PS-04-008

Cytologic diagnosis of pancreatic acinar cell carcinoma – a case report

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Background & objectives: Acinar cell carcinomas are rare malignant epithelial neoplasms, arising from the exocrine acinar tissue, with poorly defined pathogenesis. Males are more commonly affected and presenting symptoms are related to tumour growth. We present a case report on this rare entity.
Methods: We received a fine-needle aspiration (FNA) sample from a 57 year-old man with a pancreactic isthmic mass. On endoscopic ultrasound, a 5,8cm lesion, partially solid and partially cystic was found, without signs of vascular invasion or signs of regional lymph node metastasis. We performed the analysis on stained samples with PAP, MGG and a cellblock.
Results: The sample was moderately cellular, with red blood cells and trabecular formations, with pseudorosette formations, syncytial cytoplasm with round and monotonous nuclei, with occasional nucleoli. Mitosis figures were observed and necrosis was absent. On cellblock evaluation, immunohistochemistry was performed. The lesion was positive for CK AE1/AE3, CK7, Trypsin, PAS/D and negative for CK20, CD56, NSE, Synaptofysin, Chromogranin, Beta-catenin (membrane staining). This was compatible with a pancreatic acinar cell carcinoma (Category VI – Malignant, The Papanicolaou Society of Cytopathology System for Reporting Pancreatobiliary Cytology).
Conclusion: Acinar cell carcinoma has a poor prognosis, with approximately 50% of the patients have metastatic disease at presentation and a 5-year survival rate of 25%. Although aggressive, it appears to have a better prognosis than conventional pancreatic ductal adenocarcinoma. It is a rare entity without any hallmark genetic alteration, and we present this case to shed a light on the importance of immunohistochemistry and markers like trypsine while diagnosing this type of lesions, as well as the morphological aspects.

E-PS-05 | E-Posters Dermatopathology

E-PS-05-001
Pure bullous pyoderma gangrenosum, a challenging clinicopathological diagnosis - critical literature review with emphasis on diagnostic criteria

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Background & objectives: Pyoderma gangrenosum is an uncommon neutrophilic dermatosis characterized by large necrotic ulcers. Occasionally patients develop atypical presentations, including bullous lesions. Only eighteen pure cases of Bullous Pyoderma gangrenosum have been described. Our aim is highlight distinctive clinical and pathological features.
Methods: We describe a case of Bullous pyoderma gangrenosum in a 76-year-old man, with active oncological history, including a recent diagnosis of hairy cell leukaemia. We have carried out an exhaustive review of the literature where clinical and pathological details of the lesions are absent or very scant. Furthermore, many of the cases reported were mixed variants.
Results: Clinically, our case supposed a challenging differential diagnosis due to atypical clinical presentation that mimicked necrotizing fasciitis. The purple blistering appearance of the lesions in the setting of a patient with multiple treatments, raised the possibility of an adverse drug reaction. Nevertheless, the exacerbation of the large plaque after surgical procedures was a clear sign of pathergy. Histologically, there was partial preservation of the epidermis, subepidermal vesiculation and neutrophilic exocytosis. A massive neutrophilic infiltrate filled the dermis and hypodermis without vasculitis or any sign of specific infection. The patient was treated with diverse intravenous antibiotics and several surgical procedures without improvement. Finally healed after gradual weaning from immunosuppressive therapy.
Conclusion: The variety of clinical manifestations and it´s nonspecific histology, make Bullous pyoderma gangrenosum a challenging diagnosis. A good clinicopathological correlation, always in the setting of complementary tests, it´s crucial for accurate the diagnosis. This case highlights the importance of maintaining a strong clinical suspicion in a patient with rapidly progressive, noninfectious blisters that worsens after surgical procedures in the context of an hematologic disorder and G-CSF treatment (described as possible triggers).

E-PS-05-002
Telangiectasia arising in submandibular melanocytic (compound) nevus

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Background & objectives: Telangiectasia is an excessive permanent dilation of superficial blood vessels in the skin. The development of telangiectasia in the final blood vessels of dermal tumours is uncommon. The characteristics of the lesion are described and a literature review is attempted.
Methods: We present a case of a 16-year-old woman who reports the presence of a dark spot on her submandibular area for years. The last six months report alteration of the mole hue, mainly in the central areas. The dermatological examination shows a round lump with clear peripheral boundaries and a brownish uneven appearance and a surgical removal is decided.
Results: The surgical specimen consists of a fusiform part of skin with a surface of dimensions 1.5X1 cm and a thickness of 0.8 cm. In the middle of the free surface there is a hemispherical protruding dark skin formation (tumour) with a larger diameter of 0.8 cm. Histologically it shows an image of a compound nevus, in the central area of which lesions compatible with telangiectasia are found. In particular, dilated thin-walled vessels are found, which do not form a formation but grow between the cells of the nevus, and their lumen is filled with blood elements.
Conclusion: Telangiectasia can be an isolated phenomenon or as part of a generalized disorder. Secondary development may be caused by external forces such as scratching, trauma, radiation, infection etc. The distinction between a primary and a secondary lesion is not always clear. The bleeding is considered the most important complication of the lesion and when it develops in dermal tumours it causes unusual macroscopic alterations of the structure in which it grows, which can create clinical differential diagnostic problems.

E-PS-05-003
Intersticial Mycosis Fungoides. A clinicopathologic study of four cases

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Background & objectives: Instersticial Mycosis Fungoides (IMF) is a rare histological variant of Mycosis Fungoides that may mimic inflammatory dermatoses as granuloma annulare, morphea and interstitial granulomatous dermatitis. The cases of IMF from our institution have been reviewed in order to characterize it.
Methods: Four cases diagnosed with Interstitial Mycosis Fungoides (IMF). All clinical, histopathologic and immunohistochemical variables were collected. All of them were men, with a mean age of 61 years old (range 42-80) with previous diagnosis of classic MF and clinical symptoms of poikiloderma and plaque.
Results: Three patients presented annular lesions and nodules after two and four years of follow-up in one and two cases, respectively, which were biopsied. The fourth patient started with chronic purpura pigmentosa lesions and after six years of evolution, the annular lesions also appeared. In all cases, a perivascular and interstitial lymphocytic infiltrate was observed, accompanied by macrophages (CD163 positive). These were arranged in a palisade, simulating a granuloma annulare. Mucin deposition was also observed. The lymphoid infiltrate was CD4 positive. TCR-gamma gene was rearranged in all the cases, showing a monoclonal population.
Conclusion: -Diagnosis of IMF is challenging, as it mimics granuloma annulare clinically and histologically.
-In cases with previous MF, IMF is associated with clinical modifications.
-IMFs display a double population of lymphocytes and macrophages, which makes them difficult to observe/distinguish.
- It is necessary to know this rare variant in order to recognize it.

E-PS-05-004
Clear cell variant of atypical fibroxanthoma and pleomorphic dermal sarcoma: molecular characterisation of two cases
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Background & objectives: Atypical fibroxanthoma (AFX) and pleomorphic dermal sarcoma (PDS) are unusual cutaneous tumours. The molecular profile of the rare clear cell (cc) variant is unknown. We present key morphologic and molecular features of two ccAFX and ccPDS cases.
Methods: Total genomic DNA was extracted from formalin-fixed paraffin-embedded tumour tissue and next generation sequencing (NGS) was performed using the TruSight Oncology 500 assay (Illumina, CA, USA). This platform enables profiling of 523 genes for identification of DNA variants, quantification of microsatellite instability (MSI), and tumour mutational burden (TMB). Variant annotation was performed using the Molecular Tumour Board Portal (MTBP).
Results: Both tumours presented as nodular lesions on the scalp of elderly males. Microscopically, they comprised intradermal sheets of cells with abundant pale to clear cytoplasm, severely pleomorphic nuclei, and frequent mitoses. The ccPDS extended into the deep subcutis. Neoplastic cells expressed CD10 strongly and diffusely and lacked expression of other markers. Both tumours showed high TMB (ccAFX: 67.9mt/mb; ccPDS: 105.3mt/mb) and no significant MSI. Loss-of-function mutations in the TP53, CDKN2A, and NOTCH1 genes were detected in both cases, similarly to other AFX and PDS variants. TERT promoter and NOTCH2 mutations were present in the ccAFX case only whereas an APC mutation was present in ccPDS. No tumour recurrence was observed.
Conclusion: Clear cell AFX and PDS seem to share fundamental molecular driver events. Their molecular profile is also similar to that described in more common variants. Whilst no unique mutational profile was identified in our cases, presence of the genetic abnormalities described herein may increase the level of confidence in diagnosing these lesions. Adverse histologic features such as tumour necrosis, lymphovascular invasion, and extension into deep subcutis still remain essential for distinction between AFX and PDS.

E-PS-05-005
Eruptive junctional melanocytic naevi associated with cutaneous mastocytosis, a rare case report
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Background & objectives: A 32 year old Caucasian male presented with red maculopapular rashes following psychological stress, triggered by alcohol, coffee and hot water exposure, distributed all over the body and subside leaving red papules. No diarrhoea, headaches or flushing symptoms were reported.
Methods: There was dermographism and macular rashes induced by scratching on the abdomen, back and arms. Skin punch biopsies from the abdomen and the arm showed SOX10 positive small junctional nonpigmented melanocytic nests. Toludine blue and CD117 showed increased dermal mast cells. Bone marrow biopsy showed no C-Kit mutation and serum tryptase was normal. No hepatosplenomegaly/lymphadenopathy was seen on CT scan.
Results: Around 10 similar cases have been reported, including a case report by Danotti et al. There is prevalence for female patients. CD117 is thought to be expressed in 29% of melanomas, which may also have therapeutic implications. In our case CD117 was negative in the melanocytes. Hägglund et al reported an increased risk of melanoma in patients with systemic mastocytosis. The C-Kit proto-oncogen codes for the transmembrane tyrosine kinase receptor of the stem cell factor (SCF). Increased CSF induces melanocyte proliferation, melanin pigment production and deposits in keratinocytes. The papules were around a millimetre in size and none underwent recent change. This was an incidental unexpected finding on histopathology.
Conclusion: We presented a rare case of eruptive melanocytic naevi associated with cutaneous mastocytosis in a young man, which was an incidental histology finding. This rare condition confirms the similar pathogenesis between the mast cells and melanocytic naevi, related to the increased SCF stimulation. Such patients need close follow up to ensure early diagnosis of melanoma. They also need to be fully investigated to exclude systemic mastocytosis. They are offered symptomatic relief of their itching and rashes.

E-PS-05-007
Metatypical basal cell carcinoma overlying a dermatofibroma: an association never described before
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Background & objectives: Dermatofibroma (DF) is a skin tumour, mostly located on the limps. The overlying epidermis shows simple hyperplasia to basal cell carcinoma (BCC). We report a tumour consisting of DF and metatypical BCC in the outer surface of the left forearm.
Methods: A 84-year old woman presented to our dermatology clinic for evaluation of a lesion on her left posterior arm. She was uncertain as to its duration and she denied any pain or bleeding. Physical examination revealed a 13mm raised circumscribed smooth, lobulated skin nodule, with solid, whitish and

elastic cut surface. The lesion was excised and sent for histological examination.
Results: Histopathology confirmed two different lesions in association. An overlying baso-squamous BCC in the overlying epidermis and reticular dermis and an underlying symmetric relatively circumscribed with indefinite borders dermal based lesion consisting of a mixture of fibroblasts and histiocytes arranged in fascicles with storiform pattern. The BCC component was positive for CK5/6, p63, p40, BerEP4 and bcl-2 and the concomitant lesion for CD68/KP1 and negative for S-100 and EMA. The final diagnosis was of a collision tumour consisting of a metatypical BCC overlying a dermatofibroma.
Conclusion: Dermatofibromas and BCCs are common lesions. Their coexistence within one lesion is uncommon. DFs can be associated with a variety of benign lesions of the overlying epidermis including pseudoepitheliomatous hyperplasia, to basaloid proliferations to BCC, Bowen disease and melanoma. Basal cell proliferations and BCCs are said to be the result of the inductive effect of DF on the epithelial cells of the hair follicle. The association with metatypical BCC has not previously been described and can contribute to the histogenesis.

E-PS-05-008
Eccrine porocarcinoma metastasized in the lung - a case report
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Background & objectives: Eccrine porocarcinoma (EPC) is a rare malignant cutaneous adnexal tumour, representing 0.005% to 0.01% of all cutaneous tumours. Can arise de novo or from pre-existing poroma. Chronic light exposure and immunosuppression proposed as factors that contribute to the malignant transformation.
Methods: We received, from a 56-year-old female, a skin biopsy composed by small fragments of skin from inguinal region.
Results: On histological examination the dermis was infiltrated by epithelioid malignant cells with eosinophilic cytoplasm, moderate to severe nuclear atypia, prominent nucleoli and brisk mitotic activity ≥ 3-5 mitosis/1HPF. The cells are arranged in nests with fibrous septa between them. Necrosis was present. The neoplasm extends widely to the surgical margins.
Immunochemistry was positive for CK7, EMA, CK5/6, p63, EGFR, E-cadherin, CD10 and GATA-3. Ki-67 was positive 90% of neoplastic cells. Negative immunoractivity for Melan A, HMB45, ER, PgR, AR and p16 was observed. The diagnostic of eccrine porocarcinoma was made. We recommended wider skin excision and control of the regional lymph nodes, lung and bone. Further investigation revealed lung metastasis.
Conclusion: The lower extremities and head and neck are the most common primary sites for EPC. Because malignant transformation of previous benign lesion could be happened, any spontaneous bleeding, ulceration, itching, pain and sudden growth must be investigated. Due to its rarity and no specific clinical manifestations, it is generally difficult to suspect EPC as initial clinical diagnosis.

E-PS-05-009
The relative composition and distribution of the mononuclear inflammatory cell infiltrate in common melanocytic nevi
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Background & objectives: Melanocytic nevi are frequently associated with inflammatory cells of different types and varied proportions. Our study aims to evaluate the mononuclear inflammatory cell in common melanocytic nevi (CMN) with intravascular nevus cell protrusion (IVNP) and intravascular nevus cell aggregates (IVNcA).
Methods: We performed a case control study comparing 30 CMN with IVNP and IVNcA and 30 matched CMN without IVNP and IVNcA and stained them for CD3, CD 4, CD 8, FOXP3, CD 20 and CD 11c, assessing the distribution and composition of the positive cells in the inflammatory cell population with their median and p-values using the student t test.
Results: The inflammatory infiltrate in all CMN was minimal, predominantly distributed perivascular, periadnexal and in the stroma surrounding the nevi, mainly consisted of T-cells in both groups, significantly higher (p=0.047) in the nevi with IVNP and IVNcAs. CD4+:CD8+ ratio varied from 1:3 to 4:1, without noteworthy differences between the two groups and the FoxP3+ cells were very sparse regardless of the type of nevus. The monocytic/macrophagic population CD11c+ was the second largest component of the inflammatory infiltrate and remarkably higher (p=0.02) in the nevi with IVNP and IVNcAs, compared to common melanocytic nevi without these features.
Conclusion: The microenvironment of benign melanocytic lesions consists of low counts of immune cells, scattered around the stroma and nevus cells, most of which are CD3+ cells, followed by macrophages and with very few CD 20+ lymphocytes; this layout is mainly observed in nevi with IVNP and IVNcAs. A better understanding of the mononuclear cells role played in the pathogenesis of the vascular affinity of melanocytes is needed through further research.
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E-PS-05-010
Clinical pitfall, an incidental umbilical melanoma, a case report
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Background & objectives: Melanoma is the third prevalent skin cancer, commonly seen in sun-exposed skin. 43% of all umbilical tumours are malignant and classified as primary or metastatic. Primary malignancies represent 12-20% of all umbilical malignancies. Umbilical melanoma is extremely rare.
Methods: The case of umbilical melanoma operated with the previously diagnosed as granuloma was evaluated in terms of clinical and pathological features.
Results: A 48-year-old female patient presented to general surgery clinic with main complaint of abdominal pain also suffered from mild discoloration and swelling in the umbilicus. After examination the patient was diagnosed as chronic cholesystitis and umbilical granuloma and operated. The gallbladder and umbilical material of the patient sent to our laboratory. When the specimen pre-diagnosed as umbilical granuloma was examined, we saw an ulcerated, well-circumscribed nodular pigmented lesion on umbilicus with a diameter of 3 cm. As a result of microscopic examination, the case was reported as Clark level 4, pT4b melanoma. Unexpected Malignancy was reported as a panic diagnosis.
Conclusion: As in our case, the diagnosis of umbilical melanoma is often made in the late stages, possibly because the umbilicus is an area that is often not discovered during skin cancer screening and the patient delays seeking medical attention. Even in it is found to be incidental,

it is important to make a macroscopic evaluation by predicting that malignancy may exist in the umbilical material. It should be kept in mind that umbilical lesions, although rare, have a malignant potential.

E-PS-05-011
Adenolipoma: a rare benign tumour
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Background & objectives: Adenolipoma is a rare benign skin tumour, first described in 1993. We present a case of adenolipoma with a brief review of the literature.
Methods: A 60-year-old male patient presented with a solitary, slow growing, painless lump on the right thigh. The lesion was subcutaneous, and the patient underwent surgical excision.
Results: On gross resection, the lesion was soft, lobulated, yellowish mass measuring 4.7 cm in greatest diameter, with a thin encircling capsule. Microscopically, the lesion consisted of lobules of mature fat with intermixed benign eccrine glands and ducts. The morphological findings were consistent with subcutaneous adenolipoma.
Conclusion: Adenolipoma is an unusual variant of lipoma, commonly arising in arms, shoulders and chest of adults aged 25-75 years. The tumour is subcutaneous or located in the dermis and composed of mature adipose tissue and eccrine ducts and glands. The glands can show cystic dilation, epithelial hyperplasia and squamous or clear metaplasia. Differential diagnosis includes typical lipoma, nevus lipomatosus superficialis, eccrine angiomatous hamartoma, spindle cell lipoma, and cutaneous myxolipoma. Treatment and prognosis are identical to those of common lipoma.

E-PS-05-012
Viral exanthema in a COVID-19 patient
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Background & objectives: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, is quickly spreading and threatening global health. COVID-19 has been related to a variety of cutaneous manifestations with different clinical patterns. However, the identification and characteristics of COVID-19-related skin lesions remain speculative.
Methods: A 70-year-old male patient developed itchy, erythematous papule, water-filled blisters over his body, particularly on his feet and hands, one week after contracting covid and lasting for 6-7 months. Diabetes, hypertension, and chronic renal disease were all present in the patient's medical history. Histopathological examination was performed in conjunction with the clinical preliminary diagnosis of viral exanthema or allergic dermatitis.
Results: Microscopic examination revealed spongiosis, microvesiculations, and lymphocyte exocytosis in the epidermis. There were lymphocytic vasculitis pattern in the superficial and/or deep dermis with mild oedema and extravasated erythrocytes from the damaged vessels, as well as slight infiltration of eosinophils and neutrophils. In the direct immunofluorescence microscopy, no deposits were seen. The diagnosis was considered as spongiotic dermatitis and lymphocytic vasculitis. This patient was taking a lot of medications, and comorbidities could make the differential diagnosis more difficult. Therefore, the skin lesion may be associated with a primary, indirect cutaneous manifestation or drug eruption from COVID-19 infection. We needed clinicopathological correlation in the differential diagnosis.
Conclusion: Histopathology plays an important role in describing skin lesions during the COVID-19 pandemic. The effects of COVID-19 on the skin can be seen as a result of lifestyle changes during the pandemic, various medicines used in therapy, and indirectly induced vascular dysfunctions. In our case, we concluded that spongiotic dermatitis pattern and lymphocytic vasculitis may be reflected viral exanthem associated with COVID-19 infection. This is an additional case to the skin findings of COVID-19 infection that contributes to the literature.

E-PS-05-013
Cryoglobulinemia and reactive angioendotheliomatosis, secondary to multiple myeloma and Waldenström's macroglobulinemia, a report of two rare cases
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Background & objectives: A 64-year-old female presented with bilateral toe numbness and painful erythematous rash on both legs and arms, worse in colder environment.
An 81-year-old man presented with a vasculitis-type rash on the foot, legs, torso and arms, initially bullous/blistering then necrotic.
Methods: Microscopically the skin showed lobular clusters of closely packed dermal glomeruloid capillaries. There was a striking proliferation of plumb endothelial cells forming capillaries within pre-existing dilated vessels associated with red cell extravasation. The capillaries were filled with pink-staining amorphous hyaline cryoglobulins material which was PAS-positive. These were highlighted by CD34 and ERG. HHV8 and muscle specific actin were negative.
Results: The first patient was recently diagnosed with lymphoplasmacytic lymphoma with a monoclonal IgM protein (Waldenström's macroglobulinemia). The second patient had a background of multiple myeloma and mixed cryoglobulinemia. He developed sepsis and renal failure and passed away shortly afterwards. The differential diagnosis included Kaposi sarcoma, angiosarcoma, pyogenic granuloma, bacillary angiomatosis, angioacrodermatitis and angioendotheliomatosis. Reactive angioendotheliomatosis (RAE) is a rare condition, the aetiology of which may be due to local ischaemia secondary to vascular obstruction. Only a few cases were reported in association with cryoglobulinemia. Other causes include systemic or autoimmune diseases, such as chronic renal failure or cardiac valvular disease, lymphoproliferative diseases, systemic infections, antiphospholipid syndrome, rheumatoid arthritis and atherosclerosis.
Conclusion: We presented two cases of cryoglobulinemia and reactive angioendotheliomatosis, induced by lymphoblastic lymphoma and multiple myeloma. They presented with erythematous/vasculitic rash, blisters, ulcers and necrosis. Histopathology showed distinct dermal lobules of glomeruloid capillary cluster proliferation filled with PAS-positive amorphous cryoglobulins and plumb endothelial cells. Despite the benign histopathology, the condition is very serious and one patient needed intensive care ending in a fatal course due to sepsis. Treatment is supportive with prevention of secondary infection and treating the underlying cause.

E-PS-05-014
Melanoma with blue nevus-like features - diagnostic challenges and management
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Background & objectives: Melanomas can oftentimes be difficult to diagnose because of the various ways they present themselves clinically and microscopically. Diagnosing the melanoma subtype is often very challenging, but the main issue must always be that the patient receives the right treatment.
Methods: 60-year-old woman initially presents with a progressively enlarging cervical lymphnode, which showed positivity for melanoma markers, without knowing the primary melanoma site. One month later, surgical excision of a scalp lesion was performed, showing nodules located in the dermis and subcutis, without any epidermal connections, with some heavily pigmented areas, consisting in both epithelioid and fusiform malignant cells.
Results: Histological examination could not differentiate between a primary melanoma with blue nevus-like features/a melanoma arising in a blue nevus and a cutaneous metastasis of a melanoma originating elsewhere. The fact that no other significant melanocytic lesion was found made it reasonable to consider this a primary lesion. The BRAF mutation was then assessed and it's absence might also be a clue that the tumour might have developed from a blue nevus, as these usually lack the BRAF mutation.
Conclusion: Establishing whether the lesion truly belongs to the "blue line" would have required molecular tests for the GNA11 or Gnaq alterations, but what matters is that she received treatment in time, the only one available in country protocols being INFα – which has been shown to improve overall survival and recurrence-free survival in patients with high-risk melanoma. We come across pathology pitfalls daily, but it is always important to only focus on the details that could really help the patient.

E-PS-05-015
Rare association of Leishmaniasis with purpura: a case report
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Background & objectives: Leishmaniasis is a chronic disease caused by an intracellular parasite. We report an uncommon cutaneous leishmaniasis associated with lymphocytic vasculitis, clinically manifested with purpura without ulceration. This hasn't been reported in Ecuador before, although there are 1000 cases per year.
Methods: A 75-year-old female presented drug-induced vasculitis with multiple purpuric lesions on both lower extremities, treated with prednisone 60mg during 2 weeks and 20mg per day as maintenance. Two months later after resolution of skin lesions, the patient presented a single cutaneous purpuric lesion on left lower extremity.
Results: Laboratory findings presented negative antinuclear antibodies, negative anti-DNA and C3–C4 protein levels within normal range. Biopsies of this lesion were taken and showed lymphoplasmocytic inflammatory infiltrate with diffuse and perivascular distribution, fibrin deposits on arterial walls and amastigotes forms of Leishmania inside histiocyte vacuoles.
Conclusion: This infectious disease presented a wide range of differential diagnosis due to its atypical presentation. Lymphocytic vasculitis has been associated with systemic lupus erythematosus, lymphoproliferative disorders such as angiocentric lymphoma or lymphomatoid papulosis, arachnidism and borrelia burdorferi infection due to erythema migrans similar appearance. The diagnosis of leishmaniasis in this patient was made by the identification of intracellular amastigotes. This uncommon manifestation of leishmaniasis can easily be mistaken with other diseases, which should have special considerations mainly in endemic areas.

E-PS-05-016
Calciphylaxis – histopathological feeling of impending doom. A case report
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Background & objectives: Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification, thrombosis and skin necrosis prevalent in patients with uremia. The mortality rate is high, due to sepsis and internal organ failure.
Methods: We present the case of a 33-year-old female patient, smoker, obese, admitted in the hospital for intense pain on right foot, muscle weakness, necrotic lesions on the skin with a history of important comorbidities (arterial hypertension, diabetes, dyslipidemia, hyperuricemia, obliterating artery disease of the lower limbs, ESRD and COVID-19).
Results: The patient rapidly developed extensive necrotic lesions of the right food, intense pain and worsening of the general condition despite treatment. The patient underwent a transmetatarsal amputation of the forefoot. The surgical sample was sent the the Pathology Department for histopathological assessment. Despite intensive care and multiple therapeutic attempts, the evolution was unfavourable, and the patient died 3 days after surgery. Microscopically, in addition to the tissue lesions characteristic of wet gangrene, typical features of calciphylaxis were observed. There were variable stippled calcification within adipose tissue and associated fat necrosis. Thick ring-shaped calcification of arteriole and capillaries were identified. Capillary thrombosis was extensive. Also a lymphohistiocytic infiltrate was noted
Conclusion: Calciphylaxis is a rare, critical condition, sometimes difficult to diagnose. The differential diagnosis might be challenging especially in patients with multiple comorbidities. The prognosis of calciphylaxis is often unfavourable despite aggressive treatment. Histopathological features suggestive for calciphylaxis found on post-amputation resection specimens should alarm both the pathologist and the medical team caring for the patient. Despite maximal medical and surgical therapies, calciphylaxis typically results in a 60% to 80% mortality rate with sepsis being the leading cause of death.

E-PS-05-017
Pilomatrical carcinoma, a case report
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Background & objectives: Pilomatrical carcinoma is an uncommon adnexal carcinoma with matrical differentiation. In the literature, less than 150 cases have been described. We aimed to contribute to the literature re-evaluating a rare case of pilomatrical carcinoma with the new immunohistochemical methods investigated.
Methods: We reported the case of a 86-year-old male with a 3 cm ulcerated nodule on the left temporal skin. The lesion was excised in Plastic Surgery department and we stained the excision specimen with LEF-1, CDX2 and SATB2 immunohistochemical stains which were related to the SATB2/β-catenin/TCF-LEF pathway that is discussed as an important pathway in pathogenesis of randomly selected pilomatricoma.
Results: As a result of the immunohistochemical analysis we performed, although pilomatrical carcinoma and pilomatrixoma showed expression with LEF-1 and CDX-2, SATB2 showed positivity only for pilomatrical carcinoma. When we re-evaluated the case with our previous findings, we obtained findings

consistent with the literature. It is interesting that previous studies, pilomatricoma with SATB2 immunohistochemistry did not show positivity. In a recent case report in the literature, SATB2, which was applied to a case of pilomatrical carcinoma and showed positivity, was also expressed in our case.
Conclusion: In conclusion, the use of SATB2 in the differential diagnosis of benign and malignant pilomatrical tumours may be considered. Even though the results obtained in this study cannot be generalized, it may be important to study these lesions in large series in terms of giving an idea to clarify the pathogenesis and immunohistochemistry. Considered together with the literature, our case can be a clue for new pathogenetic studies.

E-PS-05-018
Clinicopathological cocordance of mycosis fungoides: 10 years of our institutional experience
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Background & objectives: Mycosis fungoides (MF) is a disease that can be diagnosed by the collaboration of a clinician and pathologist. Its differential diagnosis includes many other malignant and benign dermatoses. We evaluated the clinicopathological corelations and its importance in this study.
Methods: Between 2010 and 2021, 885 skin punch biopsies in which MF was diagnosed histopathologically or with MF in the clinical differential diagnosis were retrospectively analysed. Recurrent biopsies (76) and patients previously diagnosed with MF (17) were excluded from the study.
Results: Of the cases, no findings consistent with MF were found in 744 (93,9%) patients, whereas MF was diagnosed histopathologically in 48 (6,1%) patients. Among the 744 patients in whom MF was excluded, most common primary provisional diagnoses other than MF were psoriatic dermatitis (15%,116/744) and parapsoriasis (14%, 110/744), similar to the concordant group in which spongiotic dermatitis (16%, 8/48) and parapsoriasis (14%, 7/48) were leading.
Conclusion: When the clinical and histopathological concordance was evaluated, it was seen that the most clinically confused cases with mf were spongiotic dermatitis and parapsoriasis.

E-PS-05-019
Discrete papular lichen myxoedematosus, a rare case report and review of literature
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Background & objectives: A 57-year-old Asian female presented with widespread pruritic dark itchy papules occurring over 4 years. Examination showed bilateral, symmetrical grouped waxy 1-2m papules over the dorsa of forearms, back, and shin. She had sickle cell anaemia and beta thalassemia trait.
Methods: A skin biopsy from a papule showed focal parakeratosis, circumscribed superficial dermal mucin deposition and Alcian blue stain confirmed the presence of mucin in the upper dermis. There was no fibroblastic proliferation or fibrosis. A diagnosis of discrete papular lichen myxoedematosus (DPLM) was made. She was treated with topical steroids and urea-based emollients and responded very well with complete resolution.
Results: Lichen Myxoedematosus (papular mucinosis) is a rare heterogeneous group of cutaneous mucinoses characterised by an abnormal dermal deposition of mucin, first described by Dubreuilh in 1906 Rongioletti and Rebora describe three subgroups of LM; generalized LM (scleromyxoedema), a localized form, and an atypical variant, which is further subclassified by Nofal et al. Our case represents a subtype of LM with good response to potent topical steroids and had no association with HIV or hepatitis C infection, which has been rarely reported DPLM has good prognosis, and spontaneous remission occurs on occasions. The clinical differential diagnosis includes lichen amyloidosis. Evolution to scleromyxedema has never previously been documented in this form.
Conclusion: We presented a rare case of discrete papular lichen myxoedematosus presenting as bilateral symmetrical waxy papules on the dorsa of forearms, back, and shin.
Microscopy showed circumscribed superficial dermal mucin deposition confirmed by Alcian blue, with no fibroblastic proliferation or fibrosis. It represents one of three subgroups of LM. Our case was associated with sickle cell anaemia and thalassemia trait. They respond well to urea-based emollients and ultra-potent topical steroids and usually have good prognosis with rarely reported spontaneous remission.

E-PS-05-020
Clear cell hidradenoma of the inguinal area: an unusual case
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Background & objectives: Hidradenomas are benign adnexal tumours, usually taking place in the head limbs. Inguinal region is uncommon as a site of occurrence. Through this case, we aim to present this unusual location and discuss histological characteristics of this tumour.
Methods: We, herein, present a case of an inguinal hidradenoma.
Results: A 46- years old male presented with a painless inguinal cystic large mass growing for 12 years. A surgical removal of the mass had been performed. Gross examination showed a heterogeneous cystic mass with irregular walls. Histopathological examination showed a largely cystic proliferation. It was composed of layers of cells separated by fine branching vessels and arranged in a lobular pattern. The cells were clear, with abundant cytoplasm and monomorphic nuclei without atypia or mitosis. Immunohistochemical study showed that the tumour cells were CK5/6 positive, ACE negative and did not express kidney cell marker PAX8. These findings were consistent with a clear cell hidradenoma.
Conclusion: Hidradenomas are rare adnexal tumours. Inguinal localization is extremely rare. Histologically, the tumour has a predominantly clear cells pattern that may be challenging for the diagnosis. In fact, differential diagnosis, especially, metastatic tumours, should be ruled out using immunohistochemistry and clinical data. Clinical assessment is required to detect possible recurrences.

E-PS-05-021
Atypical hidradenoma: a case report
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Background & objectives: Atypical hidradenoma is an uncommon neoplasm, displaying atypical features in contrast to its benign counterpart hidradenoma, including nuclear hyperchromatism and pleomorphism, giant cells, focal infiltrative growth, necrosis and mitotic activity.

Methods: A 54-year-old male with no significant medical history presented with a cutaneous mass on the medial aspect of the left lower limb. Excisional biopsy specimen revealed a 3,6x3,5x1,2 cm grossly friable papillomatous lesion.
Results: Histological sections showed a poorly circumscribed adnexal tumour with irregular borders. The morphological appearance was variable throughout the tumour. Epidermis showed papillomatosis and acanthosis, composed of neoplastic cells having large, clear eosinophilic cytoplasm and small nucleoli. The infiltrating component, extending from dermis into the subcutaneous adipose tissue, was not clearly demarcated from the epidermis. However, a distinct connection to the epidermal proliferation was also not observed. The infiltrative foci showed nests of relatively fusiform cells with eosinophilic cytoplasm and conspicuous nucleoli in a markedly hyalinized stroma. Mitotic activity was found to be prominent (2 mitoses per 10 high-power fields). No necrosis, no vascular or perineural invasion were observed.
Conclusion: In conclusion, the tumour was evaluated to be consistent with atypical hidradenoma. To the best of our knowledge, there exists a limited number of cases of this neoplasm in the literature. This case report would contribute to our knowledge about this particular entity. The risk of recurrence and malignant potential of atypical hidradenomas are reported to be increased; therefore, recognising atypical features in an otherwise benign hidradenoma is crucial.

E-PS-05-022
Secondary localized cutaneous amyloidosis in mycosis fungoides
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Background & objectives: Secondary localized cutaneous amyloidosis is a histopathological finding that occurs in various in-flammatory skin diseases and epithelial skin tumours. It is often not clinically apparent. Cases of secondary cutaneous amyloidosis associated with mycosis fungoides are extremely rare.
Methods: We presented a 25-year-old female, presented with flat patches and plaques on the trunk and extremities which appeared 10 years ago, and showed a persistent course. She had not received any medical treatment for her eruptions.
Results: In the punch biopsy taken from the left leg of the patient, lymphocytes with hyperchromatic nuclei, lined up at the base of the epidermis, showing focal epidermotropism, containing peripheral halos, were observed. These lymphocytes were positive for CD3, CD4, CD8. The population of CD8+ cells predominated over that of CD4+ cells. In addition, homogeneous amorphous eosinophilic depositions were observed in the papillary dermis in focal areas. We performed Congo red staining, and the deposits were negative for this staining, however positive staining was observed for HMWCK.
Conclusion: Literature findings support the theory that amyloid materials are produced by epidermal damage. CD8+ cells are cytotoxic in nature; therefore, in our case the infiltration of many CD8+ cells can be attributed to the formation of amyloid material from attacks on epidermal keratinocytes.

E-PS-05-024
Subcutaneous fat necrosis of the newborn – case report of a rare entity
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Background & objectives: Subcutaneous fat necrosis of the newborn (SCFN) is an uncommon panniculitis of full-term neonates. Its precise incidence is unknown and the pathogenesis remains unclear. SCFN often develops in neonates who have experienced hypoxia or other perinatal stress (obstetric trauma, hypothermia).
Methods: We report a full-term girl born by vacuum-assisted vaginal delivery due to shoulder dystocia, that presented with consequent right clavicle fracture. Born to a 27-year-old mother with active COVID-19 infection and group B streptococcal (GBS) colonization, which was adequately treated at delivery. On the 4th day of life presented with multiple, tender erythematous nodules on the shoulder, axilla and back.
Results: Initial laboratory tests for electrolytes were normal. The newborn was treated with prophylatic broad-spectrum antibiotics. On the 14th day of life an incisional biopsy of one of the lesions was performed. The histologic examination revealed normal epidermis and dermis, underlying lobular panniculitis with focal fat necrosis and moderate inflammatory infiltrate, composed by lymphocytes, histiocytes, multinucleated giant cells, eosinophils and neutrophils. The adipocytes showed needle-shaped clefts and crystals in a radial-type arrangement. On the 1st- month consultation there was slight improvement of the lesion but a mild hypercalcemia was detected (Ca2+ 5,8 mg/dL (N: 4,5 - 5,3)). The histopathological findings correlated with the clinical course confirmed the diagnosis of SFN.
Conclusion: SFN has a generally good outcome with spontaneous resolution of skin lesions. Nevertheless, the diagnosis of this entity is important, once it may evolve with relevant systemic alterations, especially acute renal injury secondary to hypercalcemia, reason why monitoring is required. The main differential diagnosis for SFN is sclerema neonatorum (SN), a rare frequently fatal condition, in previously ill pre-term infants. SN presents as a rapidly spreading, diffuse confluent nodules and plaques, and it typically affects the legs, buttocks and trunk.

E-PS-05-025
Onychocytic matricoma: a case report
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Background & objectives: Onychocytic matricoma (OCM) is a benign tumour of the nail matrix, first described by Perrin et al. in 2012. It represents an acanthoma of onychocytes that clinically manifests as a monodactilus longitudinal pachymelanonychia or xantholeucopachyonychia. A new case is described.
Methods: A 70-year-old man with no medical history presented a yellowish-white thickened longitudinal stripe on the first finger of the right hand, with a more nodular erythematous zone on the lunula. It was asymptomatic but grew progressively and did not respond to topical treatment with calcipotriol/betametasone. A longitudinal biopsy of the nail matrix, nail bed and nail plate were performed.
Results: Histologically, an epithelial acanthosis forming endophytic projections with blunt edges was observed, consisting of basaloid cells showing pseudosquamous eddies, which were formed by whorls of endokeratinization with an equal distribution of prekeratogenous zones and eosinophilic keratogenous zones. Scattered melanocytes could be seen, but pigmentation of the epithelial cells was not relevant. Changes in the dermis were minimal, with isolated lymphocytes. The main histological differential diagnosis is seborrheic keratosis, in which the squamous whorls are not cornified by the cells of the nail plate and, therefore, lack

the concentric layers. Our case is consistent with the acanthotic variant of OCM. At 1-year follow-up, there was no recurrence.
Conclusion: Only 17 cases of OCM have been reported in the English literature until 2020. Clinically it shows a localized thickening of the nail plate and a longitudinal band. Histologically, the characteristic feature is acanthosis of the nail matrix and nests of prekeratogenous and keratogenous cells with variation in their components. Four histological types can be identified: acanthotic, acanthotic and papillomatous, keratogenous with retarded maturation and germinotropic. OCM should be included in the differential diagnosis of clinically longitudinal nail bands.

E-PS-05-027
Merkel cell carcinomas associated to a primary haematological neoplasm: a unique case associated to follicular lymphoma
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Background & objectives: Merkel cell carcinoma (MCC) has been associated with primary haematological neoplasms due to immune dysfunction and MCPyV reactivation. We did a 30-year review of MCC in association with a lymphoproliferative disorder and described a patient with follicular lymphoma.
Methods: We identified biopsies of cases of MCC using SNOMED coding lists from 1992 to 2022. We found 58 patients with MCC; afterward we reviewed patient history to detect associated haematological neoplasms. We describe histopathological, immunohistochemical and molecular diagnosis of Follicular Lymphoma (FL) with MCC.
Results: Fifty-eight patients were diagnosed with MCC in the last 30 years of whom 3 (5.2%) had an haematological neoplasm (chronic lymphocytic leukaemia, mycosis fungoides and FL). A 57 years-old man was diagnosed with FL grade 1-2. He was treated with R-CHOP and kept with rituximab maintenance. After 8 months of complete remission, he developed a 5 cm cutaneous nodule on his left arm. Resection specimen showed cutaneous infiltration of MCC and a close lymph node with a FL grade 1-2 (positivity for CD20, BCL-2, CD10 and BCL-6) and MCC metastasis. The sentinel lymph node had the same features and was positive for BCL-2 translocation.
Conclusion: MCC can associate a haemato-oncological neoplasia being chronic lymphocytic leukaemia the most frequent. There is only one case described in the literature with a FL and a secondary MCC, which appeared 10 months after the remission with rituximab treatment. Unlike our case, the reported one did not have a FL relapse. There can be overlapping marker expression between MCC and haematological neoplasms like our case that was positive for BCL-2 in both of them, creating potential pitfalls.

E-PS-05-028
VEXAS: case report and characteristics of a new syndrome with neutrophilic dermatosis
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Background & objectives: VEXAS is acronym for Vacuoles, E1 enzyme, X-linked, Autoinflammatory and Somatic mutation. Its cause is a somatic mutation in UBA1, a gene that encodes for E1 ubiquitin activating protein. We present a new case of this very recently described entity.
Methods: For the case report we searched the patient's electronic medical records from 2012, when symptoms started, to 2021, when diagnosis was made, including subsequent follow-up to date. For the literature review we searched Pubmed.
Results: In 2012, a 58-year-old male had skin lesions that were diagnosed as lupus erythematosus. Along the course of the disease he presented arthralgias, serositis, anaemia, thrombocytopenia, and pancytopenia. This led to a bone marrow biopsy and aspirate, that showed a myelodysplastic syndrome with vacuoles.
In 2021 showed erythematous papules and plaques that, when biopsied, exhibited neutrophils that were located in dermis and adipous tissue. VEXAS syndrome was suspected, and genetic study confirmed the mutation in UBA1 gene. Detection of the causing mutation was revolutionary because the method used started with the analysis of numerous mapped genomic sequences, in which the common findings in UBA1 led with similar clinical findings.
Conclusion: VEXAS syndrome was described at the end of 2020. It's to be suspected in older males with a combination of inflammatory signs like refractory fever and polychondritis, as well as hematologic alterations. Vacuoles in myeloid and erythroid precursor cells of bone marrow biopsy are characteristic. In the skin, causes several lesions that, in the biopsy, show a neutrophilic dermatosis. Since its description, VEXAS syndrome has explained many cases that had failed to be classified in any of the known diseases.

E-PS-05-029
Nivolumab therapy in multiple primary melanomas – a case report
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Background & objectives: Melanoma is a cutaneous malignancy that may benefit from immune therapy with checkpoint inhibitors, even in advanced stages. We report a case with two primary melanomas treated with nivolumab, highlighting the histopathological findings and the clinical evolution.
Methods: A 70-year-old man presented to the dermatologist for alopecia, when a large infiltrative tumour located on the scalp and a second pigmented lesion on the cheek were discovered. Computed tomography examination revealed that the scalp tumour was infiltrating the occipital bone, extending close to the superior sagittal sinus. As the neoplasm was unresectable, punch biopsies from both lesions were performed.
Results: The lesion on the cheek was diagnosed as melanoma in situ. Scalp biopsy showed a desmoplastic melanoma composed of a dermal fascicular proliferation of spindle cells, positive for Sox-10 and S100. BRAF molecular studies were negative. As desmoplastic melanoma is reported to respond well to immunotherapy, PD-L1 immunostaining was done, showing diffuse positivity in tumour cells. The patient was enrolled in a clinical study receiving NKTR and nivolumab (10 cycles). Given his renal disease, he then remained only on nivolumab. At follow-up, a spectacular decrease in measurements was noted in both lesions. The tolerability profile was acceptable and lesions have been stable for the past 6 months.
Conclusion: This study presents the impressive clinical evolution of a locally aggressive inoperable desmoplastic melanoma with significant shrinkage in size, associated with a tolerable toxicity profile. As the patient has a stable response to nivolumab with no imaging progression, anti-PD-1 therapy has promising results in increasing the overall survival and reducing the risk of metastases in advanced-stage melanoma.

E-PS-05-030

A case of pseudoxanthoma elasticum with severe, early-onset ocular manifestations

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Background & objectives: Pseudoxanthoma elasticum (PXE), is a rare genetic metabolic disease caused by ABCC6 gene mutations. In PXE, dystrophic calcification frequently leads to cutaneous, ocular, cardiovascular, neurological, and other manifestations. Herein we present a case with significant premature ocular manifestations.
Methods: A 22-year-old female was referred to the Dermatology Department complaining for a "plucked chicken" appearance of the skin on her neck present for two years. Physical examination revealed multiple, small, yellowish papules on the lateral aspects of the neck. Thickened, lax and wrinkled skin was observed at the flexural surfaces of her body. A skin biopsy was performed.
Results: Microscopically in the middle dermis, degenerative changes affecting the elastic fibres were recognized. The fibres were basophilic and irregular, appearing as widely dispersed granular material. Their presence was best evaluated using a Von Kossa technique. The diagnosis was compatible with pseudoxanthoma elasticum. The patient was immediately referred to the Opthalmology Department where a dilated funduscopic examination was performed and revealed the presence of bilateral angioid streaks accompanied by peau d'orange changes in the retina consisting of fine yellow drusenlike pigment irregularities.
Conclusion: Although the cutaneous manifestations usually precede the ocular findings by many years, in our patient, they appeared concurrently. Moreover, macular involvement is rarely found before the age of 40 years. Despite the fact that there is no established therapy available for PXE, early diagnosis and regular ophthalmologic counseling are prerequisites in order to prevent and control the possible adverse events caused by the disease.

E-PS-05-031

Histoprognostic factors of cutaneous melanoma in relation to metastasis at the sentinel lymph node

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Background & objectives: Identification of histoprognostic factors of melanoma is closely related to the metastatic progression and provides an important argument for the management of patients. Our aim was to identify histoprognostic factors that can predict the sentinel lymph node metastasis in melanoma.
Methods: Retrospective study of 38 melanoma with sentinel lymph node biopsy collected at Salah Azaiez Institute over a period of 15 years (January 2006-December 2021). We divided the cases into 2 groups according to sentinel lymph node status (positive or negative). For each group (N+ and N- groups), we studied the following parameters: Breslow'sthickness, ulceration and mitotic rate.
Results: Metastatic sentinel lymph node was found in 10 cases with median age of 64 years and without sex predominance. The median age in the N-group was 63 years with female predominance. For N+ group, Breslow depth varied from 7 to 11 mm with an average of 8 mm versus an average of 5 mm in the N- group (1-22). The mitotic rate varied from 7 to 12 mitoses/10HF with an average of 8in N+ group and from 0 to 9 mitoses/10HF with an average of 6 in the other group.The ulceration was present in all N+ cases and in 80% of cases in the other group.
Conclusion: The N+ group seems to have the worst histoprognostic factors. This study should be carried out on larger samples to be able to confirm our results

E-PS-05-032

Cutaneous Kikuchi-Fujimoto disease (KFD) post COVID-19 vaccination: case report

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Background & objectives: Kikuchi-Fujimoto disease is an usually cervical histiocytic necrotizing lymphadenitis, self-limited and of unknown aetiology. Recently, several patients with KFD have been described post COVID-19 vaccination. However, in this context, exclusively skin involvement has not been reported.
Methods: A 45-year-old man with a history of HIV infection, stage A2, on antiretroviral treatment and HHV-8 associated multicentric Castleman disease, presented multiple infiltrated erythematous nodular lesions on the forehead, cheek, arms and trunk, without lymphadenitis. Skin lesions appeared 2 days after receiving mRNA-based COVID-19 vaccine (Moderna) and due to clinical suspicion of lymphoma, a skin biopsy was performed.
Results: Histopathological study showed epidermis with basal hydropic degeneration and dyskeratosis. The dermis presented a perivascular and periadnexal lymphohistiocytic infiltrate with karyorrhectic debris without neutrophils next to plasma cells. Immunohistochemically, the histiocytes expressed CD68, CD163, and myeloperoxidase. Most lymphocytes expressed CD3 and CD8, and plasma cells expressed CD138, Kappa and Lambda. Immunostaining for ALK, CD10, BCL6, BCL2, S100, CD1a, CD23, CD21, CD123, Treponema, and HHV-8 was negative. Real-time PCR revealed 30 copies of EBV/100,000 cells and no HHV-6. A diagnosis of cutaneous Kikuchi-Fujimoto disease post COVID-19 vaccination was reached. Currently, the patient is stable from his immunodeficiency and without skin lesions.
Conclusion: Kikuchi-Fujimoto disease in post-COVID-19 immunization patients is a self-limited process and is clinically characterized by cervical lymphadenopathy and fever, but patients with HIV infection may present exclusively skin involvement probably due to their immunodeficiency. The temporal association between the administration of the COVID-19 vaccine and the appearance of skin lesions is a clue to suspicion. The definitive diagnosis is histopathological when demonstrating a dermal lymphohistiocytic infiltrate without neutrophilic karyorrhectic debris and co-expression of CD68 and myeloperoxidase in the histiocytes.

E-PS-05-033

Erythema elevatum diutinum in a patient with Crohn's disease: a very rare variant of chronic cutaneous vasculitis

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Background & objectives: Erythema elevatum diutinum (EED) is a very rare variant of chronic cutaneous vasculitis that evolves into a concentric fibrosis. EED has been associated with hematologic disorders, autoimmune processes and infections. Very few cases have been described with inflammatory bowel disease.
Methods: A 38-year-old man with history of factor VII deficiency and Crohn's disease (CD) of 13 years of evolution, who consulted

for a 2.5 cm indurated and painful violaceous nodule in the plantar region (head of the 5th metatarsal, left foot) of 6 months of evolution. Ultrasound findings were suspicious for mesenchymal neoplasia and a biopsy of the lesion was performed.
Results: Histological study showed abundant collagen bundles with spindle cells arranged in a storiform pattern around the blood vessels in the superficial and deep dermis. They were accompanied by mixed inflammatory infiltrate with lymphocytes and neutrophils as well as isolated images of leukocytoclastic vasculitis. The following immunohistochemical (IHC) techniques were performed: EMA, Desmin, AML, claudin, CD34 and s100 were negative. The ki-67 proliferation index was less than 10%. The clinicopathologic and IHC findings together with the presence of leukocytoclastic vasculitis helped in the diagnosis of EED.
Conclusion: The histopathologic features of EED vary according to the age of the lesions, with development of variable fibrosis and fasciculated spindle cell proliferation in late stages. The differential diagnosis is made with an inflammatory pseudotumour, dermatofibrosarcoma protuberans, sclerotic neurofibroma, sclerosing perineuroma, tendon sheath fibroma, and hyalinized leiomyoma. The aetiology of EED is unknown; it has been proposed to be an immunocomplex-mediated disease, with viral or bacterial antigens being involved, which would explain the association between EED and CD.

E-PS-05-034
The clinical and pathological features of nevus associated melanomas
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Background & objectives: The purpose of this study was to identify the cases of nevus associated melanomas (NAMs), evaluating the clinical and pathological features.
Methods: From the database of our pathology department, we selected the cases diagnosed as primary cutaneous melanomas between 2016 and 2021, extracting the nevus associated melanoma cases.
Results: We identified 213 cases of cutaneous melanomas, the NAMs representing 10% (21 cases) - 66.6% females, 33.3% males. The median age at diagnosis was 50 years (females) and 56 years (males). The majority of the NAMs presented a dysplastic nevus (52%). Superficial spreading melanomas, with a vertical growth phase predominated (57%), followed by melanoma in situ (14%). In the invasive melanoma group (18 cases), we noticed more often a Breslow index $\leq$ 1mm (45%), a II&III Clark level (50%), a pT1 stage (50%), a mitotic rate of 1 mitosis/mm² (55%) and brisk inflammatory infiltrate (50%).
Conclusion: The median age of the females diagnosed with NAMs was lower compared with the median age of the males. The majority of the NAMs were represented by superficial spreading melanomas with a vertical growth phase, in the presence of a dysplastic nevus. In these cases predominated a low Clark level and Breslow index, a decreased pathological stage and mitotic rate, being associated more often with a brisk inflammatory infiltrate.

E-PS-05-035
Metastatic male breast carcinoma in the skin. Report of a rare case
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Background & objectives: Breast cancer is one of the rarest malignancy in men. These tumours have a high tendency to hematogenous metastasis, often affecting the bones, lungs and liver. Although in some cases, lesions of atypical organs, such as skin, are also possible.
Methods: We present a case of metastatic invasive ductal breast carcinoma to the skin in a young male. In 2015 he underwent complex treatment invasive ductal carcinoma of the left breast. In 2021, he was again admitted with a painless mass of the skin of the scalp measuring 2x2.5x2 cm. A biopsy was performed followed by a histological and IHC study.
Results: Histological examination revealed the tumour composed of cells with eosinophilic cytoplasm and oval pleomorphic nuclei, with indistinct cell and nuclei boundaries. Tumour cells form cord-like, glandular and cribriform structures that infiltrate the dermis and subcutaneous fatty tissue. The tumour wasn't associated with the epidermis. The IHC study showed that tumour cells expressed CK7, GCDFP15, GATA3, ER, PR, and HER-2. Also was the lack of expression CK20 and all melanocytic markers in the tumour. The immunophenotype of the tumour corresponds to a previous carcinoma of the breast.
The diagnosis of metastatic invasive breast carcinoma NST type was made.
Conclusion: In this article we have presented a rare case of metastatic male invasive breast carcinoma of NST type in the skin of the scalp. This case expands our understanding of the nature of metastatic skin cancers and once again proves that when you see stripes, it can still be tigers.

E-PS-05-036
A case of acantholytic squamous cell carcinoma of the skin
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Background & objectives: Acantholytic squamous cell carcinoma (ASCC) is an uncommon high-risk histopathologic variant of cutaneous squamous cell carcinoma (SCC). It is generally more aggressive and have a worse prognosis than the other SCC subtypes. The exact diagnosis is challenging.
Methods: A 63-year-old man, with no history, presented with an erythematous nodule in the temporal region since 4-months. On examination, a non-inflamed slightly pruritic hyperkeratotic papule was located in the temporal region. Clinically, prurigo nodularis, seborrheic keratosis, and SCC were suspected. A biopsy was performed for making the diagnosis.
Results: On microscopic examination, the tumour was composed of epidermal-derived cystic proliferation extending into the superficial dermis with acantholysis foci in tumour nests, creating the appearance of glandular differentiation. This aspect is due to the loss of intercellular cohesion between malignant squamous cells. The pseudolumina contained acantholytic and atypical dyskeratotic cells, and cellular debris. There was no evidence of true glandular differentiation or mucin production. The overlying epidermis showed hyperkeratosis and parakeratosis. On the immunohistochemical studies, the acantholytic tumour cells were positive for CK with a cytoplasmic staining pattern and for p40 supporting a squamous epithelial origin. Final diagnosis of ASCC was retained.
Conclusion: ASCC is characterised histologically by a combination of typical SCC and pseudoglandular structures,

dyskeratotic cells and prominent acantholysis. It is usually found on the sun exposed areas such as the face and the neck in the elderly with a male predominance. It presents as a nodule with various colors, accompanied by scaling, crusting, and ulceration like the other variants. Histological examination is necessary for making the accurate diagnosis. ASCC is a more-aggressive tumour with higher potential for recurrence or metastasis.

E-PS-05-037

A rare and sometimes fatal syndrome: Stevens-Johnson

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Background & objectives: In 1922, Stevens and Johnson described a strikingly distinct disease in 2 children as an "extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis."
Methods: We herein present the case of a 49-year-old man with a history of stage IV follicular lymphoma that was being treated with antibiotics for an infected skin ulcer. On the 14th day of his hospital stay he developed a generalized pruritic and painful skin rash with oral mucosal involvement. The rash progressed with the formation of vesicles and skin erosions.
Results: The patient was submitted to a skin biopsy to try to distinguish between the clinical differential diagnosis of erythema multiforme and Stevens-Johnson syndrome. We received a skin punch biopsy measuring 6 mm diameter and 4 mm thick with no apparent lesions on the epidermal surface. Histologic examination showed numerous apoptotic bodies at different levels of the epidermis, in some areas with confluent necrosis of the epidermis and focal lymphocyte exocytosis. Apoptotic bodies were also identified on the follicular epithelium. The dermis showed only a mild superficial perivascular lymphohistiocytic inflammation. All these changes were compatible with the clinical diagnosis of Stevens-Johnson syndrome and the presumable drug responsible was piperacillin-tazobactam.
Conclusion: Stevens-Johnson syndrome is a rare, severe, immune-mediated cutaneous reaction usually secondary to an idiosyncratic reaction to medication, although infection with Mycoplasma pneumoniae is also a well-documented cause. The histologic features are variable epidermal apoptosis associated with basal cell hydropic degeneration or subepidermal vesiculation. Lymphocytic exocytosis may be present and a mild perivascular infiltrate of lymphocytes, macrophages, and melanophages is present in the superficial dermis. The mortality is approximately 5% and, sadly, our patient died 4 days after the skin biopsy.

E-PS-05-038

Pleomorphic basal cell carcinoma of the eyelid: an uncommon case report

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Background & objectives: Pleomorphic basal cell carcinoma (BCC) is a rare variant of BCC characterized by the presence of scattered large, pleomorphic cells. It is commonly located on the head and neck. The prevalence is unknown, fewer than 60 cases are reported in the literature.
Methods: A 82-year-old female without any particular medical history, presented with a left lower external eyelid nodule. Ophthalmic examination revealed a firm pigmented lesion at the eyelid, measuring 1 cm with surface irregularity and ulceration, and bleeding on contact. BCC was suspected, and a full-thickness eyelid resection was performed. The specimen was oriented and referred to pathological diagnosis.
Results: On gross examination, the specimen is centered by pigmented lesion with ulcerating surface measuring 1cm x 0,9cm. Surgical margins were distant from the lesion. On histological examination, the lesion was composed of nests of basaloid cells with peripheral palisading and stromal retraction. Tumour cells were predominantly small with scant cytoplasm and monotonous nuclei. Scattered giant cells with large, irregular, hyperchromatic nuclei and prominent nucleoli were observed. Mitoses were numerous with frequent atypical ones. The overall histologic features were highly suggestive of pleomorphic BCC. Surgical margins were free.
Conclusion: BCC has several histologic subtypes that often have variable outcomes and prognoses. Pleomorphic BCC is an uncommon pathologic variant of unknown pathogenesis. Eyelid localization is extremely rare, with only one case reported in the literature. The cardinal histological sign is the presence of scattered enlarged mononuclear and/or multinucleated tumour cells. However, the presence of atypical giant cells doesn't worsen the prognosis which is similar to the classical variant. Histological differential diagnosis of BCC is sometimes challenging, especially with adnexal tumours.

E-PS-06 | E-Posters Digestive Diseases Pathology - GI

E-PS-06-001

Superficial "early" colon cancer showing extraordinary distant metastases, simulating a gynaecologic origin – potential diagnostic pitfall

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Background & objectives: Herein, we describe an exceptionally rare case with superficial bowel cancer showing extensive peritoneal, including omental, dissemination accompanied by ovarian metastases. The patient, a 70-year-old postmenopausal Japanese woman, presented with abdominal distension.
Methods: Computed tomography revealed huge bilateral ovarian tumours with multiple peritoneal metastases, suggesting advanced ovarian cancers (cT3cNXM0). The salpingo-oophorectomy specimens contained grey-whitish to reddish brown, solid tumours with cystic formation, measuring 15x9x7 cm in the right ovary and 18x10.5x9 cm in the left ovary, respectively. Furthermore, numerous omental nodules, up to 1.2 cm in maximum diameter, had similar cut surface appearances.
Results: These invasive tumours were histopathologically composed of tubular, cribriform and/or papillary growths of columnar carcinoma cells with enlarged, hyperchromatic nuclei with distinct nucleoli. Coagulation necroses were pronounced. Immunohistochemically, the carcinoma cells were diffusely positive for cytokeratin (CK) 20, CDX2 and SATB2, and negative for CK7, PAX8 and ER. These pathological features suggested metastatic colon adenocarcinoma. We thus performed lower gastrointestinal endoscopy and detected a superficial, elevated lesion with a depressed area, measuring 15 mm, in the sigmoid colon, suggesting submucosal invasion. This lesion was pathologically confirmed to be tubular adenocarcinoma. Also, macroscopic peritoneal disseminated

lesions on the surface of the liver, subdiaphragmatic region and rectal serosa (numerous) were not removed.
Conclusion: It is noteworthy that so-called 'early' colon cancer can present with unusual distant metastases, mimicking primary ovarian cancer. We know that there is some morphological overlap between endometrioid carcinoma and conventional colon cancer. Therefore, it is worth considering a colorectal origin if the tumour shows endometrium-like, but monotonous, carcinoma cell proliferation and is free of squamous differentiation, as well as having notable necrotic findings on histological examinations of gynecological organs. An accurate diagnosis, validated by immunohistochemistry, will allow appropriate treatment.
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E-PS-06-002
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) arising from long-segment Barrett's oesophagus showing exceptionally aggressive clinical behaviour
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Background & objectives: Herein, we describe the first case with double primary mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) and conventional adenocarcinoma, arising in Barrett's oesophagus. A 68-year-old woman had been diagnosed with 0-IIa type adenocarcinoma in the background of long-segment Barrett's oesophagus, 3 years earlier.
Methods: She underwent ESD and the pathological diagnosis was tubular adenocarcinoma, well differentiated, with slight submucosal invasion. There was no lymphovascular invasion and the margins were intact. Although annual follow-up had subsequently been performed, the patient was brought to the emergency room. A CT scan of the head showed multiple cerebral metastases and PET-CT revealed numerous osseous and nodal involvements.
Results: We performed upper gastrointestinal endoscopy and detected metachronous type 3 esophageal cancer. Multiple biopsy specimens histopathologically contained invasive neoplasm composed of neuroendocrine carcinoma (NEC) and adenocarcinoma, moderately to poorly differentiated. The NEC element showed diffuse proliferation of primitive cancer cells possessing fine-granular cytoplasm and nuclei with prominent nucleoli, whereas the adenocarcinoma component had tubules or nested growth of basophilic cells. Immunohistochemically, the NEC cells were diffusely positive for synaptophysin, with focal expressions of INSM1, chromogranin A and NCAM, whereas adenocarcinoma cells were mostly negative for these NE markers. The Ki67 labelling index was 90% at the hot spots in both types.
Conclusion: The patient died 3.5 months after the biopsy-based histological diagnosis. In the esophageal oncology field, patients with MiNEN are reportedly more likely to be diagnosed at an earlier stage and have significantly longer survival than those with pure NEC. Unfortunately, our present Barrett's MiNEN showed extremely aggressive biological behaviour.
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E-PS-06-003
Prevalence and impact of false negative digestive biopsies
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Background & objectives: Gastrointestinal (GI)endoscopy with biopsy is usually necessary to confirm the malignancy. However, biopsy results may be negative in some cases leading to a delay for diagnosis. The purpose of this study was to assess the prevalence of false negative biopsies among patients with GI-tumours.
Methods: We have retrospectively collected 46cases of digestive biopsies performed for GI endoscopic looking-tumour and addressed to our pathology department (2013-2022). Clinical and endoscopic data were retrieved from the patient's medical record. Pathological findings have been collected from the pathology report. We have especially focused on: number of biopsy fragments, number of serial cuts performed, ulceration, inflammatory changes, acellular mucin, burden artifacts and first-final histological diagnosis.
Results: Mean age of patients was 61,1years-old with a sex ratio of 4,75. In 5 cases the biopsy was negative for malignancy. The mean number of biopsy fragments was 8(5-10). Systemic serial cuts were performed in 4cases (1-4). Ulceration and inflammatory changes were found 2cases, acellular mucin in 1case.In 3 cases, the histological diagnosis was villous tubular adenoma with either low- or high-grade dysplasia. In one case, the tumour was firstly diagnosed as MALT lymphoma and follicular gastritis in another case. In all cases, supplementary biopsies have been performed. The final diagnosis was mucinous adenocarcinoma (2cases), well differentiated adenocarcinoma (1case), signet-ring cell carcinoma (1case), collision tumour associating MALT-signet ring cell carcinoma (1case).
Conclusion: The prevalence of false negative biopsies remains low (10,8%). The main risk-factors associated with false negative biopsies is the mucinous and signet-ring cells histological subtype. The number of biopsy fragments and serial cuts doesn't seem to impact the histological diagnosis. The false negative biopsies in our study didn't affect the patient's outcome since second and third biopsies have been performed within few days.

E-PS-06-005
Multifocal small bowel adenocarcinoma associated with Crohn's disease – case report
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Background & objectives: Small bowel carcinomas are rare, but some predisposing factors exist including Crohn's disease. Inflammatory bowel disease (IBD) is also a risk factor for occurrence of synchronous carcinomas though affecting mostly the large bowel.
Methods: We report a case of a 37-year-old male patient with Crohn's disease and multifocal small bowel adenocarcinoma of distal jejunum. The patient had a history of Crohn's disease lasting for 15 years with previous ileo-cecal resection and progression despite the biological treatment. Currently the patient was admitted with acute intestinal obstruction due to complete jejunal stenosis.
Results: The resection specimen was composed of stenotic and dilated part of small bowel measuring 40 centimetres in total. Advanced invasive high-grade adenocarcinoma infiltrating through serosa was detected in the stenotic area including metastatic

infiltration of four lymph nodes. Surrounding mucosa of the stenotic and farther dilated bowel showed multiple extensive areas of IBD-associated high-grade dysplasia separated by foci of non-dysplastic epithelium. In the background of the dysplastic changes there were found seven additional synchronous adenocarcinomas with variable depth of invasion. Predominance of not otherwise specified morphology was seen with minority of poorly cohesive and signet-ring cell morphology.
Conclusion: Immunohistochemistry revealed aberrant p53 expression and loss of e-cadherin staining in neoplastic cells irrespective of the morphological type. Molecular analysis revealed pathogenic somatic mutations in TP53 and CDKN2A genes.
Hereby presented case with advanced adenocarcinoma of small bowel underscores the difficulty of surveillance and preventive strategy of small bowel IBD associated neoplasia. Presence of extensive preneoplastic lesion and multifocality of the neoplasia also points out the possible effect of field cancerization of small bowel mucosa in the setting of IBD.
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E-PS-06-006
Extra-appendiceal goblet cell adenocarcinoma: a new entity or an old companion in a new location?
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Background & objectives: According to the current WHO classification, goblet cell adenocarcinoma is a rare appendiceal amphicrine tumour containing goblet-like mucinous cells with variable numbers of endocrine and Paneth-like cells. We present a case of a goblet cell adenocarcinoma of the ascending colon.
Methods: A 66-year-old man was admitted to an external institution for colon tumour examination. CT scan confirmed an ascending colon neoplasm, but enlarged mesenteric and retroperitoneal lymph nodes were also present raising suspicion of lymphoma. A biopsy ruled out lymphoma and diagnosis of adenocarcinoma was established. The patient was transferred to our hospital for surgery and right sided hemicolectomy was performed.
Results: Gross examination revealed an ulcerated tumour measuring 5 cm with infiltration of muscular wall as well as extensive infiltration of the surrounding adipose tissue and serosal perforation. Histologic examination showed a tumour composed of goblet-like cells with small, compressed nuclei with intracytoplasmic mucin and cuboidal epithelial cells with mitotic activity and focal hyperchromasia. Tumour cells were arranged in an organoid pattern. Appendix was free of tumour. Alcian PAS stain highlighted the intracytoplasmic mucin. Immunohistochemical staining for cytokeratin AE1/AE3 and synaptophysin showed a diffuse positive reaction. These findings were consistent with the diagnosis of goblet cell adenocarcinoma.
Conclusion: Several previously published cases show that goblet cell adenocarcinoma can also occur in other parts of the gastrointestinal tract. In colon, it can easily be mistaken for signet ring cell carcinoma. Recent studies have shown that extra-appendiceal goblet cell adenocarcinoma is a distinct morphological, immunohistochemical, immunological and transcriptomic entity. Further studies should compare its pathological, molecular and clinical characteristics with appendiceal goblet cell adenocarcinoma and possibly reclassify it as a new type of amphicrine tumour not limited to the appendix.

E-PS-06-008
Clinicopathological features of a rare subtype of gastric neoplasm
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Background & objectives: Gastric carcinoma (GC), the third most common cause of cancer-related mortality, includes various subtypes, one of them being GC with lymphoid stroma, comprising between 1-7% of cases. The aim of this study is to investigate the clinicopathological features of GCLS.
Methods: We report the case of an 82year-old male investigated for an episode of massive upper gastrointestinal bleeding and important weight loss in another medical centre. The endoscopic examination revealed a gastric tumour localized on the lesser curvature. After being transferred in our hospital and further investigations, the patient underwent total gastrectomy with omentectomy, esophago-jejunal anastomosis and regional lymphadenectomy.
Results: The macroscopic examination of the specimen revealed an ulcero-infiltrative lesion measuring 4.5x4x2.3 cm, infiltrating the whole gastric wall, without perforating the serosal layer and plenty whitish and firm consistency lymphatic nodes located in the fatty tissue nearby the tumour.
On microscopic exam, we found a poorly-differentiated malignant epithelial proliferation with few glandular structures, small trabeculae and nests of epithelial cells embedded in a dense lymphoid infiltrate reminiscent of lymphoid tissue. Lymphovascular invasion or peri-neural growth it is not detected. We examined 24 lymphatic nodes, half of which were found with metastatic carcinoma.
Conclusion: GCLS is a rare subtype of gastric cancer associated with EBV infection and microsatellite instability. Unlike the common subtype of GC, GCLS rather affects the proximal stomach or the gastric stump. The characteristic microscopic finding of GCLS is peritumoral and tumour-infiltrating lymphocytes, but medullary carcinoma is also described in colorectal or breast localization. Patients with GCLS have better survival rates than those non-GCLS, so it's important to recognize this subtype of GC for predicting the patient's prognosis and particular treatments.

E-PS-06-009
Incidence of dysplasia in Barrett's oesophagus
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Background & objectives: The definition of Barrett's oesophagus is debatable. While most cases of esophageal adenocarcinoma develop at background of intestinal metaplasia (IM), molecular findings suggest non-IM as ancestor clone of cancer. Our aim was to compare dysplasia incidence in IM and non-IM.
Methods: Biopsy was performed in 142 patients with segment of metaplasia in distal oesophagus ranged from C0M1 to C15M15. Biopsy specimens were fixed in 10% neutral buffered formalin and stained with haematoxylin-eosin and combined PASD/Alcian Blue. Immunohistochemical evaluation with Muc2 was performed in dubious cases to identify true goblet cells. Dysplasia was confirmed by 2 pathologists experienced in gastrointestinal pathology.
Results: Difficulties in establishing metaplasia type because of so called pseudo-goblet cells occurred in 25 of 142 patients (17.6%), among them 23 cases (92%) appeared to be non-IM after immunostaining with Muc2. IM was detected in 86 patients,

including 23 (26.74%) cases with dysplasia: 21 patients with low-grade and 2 patients with high-grade dysplasia. Non-IM was observed in 56 patients: 30 cases of cardiac type metaplasia and 26 cases of oxynto-cardiac metaplasia. Dysplasia was identified in 2 patients (3.57%), both high-grade dysplasia on background of cardiac type metaplasia. Dysplasia was never found on background of oxynto-cardiac metaplasia.
Conclusion: In our single centre experience, incidence of dysplasia was much higher in patients with IM compared with non-IM of distal oesophagus (Fisher exact test, $p = 0.0024$), which is consistent with generally accepted concept of carcinogenesis in distal oesophagus. Nonetheless, rate of high-grade dysplasia didn't differ between groups (Fisher exact test, $p = 0.6496$). Almost 1/5 of cases with columnar-lined oesophagus was challenging for metaplasia type identification and required immunohistochemistry with Muc2. Majority of these cases appeared to be non-IM.

E-PS-06-010
Immunohistochemical evaluation of diffuse gastric cancer morphological variants
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Background & objectives: Transcriptome analysis revealed distinct subtypes of diffuse-type gastric cancer (DGC): DGT arising de novo and DGT originating from intestinal-type gastric cancer (IGC) cells. The aim of our study was to develop morphological and immunohistochemical criteria for subtyping of DGT.
Methods: Fifty patients with DGC were included in the study. DGT was established based on morphological exanimation of specimens stained with haematoxylin and eosin and combined PAS/AB for signet-ring cells identification. Immunohistochemical study was performed with E-cadherin, CK7, CK20, CDX2, Hepatoc, Muc1, Muc2, Muc5AC, HER2, PD-L1. Monoclonal antibodies to MSH2, MLH-1, PMS-2 and MSH6 we used for microsatellite instability (MSI) detection.
Results: Four patients were HER2 positive, two patients were indefinite for HER2. PD-L1 staining results were the following: Combined Positive Score (CPS) was >1, but <10 in 4 cases, CPS >10, but <20 in 2 cases and CPS = 100 in one patient. MSI-High was detected in 2 cases and MSI-Low in one patient, both patients harboured MSH6 mutation. All patients with MSI were of higher age (> 75 years). There were no significant differences in immunophenotype using extensive antibody panel, but we noticed some features in mucin profile special for MSI. Further investigations are needed to confirm our findings.
Conclusion: No significant immunophenotype features special for different morphological subtypes of DGC were identified, but we suggest that further studies of mucin profile in patients with MSI are of value. We suppose that older age and MSI are indicative for DGT originating from intestinal-type gastric cancer. Whether mixed type gastric cancer may represent a transitional form between IGC and DGT remains a question.

E-PS-06-011
Oesophageal squamous papillomatosis: a case report
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Background & objectives: Oesophageal squamous papilloma (OSP) is a benign uncommon papillary epithelial polyp with uncertain aetiology. It's usually an asymptomatic solitary lesion of the lower oesophagus, commonly occurring in male adult. We report a rare case of Oesophageal papillomatosis (OP).
Methods: 57-year-old women, with no medical history, presented with epigastric pain and two episodes of hematemesis. She underwent an initial oesophagogastroduodenoscopy (OGD) with biopsy. Subsequently, endoscopic follow-up with repeated biopsies was performed.
Results: The OGD showed multiple circumferential pseudopolypoid formations, spread over 6 cm of the lower oesophagus. Elsewhere, the oesophageal mucosa was normal. Histological examination of biopsy specimens, showed a papillary exophytic proliferation of squamous epithelium, lining fibrovascular cores of lamina propria. The squamous epithelium presents focal parakeratosis but does not exhibit dysplasia or evidence of viral infection. There was no invasion of the lamina propria. The final diagnosis was OP associated with hiatal hernia and chronic gastritis. Endoscopic monitoring did not reveal any progression of lesions with similar pathological features. The decision of medical staff was to continue the endoscopic surveillance.
Conclusion: Fewer than 20 cases of OP were reported in the English literature. Symptoms, like bleeding or dysphagia, may be seen in papillomatosis. Chronic irritation and HPV infection are the most reported aetiologies in literature. The role of HPV infection is not well proved. Generally, the OSP does not recur after resection. However, OP has an unknown potential for malignant transformation, with currently no guidelines for endoscopic surveillance. Therefore, more cases need to be published.

E-PS-06-012
Granular cell tumour of the appendix – an extremely rare case report
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Background & objectives: Granular cell tumour (GCT) is a benign lesion of neural/schwannian origin most frequently found in skin, subcutaneous tissue and oral cavity mostly in black middle-age women. They can involve any organ, including the gastrointestinal tract. The appendicular involvement is extremely rare.
Methods: We report a case of a 30-year-old pregnant female, recurring to the emergency department with two days persistent pelvic pain. The blood test indicated leukocytosis, neutrophilia and elevated concentration of C-reactive protein. Abdominal ultrasonography revealed an outer appendiceal diameter of 8mm, with markedly thickened and stratified wall and increased density of the surrounding fat tissue consistent with a phlegmon.
Results: A laparoscopic appendectomy was performed. Gross examination showed appendiceal wall markedly thickened and the lumen filled with fecal material.
Histological analysis revealed a florid granulomatous chronic inflammation in the tip of the appendix. Adjacent there was a well-circumscribed and uncapsulated nodule with 0.5cm in diameter confined to submucosa. It was formed by nests of epithelioid cells with abundant granular eosinophilic cytoplasm and central small round nuclei. It was devoid of cytological atypia and necrosis. Immunohistochemistry revealed S-100 diffuse strong positivity, suggestive of Schwann cell origin. Tumour also displayed SOX-10 nuclear expression and CD68 membranous expression in the tumour and in granulomas found in the wall of the appendix.
Conclusion: 5–11% of GCT occurs in gastrointestinal tract, with only fourteen cases reported in the appendix. Literature suggests that chronic inflammation surrounding the GCT in the appendix may be a predisposing condition, favoring its emerging. These

findings support the hypothesis that GCT is associated with reactive changes of the neural/schwannian cells, rather than a true neoplasm. This case documents a granulomatous appendicitis (which is a rare entity, <2% of appendectomies) and a GCT as a cause of appendicitis.

E-PS-06-013

Clinicopathological and histomorphological association in K-ras mutated colorectal cancer

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Background & objectives: KRAS mutation is frequently identified in advanced colorectal carcinoma (CRC)and its prognostic significance with histological features have remained to be clarified. The aim of this study is to evaluate the clinicopathological and histomorphological characteristics in K-ras mutated patients with CRC.
Methods: In this retrospective study, 420 CRC patients who underwent surgical treatment in our hospital (January 2018- December 20200 have been included. K-ras mutation testing was performed in 265 patients, detected by Cobas K-ras mutation kit to identify frequent mutations (codons 12,13,61). Clinicopathological and histomorphological data were compared with the K-ras status and correlations were evaluating using Pearson's Chi-square test.
Results: K-ras mutations were found in 148 patients (39,2%), frequently identified in older males, and in advanced stages of the disease. There was association of the K-ras mutation with the degree of tumour differentiation (G3), tumour necrosis and inflammatory response of the tumour tissue ($p<0.05$). No association was found between the mutational status and the tumour extention, localization, lymphonodal status and tumour type.
Conclusion: According to the certain limitations of this retrospective study using a single detection kit that include common codon changes in K-ras gene it is obvious that further studies on the histological results and their prognostic value of rare KRAS codon variants are necessary. From the other perspective, the present study demonstrated a moderate association between KRAS-mutated CRCs and specific histology, and, to a certain degree, an association between histology and prognosis, according to KRAS mutation status.

E-PS-06-014

The role of IL-23 positive cendritic cells in development of gastric cancer

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Background & objectives: Many molecular and cellular factors play an important role for development of gastric cancer prognosis and progression. The aim of our study was to investigate infiltration with IL-23 positive dendritic cells (DCs) and clinicomorphological parameters in the progression of GC.
Methods: We investigated 40 patients, having GC immunohistochemically with antibodies against IL-23, CD83 and S100. The clinicopathological parameters and survival were analysed retrospectively.
Results: The infiltration with IL-23+DCs in tumour stroma was 26.92+/-7.5 cells/mm2, and in tumour border - 59.3+/-11.8 cells/mm2 ($p=0.024$, Wilcoxon Signed rank test). 87.1% of the patients with low infiltration were in T3 and T4 tumour stage vs. close to 50% from group of patients with high infiltration were in the same stage ($p=0.003$). In addition, 65% from low differentiated tumours were with low infiltration with DCs, vs. low infiltrated with DCs moderate and high differentiated tumours ($p<0.001$).
Conclusion: Our results suggest that IL-23 positive dendritic cells play role in tumour progression and could be useful as a prognostic marker of in gastric cancer patients.
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E-PS-06-015

A study of HLA-G expression profiling in colorectal cancer

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Background & objectives: Human leucocyte antigen(HLA)-G is a powerful molecule involved in immune tolerance. Previous studies have proposed HLA-G as a potentially good candidate for immune-checkpoint target immunotherapy. We aimed to assess the expression of HLA-G in colorectal cancer(CRC) according to clinicopathological characteristics.
Methods: Immunohistochemical analysis was performed on a total of 22 patients with CRC and their adjacent normal tissues using the 4H84 anti-HLA-G monoclonal antibody. Staining intensity was assessed. Expression levels were classified semi-quantitatively based on immunoreactive cells percentage. Clinico-pathological characteristics were recorded.
Results: Patients age range was of 31 to 93 years (mean = 63 years). HLA-G was significantly expressed in all CRC tissues (100%) and under-represented in normal tissues (10%) (Mann Whitney U test: $p< 0.0001$). The scores of expression of HLA-G in tumour tissues were highly intensive compared to normal tissues ($p<0.0001$). Interestingly, high HLA-G expression was reported in early stages (I+II) compared to advanced stages (IV+V) without significance ($p=0.635$).
Conclusion: Altogether, our results showed that HLA-G could be proposed as a candidate biomarker that can be useful for the evaluation of patients' prognosis and a potential target for CRC therapy.

E-PS-06-016

Fibrosis of the muscular layer of the colon as a predictor of the complicated course of diverticulosis

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Background & objectives: Colonic diverticulosis is an actual problem of modern healthcare with complicated diverticulosis being a life threatening condition. The aim of our study is to determine the morphological predictors of the complicated diverticulosis.
Methods: We analysed 79 consecutive cases of left-sided hemicolectomy, 15 cases were studied comprehensively. Surgical specimens were fixed in 10% neutral buffered formaline and stained with haematoxylin and eosin and Mallory. Morphometric evaluation was performed in order to assess the area of fibrosis in the muscular layer of the colon outside the diverticula in 20 fields of view at x200 magnification.
Results: Among 15 extensively studied cases 6 patients (40.0%) had complicated diverticulosis of the colon, 5 (33.0%) presented

with uncomplicated diverticulosis and 4 (27.0%) had no diverticula of the colon (comparison group). The area of fibrosis in muscular layer of colon progressively enhanced from comparison group to complicated diverticulosis group. In cases with complicated colonic diverticulosis fibrosis of the muscular membrane was 106.5 times more prominent (21.3%) and in cases with uncomplicated diverticulosis - 39 times more extensive (7.8%), both compared with comparison group (0.2%).
Conclusion: The present study demonstrates that the area of fibrosis of the muscular membrane is significantly more extensive in patients with complicated colonic diverticulosis (106.5 times) and in patients with uncomplicated course of diverticulosis (39 times) compares with the comparison group. Our results indicate that the presence of fibrosis in the muscular membrane of the colon should be considered as a predictor of the development of diverticulosis, and its severity being a predisposing factor for complicated course of the disease.

E-PS-06-017
An unusual histopathological morphology of collagenous gastritis
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Background & objectives: Collagenous gastritis is an extremely rare and poorly understood disease defined by subepithelial collagen deposition and inflammatory infiltrate in the lamina propria.
Methods: We present the case of a 27-year-old women with dyspepsia for 2 to 3 years with no other red flag symptoms and distinctive findings in her physical examination. Extensive blood workup including autoimmune disease screening panel, computed tomography and upper endoscopy were performed.
Results: The blood workup revealed features of iron deficiency anaemia. Computed tomography scan demonstrated stomach antral wall thickening with no other significant findings within the rest of the intestinal tract. An upper endoscopy showed diffuse nodular thickening in stomach antrum and corpus with severe atrophy. Histopathological examination of the stomach biopsy specimen showed atrophic gastritis with extensive collagen deposition within the subepithelial region and extending throughout the lamina propria into the submucosa, confirmed by masson-trichrome stain. No amyloid deposition or features of IGG4 related disease demonstrated. A diagnosis of collagenous gastritis was made after excluding differential diagnoses such as systemic sclerosis and IgG4-related disease.
Conclusion: We present an unusual case of collagenous gastritis with diffuse collagen deposition within the full thickness of the mucosa. Although such extensive collagen deposition secondary to autoimmune and IgG4-related conditions must be considered, our case has shown that collagenous gastritis cannot be excluded. We hope it's unusual finding will benefit other diagnosing clinicians having similar problems.

E-PS-06-018
Prognostic significance of cyclin D1 over-expression in colorectal cancer
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Background & objectives: CyclinD1 is a key regulatory protein and is over-expressed in many cancers.The main aim of the study is to examine the expression pattern of cyclin D1 and its correlation with the different clinicopathological features in colorectal cancer (CRC).
Methods: The archival tumour blocks were analysed using immunohistochemistry for CyclinD1 over-expression in 32 CRC patients diagnosed from 2013 to 2019 at the Pathology Department Interior security hospital,Tunisia.The nuclear staining of cyclin D1 was reported in score to define Low and High score.Fisher's exact tests was performed to extract the significant level of association between cyclinD1 over-expression and the clinicopathological parameters.
Results: Mean age of patients was 64,5 with a sex ratio of 2,2. The commonest histological type was adenocarcinoma, seen in 30 cases (94%), and the majority of the tumours were moderately differentiated. Approximately 62.5% of cases had positive lymph node. Distant metastases were seen in 46% of cases.Cyclin D1 over-expression was absent in normal mucosa. In CRC, Cyclin D1 was expressed at high levels in 46% of case. No significant correlation was observed between Cyclin D1 over-expression and age, gender, tumour size, location, type, tumour differentiation, lymph node involvement and lymphovascular invasion. However, Cyclin D1 over-expression exhibited a significant correlation with, distant metastasis (p=0.034) and AJCC staging (p=0.034).
Conclusion: The role of cyclin D1 over-expression in CRC is somewhat controversial.While some reports have observed a significant association between its expression and poor survival outcomes, others have reported it as a marker of a good prognosis. In our study, Cyclin D1 over-expression increases during normal-adenoma-carcinoma sequence. The significant association observed between Cyclin D1 over-expression, distant metastasis and advanced tumour stage clearly suggest the role of Cyclin D1 in the carcinogenesis and progression of CRC.

E-PS-06-019
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of the Vater Ampulla in a Portuguese patient: a case report
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Background & objectives: Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are defined by WHO as mixed neoplasms with neuroendocrine and non-neuroendocrine components. Described in various organs, these neoplasms are commonly found in the Pancreas and Gastrointestinal tract, being rare in the Vater ampulla.
Methods: We describe a case of a 74-year-old woman, referred to our hospital's oncologic reference centre for hepatobiliary and pancreatic cancer. Patient initially presented with new-onset Diabetes and was diagnosed with a tumour of the Ampulla, without radiological evidence of metastatic disease. Cytology examination from fine needle aspiration suggested carcinoma.
Results: A pancreatoduodenectomy was performed. On gross examination there was a lesion confined to the Ampulla with 2.4 cm, composed of a white and friable tissue. Histopathologic examination revealed an ampullary mixed neoplasm with a large cell neuroendocrine carcinoma and a non-neuroendocrine component: moderately differentiated adenocarcinoma, with pancreatobiliary phenotype without microsatellite instability. Tumour was limited to Ampulla and lymph nodes were free from metastatic disease – pTMN: T1a N0.
Conclusion: MiNENs of the Ampulla of Vater are described only in scarce case reports. MiNEN are highly aggressive and with high

risk of metastatic disease, but in our case the tumour was detected in an early stage and was confined to the Ampulla. After 2 months the patient is alive and well without signs of relapse. Further investigation is needed to expand our knowledge and improve diagnosis and treatment of these patients.

E-PS-06-020

Intestinal obstruction as initial manifestation of lobular breast cancer metastasis. A case report

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Background & objectives: Breast cancer is the most prevalent malignancy affecting women, usually metastasizing to the bones, lung and liver. Gastrointestinal tract metastases are rare, mostly involving the stomach. An unusual case of lobular breast cancer primarly detected as abdominal carcinomatosis is presented.
Methods: A 49-year-old woman without a known history of breast cancer was admitted with ileus, having mentioned only minor symptoms of dyspepsia during the last 6 months. The exploratory laparotomy revealed massive carcinomatosis affecting the peritoneum, ovaries, cecum and transverse colon. Bilateral salpingo-oophorectomy, right hemicolectomy and partial peritonectomy were performed. Grossly, the tumour areas had a brownish micronodular appearance.
Results: Microscopically, the tumour consisted of small sized cells with round or ovoid nuclei and scant cytoplasm arranged in single files, cords and nests. The immunohistochemical analysis showed positive staining for CK7, GATA 3, GCDFP-1, CK903, P120 and negative for CDX2, CK20, and e-cadherin. ER and PR receptors were strongly positive (80% and 40% respectively). Her2/neu was negative (1+). Both morphological and immunohistochemical results confirmed the diagnosis of metastatic lobular breast cancer. No abnormal findings were found on breast ultrasound and digital mammography that followed.
Conclusion: Abdominal carcinomatosis of breast cancer has a prevalence of 0.7% and can be detected on initial diagnosis in some cases. Since the signet-ring morphology of lobular carcinoma may mimic gastric carcinoma, differential diagnosis may be challenging. Even with a known history of breast cancer, abdominal metastases can be overlooked on a long disease-free interval. Immunohistochemical analyses are necessary in the majority of cases.

E-PS-06-021

Crawling-type gastric adenocarcinoma with progression to signet-ring cell (diffuse) carcinoma

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Background & objectives: Crawling-type gastric adenocarcinoma (CTAC), also designated as intestinal-type adenocarcinoma with anastomosing glands, is a rare variant of gastric cancer with specific morphological and molecular characteristics. We present two cases of CTAC and review the morpho-molecular features of this rare entity.
Methods: Case 1: 61-year-old woman referred to our hospital with the diagnosis of diffuse/signet-ring cell (SRC) carcinoma of the antrum. Endoscopy revealed a 1.2x1.0 cm lesion, slightly elevated and centrally depressed, removed by endoscopic submucosal dissection (ESD).
Case 2: 77-year-old woman referred for SRC carcinoma of the incisura. Endoscopy revealed focal irregularity of gastric mucosa with 0.5x0.2 cm, removed by ESD.
Results: Both lesions consisted of branching, anastomosing, "letter-shaped" glands with low-grade atypia. Intramucosal diffuse (SRC) carcinoma (pT1a) was identified adjacent to the glandular component, representing a major part of the lesion in case 1 and only a small focus in case 2. Neoplastic glands displayed gastric phenotype in case 1; by immunohistochemistry, there was expression of MUC5AC and MUC6 in the glandular component; intestinal markers (CDX2, CD10, and MUC2) were negative and the SRCC component showed abnormal E-cadherin expression. Case 2 was almost entirely constituted by anastomosing glands with goblet cells, mimicking dystrophic intestinal metaplasia (IM), and IM was observed in the background mucosa.
Conclusion: CTAC associated to diffuse (SRC) carcinoma represents a rare subtype of gastric cancer with distinctive morphologic and molecular characteristics. Its recognition is crucial, due to the possible progression to diffuse (SRC) gastric carcinoma (doi:10.1007/s10120-012-0173-2), as occurred in our cases. CTAC may harbour molecular alterations typically found in diffuse gastric carcinoma (doi:10.1038/s41379-018-0181-9), which offer an explanation for CTAC de-differentiation. Pathologists should be aware of this peculiar entity, also for the importance of distinguishing CTAC from its mimickers, namely dystrophic intestinal metaplasia.

E-PS-06-022

Hepatoid gastric carcinoma metastatic to the skin - a case report

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Background & objectives: Hepatoid adenocarcinoma of the stomach (HAS) is a rare aggressive tumour with hepatocellular differentiation. Skin metastasis of HAS is an unusual site. It usually occurs in elderly patients and often is diagnosed in advanced stage.
Methods: A 87-years-old male was presented to our hospital for a large skin lesion on the back. A skin biopsy was made. There is no clinical history of cancer.
Results: The pathologic examination revealed, in the subcutaneous tissue, an invasive high-grade carcinoma with solid and tubular pattern, intracellular mucin producing cells (signet-ring like cells) and necrosis. Histochemical stains PAS (+), Alcian Blue (+) and PAS-D (-) showed the presence of neutral and acid mucins.
The immunohistochemistry was positive for CK7, EMA(MUC1), MUC5AC, CA9/19, HepPar1, TTF-1 (cytoplasmic expression). Ki-67 was positive in 50% of neoplastic cells. Negative immunoreactivity was found for Napsin A, CK20, CDX2, MUC2, Melan A, HMB45 and S-100. Based on morphological and immunohistochemical features a diagnosis of a high grade hepatoid adenocarcinoma with putative gastrointestinal origin was made.
Further investigation confirmed the gastric origin.
Conclusion: The HAS is a very rare entity. Making the diagnosis of this tumour type is a dilemma for the pathologist and the clinician and may lead to misdiagnosis. The main differential diagnosis is with hepatocellular carcinoma, especially if the primary lesion is found in the liver. Due to its rarity, there is no consensus regarding therapy. Treatment of metastatic disease remains to be defined.

E-PS-06-023

The effect of counting mitosis by phosphohistone-3 immunohistochemistry on risk categorization in gastrointestinal stromal tumours

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Background & objectives: The number of mitoses is among the criteria for risk categorization in gastrointestinal stromal tumours (GISTs). In this series, mitotic count by phosphohistone-3 (PHH3), a mitotic biomarker, is compared with hematoxylin&eosin (H&E) mitotic counting to understand risk category migration.
Methods: In a series of 38 GIST patients, mitosis was counted with 3 methods, in 5 mm2 area: 1) All the mitotic figures in H&E stain (H&EM), 2) Only PHH3 positive cells with mitotic morphology (PHH3+MM), 3) All PHH3 positive cells (PHH3+). The risk group of each case was determined with each method and stage migration with PHH3 methods was evaluated.
Results: The number of mitoses was lower in 4 (10.50%) cases, equal in 8 (21%) cases, and higher in 26 (68.50%) cases in PHH3+MM compared with H&EM method. In the PHH3+MM method, the risk category was increased in 5 (13%) patients, compared with H&EM. In the PHH3+ method, including tumour nuclei probably at prophase, rates were higher than the first method. The number of mitoses was equal in 5 (13%) and higher in 33 (87%) cases; 16 (42%) patients were reclassified in a higher risk category compared with H&EM. None of our patients migrated to a lower risk category group in both methods.
Conclusion: Our results emphasize that when the method is changed, there is a migration to a higher risk category in GISTs. Therefore, H&EM should be the gold standard till the morphologic criteria of alternative methods like PHH3 counting is strictly described and risk categorization according to such methods is specified in large series with prognostic information.

E-PS-06-024

Primary retroperitoneal mucinous neoplasia with borderline malignancy / with low malignant potential

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Background & objectives: An 83-year-old female patient complained of leg swelling present for several weeks. MRI imaging showed a left-sided, very large multiloculated cystic lesion, extending from the renal lodge to the inguinal canal.
Methods: Thin-walled cysts without internal structure were initially interpreted as lymphangioma. An area of contrast-enhancing intraluminal proliferations in the mid-abdomen was considered a secondary malignancy. Intraoperatively, a 29 x 20 x 7 cm mass fused to the descending colon was found. Complete surgical removal without cyst rupture was achieved.
Results: Macroscopically, several cysts filled with viscous mucus were noted. Microscopically, the fibrous wall was lined by mucinous epithelium without cytological atypia. The suspicious finding on imaging corresponded to a thick-walled cyst with complex papillae, low-grade atypia and a markedly increased proliferation index with Ki-67. Immunohistochemistry confirmed intestinal differentiation with positivity for CDX-2, CK20, CEA, mucin2, mucin 5AC, and ß-catenin. Microscopically, there was also focal epithelial rupture with associated histiocytic demarcation and calcifications as well as fibrous adherence to the colonic wall. An infiltrative growth pattern was not found.
Conclusion: We diagnose the very rare entity of a primary retroperitoneal mucinous tumour of borderline malignancy/ with low malignant potential. Metaplastic emergence from scattered multipotent mesothelial cells is a widely accepted theory regarding the histogenesis of these lesions. Currently, the patient remains well at follow up of six months without any additional therapy. A favourable prognosis can be assumed with complete surgical removal.

E-PS-06-025

A rare case of colon adenosquamous carcinoma

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Background & objectives: Colon adenocarcinoma (AC) is the third commonest carcinoma worldwide, but primary colon adenosquamous carcinoma (ASC) is an unusual variant accounting for < 0,1% of the tumours. We present a rare case of colon adenocarcinoma and brief review of the literature.
Methods: A 53-year-old male with hematochezia underwent colonoscopy with endoscopic polypectomy and ink spotting for an ascending colon polyp. Microscopic examination revealed an adenoma with high grade dysplasia. Subsequently a right colectomy was performed. On gross sectioning, we observed a haemorrhagic inked area of the mucosal surface measuring 3cm and thorough sampling was performed.
Results: Microscopical examination revealed residual adenomatous elements of the mucosa with low grade epithelial dysplasia and an underlying submucosal carcinoma, low grade. It consisted of a well differentiated glandular carcinomatous component with a CK7(-), CK20(+), CDX2(+) immunophenotype and a well differentiated squamous cell carcinomatous component with a p63(+), p40(+), CK5/6(+) immunophenotype. The morphological and immunohistochemical findings were consistent with an ascending colon adenosquamous carcinoma.
Conclusion: Colon ASC is more commonly located at the right colon. There are four hypotheses on the ASC histogenesis that include ectopic squamous cells, transformation of uncommitted basal cells, squamous metaplasia of glandular epithelium and squamous metaplasia of adenocarcinoma cells. ASC has worse prognosis than AC, since 5-year survival rates of ASC and AC are approximately 30% and 50–60%, respectively and complete surgical excision is mandatory.

E-PS-06-026

Glomus coccygeum: a case report of an incidental finding

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Background & objectives: Glomus coccygeum is a phylogenetic vestigial anatomical structure consisting of an arteriovenous anastomosis surrounded by glomus cells, involved in thermoregulation. It is incidentally found in sacrococcygeal resection specimens resected in patients with coccygodinia or advanced rectal and uterine carcinomas.
Methods: We describe a case of glomus coccygeum incidentally identified in the recurrence sacrococcygeal resection specimen of a 52 years-old man diagnosed with colorectal adenocarcinoma with mucinous differentiation.
Results: Macroscopically, it was a well-defined whitish nodular lesion with cartilaginous consistency, measuring 0,6x0,5 cm. Histologic examination revealed a well-circumscribed appearance with densely packed clusters and nests of glomic cells, intimately associated with vascular channels and nerve fibres, embedded in fibrous connective tissue. The cells were epithelioid, with eosinophilic

cytoplasm and round nuclei with finely dispersed chromatin. Cellular atypia and necrosis were absent. Immunohistochemistry stains revealed the epithelioid cells to be positive for muscle specific actin, vimentin and CD34 and negative for epithelial markers, EMA, neuroendocrine markers and enolase, with low proliferative activity. S-100 and CD31 stains highlighted associated nerve fibres and endothelial cells lining blood vessels, respectively.
Conclusion: Glomus coccygeum is a nonpathological structure whose incidentally observation may cause significant problems for pathologists unfamiliar with this lesion. According to the literature, its prevalence and functional significance are uncertain but its accurate diagnosis is important to avoid confusion with other sacral tumours.

E-PS-06-027
Epidemiological, clinical, and pathological aspects of early gastric cancer in Tunisian people
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Background & objectives: Early gastric cancer (EGC) is defined as being confined to gastric mucosa or submucosa. Its detection has increased in recent years due to advances in endoscopic techniques. Our aim is to analyse it's epidemiological and clinico-pathological characteristics in Tunisian patients.
Methods: We collected, during 30 years, 18 cases of EGC, diagnosed in the department of pathology of Habib Bourguiba Hospital within the period lasting from January 1992 to December 2021.
Results: The mean age at diagnosis was 57,8 years witha sex-ratio of 2. Fibroscopy showed an ulcerated aspect of the mucosa. The metastatic workup revealed inguinal lymphadenopaties in only one case. Patients underwent either total or sub-total gastrectomy. Median tumour size was 2,4 cm. It was mostly located in the lesser curvature (7 cases). Histologically, half patients had a carcinoma limited to the mucosa and the onther half had a carcinoma extending to the submucosa. Helicobacter pylori infection was associated in 66,6% cases. Rate of lymph node metastasis was 0% in patients with adenocarcinoma confined to the mucosa, yet it was 44,4% in patients with carcinoma extending to the submucosa.
Conclusion: Prognosis of EGC is excellent. The disease-free 5-year survival rate usually exceeds 90%. Patients with high risk of recurrence may be identified in relation with prognostic factors like histopatologic type, parietal extension and mainly lymph node invasion. Endoscopic mucosal resection can be indicated for EGCs confined to the mucosa having virtually no possibility of lymph node metastasis.

E-PS-06-028
Clinicopathologic features of appendicular endometriosis: a retrospective case series of two university hospitals
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Background & objectives: Endometriosis is a benign gynecological condition. It sometimes appears in the appendix mimicking acute appendicitis or as an incidental finding in appendectomy specimens resected for other gynecologic or digestive pathologies, or other conditions of the appendix such as mucocele.
Methods: The pathology archives of two University Hospitals were reviewed to search for cases with a diagnosis of appendicular endometriosis in a 20-year period (2000-2022). The slides were reviewed for microscopic data of interest. The medical records of the patients were reviewed for demographic and clinical data that might have some implication with this pathology. A descriptive statistical analysis was performed.
Results: The sample was 105 women, age range 15-91 years (median 39.47). 64 patients had history of: endometriosis (21%), pregnancy/abortion (49.5%) and tumours (10.5%).70.5% presented as acute abdomen. Appendectomy was performed in the context of intestinal subocclusion in 9.5% cases.Endometriosis was mainly located at the tip (55.2%) followed by body and base. As for wall involvement in decreasing order: muscularis propria (50.5%), serosa and subserosa. The predominant type of endometrial stroma was atrophic along smooth muscle hyplerplasia. The most frequent accompanying histological findings were acute appendicitis (41%) and periapendicitis (34.3%).No epithelial proliferative changes with atypia or malignant transformation were identified. In 16 patients, endometriosis was found in other locations (8.6% gynecologic, 6.7% ileal).
Conclusion: Appendiceal endometriosis occurs in a wide age range. There is a high prevalence of previous gynecobstetric history in affected patients. Clinically, the most frequent presentation of appendiceal endometriosis is acute appendicitis, thus it should be included in the differential diagnosis in women presenting with pain in the right iliac fosa. It can be found incidentally accompanying other pathologies.

E-PS-06-029
Primary leiomyosarcoma of the stomach: a case report
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Background & objectives: Gastric leiomyosarcomas are extremely rare tumours. Few cases have been reported since the early 2000s, which can be considered the "post-CD117" era. It is thought that most of the cases reported before this period are gastrointestinal stromal tumours.
Methods: A 72-year-old female presented with abdominal pain, loss of appetite, anaemia, and melena for the past 7 days. Gastroscopy revealed a giant polypoid mass in the gastric fundus and body. Biopsies were obtained and reported as sarcoma with smooth muscle differentiation. PET/CT examination showed no suspicious metastatic lesions and the patient was treated with partial gastrectomy.
Results: Macroscopic examination demonstrated a 12x9x4,5 cm protruding giant polypoid/nodular mass with a central necrotic depressed area. Microscopically tumour showed full-thickness invasion with both infiltrative and expansile borders and consisted of spindle-shaped atypical cells with brisk mitotic activity. There was 10 % of necrosis and up to 44 mitoses in 10 high-power fields. Immunohistochemically tumour cells were positive for SMA, Caldesmon, Calponin, and Desmin whereas CD117, DOG-1, CD34, MyoD1, Myogenin, S100, and ALK were negative. KI-67 proliferation index was 70%. There was no evidence of lymphovascular or perineural invasion. Surgical margins were free from tumour. The case was signed out as leiomyosarcoma, grade 3, and score 6 according to FNCLCC.
Conclusion: Gastric leiomyosarcomas are rare tumours and the diagnosis can be challenging without immunohistochemical analysis like in resource-limited laboratories. Even immunohistochemical findings can sometimes be confusing, as caldesmon, known to show smooth muscle differentiation, can be

positive in some GISTs. Treatment largely depends on the surgery. Adjuvant chemotherapy and radiotherapy have shown only limited benefit in the treatment.

E-PS-06-030

Serrated gastric adenocarcinoma developed on a Hyperplastic polyp: a new case

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Background & objectives: Gastric serrated neoplasia are recently recognized entities that has been rarely described and poorly characterized. Fewer than 16 cases of gastric serrated adenomas were reported. We present a less common case of Serrated adenocarcinoma developed on a gastric hyperplastic polyp(GHP).
Methods: A 69-year-old woman with no past medical facts, presented vomiting, gastric pain, and loss of weight. An upper endoscopy followed by CT scan were performed. Finally, the patient underwent subtotal gastrectomy with lymphadenectomy and Finesterer gastrojejunal anastomosis.
Results: The upper endoscopy showed a circumferential antral tumour. CT scan confirmed its presence and showed an association with perigastric lymph nodes with no hepatic or pulmonary metastases. Gross examination of the later specimen showed an exophytic, ulcerated and infiltrative tumour in the antrum. Histologically, there was a Carcinomatous component showing glands with marked serrated neoplastic epithelium resulting in a sawtooth like architecture. The serrated glands were covered by pleomorphic cells. The tumour was developed on hyperplastic polyp. No metastases were detected in any of the 30 lymph nodes and the tumour was classified pT3N0. Elsewhere, the gastric mucosa showed chronic gastritis with intestinal metaplasia.
Conclusion: Malignant transformation of GHP is very uncommon with an incidence ranging from 0.3 to 3%. Serrated gastric neoplasia are also exceptional lesions. The first case published was a degenerated serrated adenoma described by Rubio. The invasive carcinoma component of degenerated serrated adenomas, described in literature, may retain the serrated configuration. Immunophenotypic and molecular features of 9 gastric serrated adenomas were explored. They don't completely share the same profile of its colorectal counterpart. Therefore, more cases are needed to be published.

E-PS-06-031

Collagenous gastritis: clinico-pathological spectrum of 4 cases in a 28 year single centre retrospective study

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Background & objectives: Collagenous gastritis is an uncommon disease characterized by the deposition of a subepithelial collagen band thicker than 10 μm and the presence of inflamatory mononuclear cells in the lamina propia. We report the clinical and histopathologic features of this disease.
Methods: We performed a single-centre, retrospective study of patients with confirmed collagenous gastritis over a 28- year period of time found in our database. The following parameters were recorded: patient clinical history, endoscopic findings, histologic features, treatments and the presence of other diseases.
Results: The study consisted of 4 cases. The median age was 12 years. There was not gender predominance (2 females, 2 males). All of them presented abdominal pain and 2 also had anaemia at diagnosis. The endoscopic findings were: mucosal erythema (n=2), exudates (n=1) and nodularity (n=1). The distribution of collagen deposition was: corpus (n=1), antrum (n=1), corpus and antrum (n=1) and fundus, antrum and cardias (n=1). 3 presented acute gastritis and none had the evidence of Helicobacter pylori infection. One of the patients (25%) had been previously diagnosed of celiac disease (n=1). 3 patients were treated with iron and proton-pump inhibitor and the other one did not received farmacologic treatment.
Conclusion: Although collagenous gastritis is a rare clinicopathology entity, familiarity and awareness of the disease is vital for accurate pathological diagnosis. The most frequent symptom at diagnosis is abdominal pain. The endoscopic findings are nonespecific, varying from mucosal erythema, exudates and nodularity. There is a variability in the collagen deposition localization. There does not seem to be association between gastritis and Helicobacter pylori infection. Commonly, is associated with other autoinmunne disorders such as celiac disease.

E-PS-06-032

A rare case of gastrointestinal stromal tumour (GIST) of the appendix

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Background & objectives: Gastrointestinal stromal tumours (GISTs) are the most common gastrointestinal mesenchymal tumours. However, less than 1% of cases arise within the appendix, and few cases are reported in previous literature.
We present a case of appendiceal GIST presenting as acute appendicitis.
Methods: A 57-year-old male presented with a three day history of lower abdominal pain and nausea. A computed topography (CT) scan showed features of acute appendicitis and an enhancing soft tissue lesion at the appendix tip. The patient underwent laparoscopic appendicectomy.
Results: Macroscopically the appendix showed a 10x10mm firm pale area present within the tip. Microscopy showed a nodular aggregate of ovoid, spindled and polygonal cells, with admixed dense pink spherical deposits. The tumour cells showed positive staining with CD117, DOG1 and CD34. Staining was negative with BCL-2, CD56, CD99, S100, SMA, STAT6, synaptophysin, desmin and ALK1, confirming a diagnosis of GIST. The mitotic count was one per 50 high powered fields. After multi-disciplinary team discussion this patient was managed as a low-risk GIST with planned radiological interval follow up. The patient has remained well post-operatively.
Conclusion: Whilst the majority of GIST's have a benign clinical course, metastasis can occur in 25%. Risk stratification based on clinical and pathological parameters and genetic testing determines subsequent management. This case highlights the importance of awareness of GIST occurring in the appendix. This is a rare entity and the histopathologist plays in crucial role diagnosis and management.

E-PS-06-033

Peculiar morphology in colonic adenocarcinoma arising from a traditional serrated adenoma

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Background & objectives: Micropapillary features in a colorectal carcinoma are associated with a poor prognosis because of the aggressiveness of this variant. They present at a higher stage, with increased incidence of lymphovascular invasion and lymph node metastases.
Methods: We present the case of a 64-year-old male known from 2020 with a sessile polyp located at the cecum-ascending junction, a recto-sigmoidal well differentiated adenocarcinoma (pT2N0) irradiated followed by surgery and a frontal left sided meningioma. This year's biopsy was reported as tubulo-villous adenoma with high-grade dysplasia and he presented in our clinic for the surgical treatment.
Results: On gross examination there was a 4 cm flat lesion, occupying three quarters of the colon's circumference. On microscopy the tumour had features of a flat traditional serrated adenoma, with more than 50% showing ectopic crypt formation and typical cellular features with abundant eosinophilic cytoplasm and penicillate, centrally located nuclei. There were multiple foci of invasive carcinoma involving the upper submucosa, showing mostly micropapillary architecture - small clusters of cells delineated by stromal retraction. The cells showed marked pleomorphism, abundant eosinophilic cytoplasm and prominent and multiple nucleoli. There was a marked neutrophil rich inflammation, including intra-tumoral micro-abscesses. We identified vascular and perineural invasion, without lymph node metastases.
Conclusion: This case was signed out as flat TSA with multiple foci of micropapillary adenocarcinoma(pT1pN0). This is an interesting case because of the clinical course of the patient and the unusual morphology of this carcinoma.
This carcinoma was this patient's third tumour, that we know of, and the association with a meningioma and a serrated lesion is rare and could be syndromic. More tests need to be done in order to find the correlation between these entities if there is one.

E-PS-06-034
Osseous metaplasia in colon cancer: a case report and literature review
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Background & objectives: Osseous metaplasia is defined as heterotopic bone formation. It is exceedingly rare in colorectal cancer, with an incidence of 0.15% (33 cases reported since 1992). We present a case of osseous metaplasia in colonic adenocarcinoma and review the relevant literature.
Methods: A 70-year-old male without any specific peculiar history presented with complaints of abdominal pain and constipation. The laboratory results revealed anaemia and elevated inflammatory markers. A computed tomography showed focal asymmetric and irregular thickening of the transverse colon along with regional adenopathy. The patient underwent an extended right hemicolectomy.
Results: A fungating firm tan-brown tumour measuring 3.5 cm in the direction of maximum dimension with serosal invasion was identified on gross examination. Microscopic features were that of a gland-forming tumour with focal cribriform architecture and central necrosis. The tumour stroma contained scattered trabecular bone lamellae of variable size outlined by osteoblasts and osteoclasts without pleomorphic stromal cells or atypia. Calcifications, bone marrow or cartilage formation were not observed. Mismatch repair protein expression was normal. The tumour was diagnosed as stage IIIB (T4a, N1b, M0) colon carcinoma. Six months after the operation, the patient was still alive and free of local recurrence.
Conclusion: Although colorectal cancer is one of the most common cancers, the finding of intratumoural osseous metaplasia is rare. It is important to recognize it in order to avoid misdiagnosis, as it may resemble soft tissue neoplasms or bone invasion. Although there is insufficient data, it seems to have no clinical or prognostic significance. Further research is needed to elucidate the mechanisms involved.

E-PS-06-035
Volume of resected tumour as indicator of colorectal cancer dynamics
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Background & objectives: Despite the improvement of early diagnostic methods, late–stage colorectal cancer is diagnosed in more than 25% of patients. Thus, the problem of detecting early stages and detectability of colorectal cancer as a whole remains unresolved.
Methods: Data from 527 patients suffering from colorectal cancer who underwent primary tumour resection. Based on the data obtained from the description of the removed intestinal fragments, the volume of the tumour was calculated. The dynamics of changes in tumour volume in patients suffering from colon cancer was studied taking into account the age groups of patients.
Results: In the studied material, the tumour volumes varied significantly: from 0,1 cm3 to 1650 cm3 (average volume 37,3 cm3). In all the studied age periods, the incidence of tumours of different volumes was similar. The largest and smallest neoplasms are less common, in 3,5% and 4,6% of cases, respectively. It can be assumed that tumours with a small volume are not often found due to rapid progression, and after reaching a certain volume (16-32 cm3, the diameter of such foci varies between 2.5-3.5 cm), their growth is significantly inhibited and only in a few cases tumours grow to gigantic sizes.
Conclusion: The change in tumour volume in colorectal cancer occurs non-linearly, explosively. Tumours with a small volume are rare in patients in different age groups. This may be due to their rapid tumour growth. Such an active progression of tumours may explain the low rates of tumour detection in the early stages.

E-PS-06-036
Multiple peritoneal calcifying fibrous tumour: a case report
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Background & objectives: Calcifying fibrous tumour (CFT) is a rare benign mesenchymal tumour. The majority are solitary lesions, cases of multifocal tumours are extremely rare. We report a case of multifocal peritoneal CFT in order to discuss histopathologic features and differential diagnosis.
Methods: A 25-year-old woman, presented with multiple peritoneal nodules and a left ovarian mass. Left oophorectomy with excisional biopsy of two nodules were performed, in front of a radiological suspicion of malignant ovarian tumour with peritoneal carcinosis. Macroscopically, the gross nodule was well-circumscribed, measuring 5x4,5x4,5 cm. The surface cuts were gray-white fasciculated. The left ovariectomy contains two haemorrhagic cysts.
Results: Histopathologically, the nodules consisted of well circumscribed, unencapsulated, abundant paucicellular, hyalinized collagenous tissue. That contain bland spindle cells with a sparse lymphoplasmatic infiltrate and lymphoid aggregates. There was neither cellular atypia nor mitotic figure. Multiple foci of calcification were scattered throughout the lesions. Immunohistochemical staining showed a positivity with CD34 while AML, H-Caldesmon,

CD117, Dog1, ALK-1, Desmin and Inhibin-alpha were negative. The lesion was diagnosed as calcifying fibrous tumour. The ovarian cysts were yellow body haemorrhagic cysts and follicular cysts.
Conclusion: The CFT is a rare tumour with a distinctive histological presentation. That usually occurs in children and young adults. Several sites have been reported but predominantly in the gastrointestinal tract. Usually presented as a solitary lesion, however, multifocal tumours have been observed in up to 10% of cases, in some studies. The diagnosis is based on histology, because clinical and radiological features are nonspecific. Awareness of this entity is crucial to distinguish it from peritoneal carcinosis and other mesenchymal tumours.

E-PS-06-037
An unexpected Lynch Syndrome patient, Muir torre variant
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Background & objectives: As immunotherapy is now FDA approved as first-line setting in metastatic or unresectable mismatch repair (MMR) defective gastrointestinal tumours it has become even more crucial to identify them.
Methods: A peculiar case of a 52 years-old male with an important weight loss, jaundice with hyperbilirubinemia and increased of the other hepatic markers. No apparently relevant past medical history was reported. He underwent routine blood tests, tumoral markers and further investigation through imaging revealed dilatation of the intrahepatic biliary ducts and a polypoid mass of the papilla.
Results: Microscopically after formalin-fixation, paraffin-embedding, hematoxylin-eosin fixation and immunohistochemical stain the diagnosis of ampullary adenocarcinoma was made.
Taking into account the young patient age his medical history was further investigated and were taken aback by what we discovered. Ten years before he was diagnosed with a sebaceous adenoma with the loss of MSH2/MSH6 MMR proteins. With this new information we tested the ampullary tumour for MMR protein expression and the result was the same; also, his family history was significant. NGS molecular analysis of MSH2, MSH6 and EPCAM genes discovered a pathogenic variant of MSH2 gene. Considering all the data the patient was labelled as LS, Muir-Torre variant.
Conclusion: This is a remarkable example of how important is not only to make the correct diagnosis but also to always evaluate the medical and familiar history of patients which is crucial to identify LS or MMR defective patients but also to give them the best possible therapeutic opportunity since the advent of tissue-agnostic anti-cancer drugs.

E-PS-06-038
Morphogenetic role of mast cells in colorectal cancer
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Background & objectives: Mast cells are found in various tumours and one of the main cells of the tumour microenvironment with different effects. However, the assessment of the role of mast cells in tumour morphogenesis does not always give an unambiguous result
Methods: 46 patients with diagnosed colorectal cancer and detected mast cells by immunohistochemical method, on paraffin sections using monoclonal mouse antibodies to Tryptase and Chymase. Mast cells ware quantified in the tumour and at the invasive margin of the tumour. The degree of mast cell degranulation was also determined.
Results: The mast cells are widely represented in the tumour microenvironment, but predominate in the invasive margin of the tumour rather than in its centre. At the same time, the functional activity of mast cells was distributed in the opposite way. Mast cells with the greatest degranulation were just observed in the tumour itself. And in the invasive region, mast cells were functionally less active or inactive, despite the quantitative advantage. Quantitative assessment of mast cells revealed no correlation with life expectancy, the presence of regional metastases. There is a decrease in the amount of cells with a decrease in the degree of differentiation of the tumour (in the invasive region).
Conclusion: Mast cells are widely represented in the tumour microenvironment in colorectal cancer. There is a significant advantage in their number in the invasive edge of the tumour. But it is impossible not to take into account their functionality. The decrease in the number of mast cells in the tumour tissue may be due to their increased activity in this area, and not to their exclusion from the morphogenetic process.

E-PS-06-039
Visceral leishmaniasis presented as colitis in a patient with multiple myeloma
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Background & objectives: Visceral Leishmaniasis (VL) is a potentially fatal parasitic disease and the most severe form of Leishmaniasis caused by protozoa of the species Leishmania. VL usually affects the bone marrow, the liver and the spleen of immunocompromised patients.
Methods: A 67-year-old man was admitted with persistent bloody diarrhea. The patient was immunosuppressed with a medical history of renal transplantation and multiple myeloma under treatment. Colonoscopy findings included erythema, oedema, erosions-ulcers and pseudopolyps distributed in a continuous fashion suggesting inflammation of the entire colon. Multiple biopsies were taken from all colon segments.
Results: Histological examination of large intestinal mucosa was compatible with the endoscopic findings of colitis revealing a mild crypt architectural distortion, mucosal surface erosions and a moderate to severe neutrophilic and eosinophilic inflammatory infiltration of the lamina propria. Moreover, a striking finding in all biopsy samples was the presence of numerous macrophages (some of them enlarged) in the lamina propria, containing abundant and dense intracytoplasmic microorganisms. Their morphology (round to oval, uniform and hematoxylinophilic) was strongly suggestive of Leishmania amastigotes. Giemsa histochemical stain also highlighted the morphology of Leishmania parasites. The diagnosis of Leishmania infection was confirmed by serological tests and the patient responded well to the treatment with amphotericin B.
Conclusion: The involvement of the gastrointestinal tract is unusual in Leishmaniasis and is considered as an atypical feature of VL. Intestinal VL affects mainly the duodenum whereas colonic VL is extremely rare and has been reported predominantly in immunosuppressed patients. Colonic VL may present macroscopically as colitis but usually the musosa appears normal and the diagnosis is based on the histological findings. Pathologists should be aware of the presence of Leishmania parasites in colon biopsies from immunocompromised patients with diarrhea.

E-PS-06-040

Mixed neuroendocrine-non-neuroendocrine neoplasm of the ampulla of Vater: a case report

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Background & objectives: Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of the ampulla is extremely rare, with only 20 cases reported in the literature. The aim of this observation is to report a case of MiNEN in the ampulla and study its clinicopathological features.
Methods: A 62-year-old woman presented with jaundice. The CT scan and MRI revealed an ampullary mass with a highly vascularised pattern, and dilatation of both the common bile duct and the main pancreatic duct. Endoscopic ultrasound found a solid tumour at the ampulla, infiltrating the duodenal muscle layer. A biopsy was performed and concluded to ampullary adenocarcinoma. The patient underwent pancreaticoduodenectomy.
Results: The surgical specimen showed a tumour measuring 20×18 mm on the ampulla. Histologically, this tumour was composed of two different components: the first component consisted of a well-differentiated adenocarcinoma (50% of the tumour). The second component was formed by intermediate-to-large-sized neoplastic cells showing solid-nest growth. These cells presented a high degree of cytologic atypia with prominent nucleoli. The mitotic rate was evaluated at 12/10HPF. Immunohistochemical analysis demonstrated that the latter component was positive for synaptophysin and chromogranin-A. The cells had a Ki-67 index higher than 20%. This component was diagnosed as large-cell neuroendocrine carcinoma. The diagnosis of MiNEN of the ampulla was retained.
Conclusion: The diagnosis of MiNEN constitutes a real challenge, because of the absence of typical clinical symptoms or imaging findings. Histologically, the presence of two components with neuroendocrine and non-neuroendocrine features is needed. Thorough sampling of the specimen is necessary for detection of these two components. The confirmation of the diagnosis is based on immunohistochemical staining. The main treatment is radical surgical resection. Further research are mandatory to establish the best method of diagnosis and treatment of these tumours.

E-PS-06-041

Dedifferentiated liposarcoma of the cecum and right adrenal gland, leiomyosarcoma phenotype

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Background & objectives: The patient, a 59-year-old Japanese woman, presented with a palpable mass in the upper, inner portion of the right breast. Ultrasound-guided, core needle biopsy of the breast lesion was performed, yielding a histological diagnosis of invasive mammary cancer.
Methods: Computed tomography (CT), to search for metastases, incidentally revealed an ileocecal mass. Endoscopy of the lower intestinal tract detected an extramural mass, and the subsequent biopsy result was negative for neoplasm. The patient underwent laparoscopic ileocecal resection and total right mastectomy. A lobulated gray-whitish, cecal tumour, measuring 58x45x35 mm, was identified from the muscularis propria to the subserosal membrane.
Results: Histopathologically, spindle cell sarcoma with nuclear polymorphism as well as mitotic activity showed distinct eosinophilic myofilaments in the cytoplasm. Immunohistochemically, cancer cells were diffusely positive for desmin, α-SMA, and h-caldesmon. These findings were considered to indicate leiomyosarcoma. In addition, the right breast cancer corresponded to a primary neuroendocrine neoplasm. A right adrenal tumour was detected by CT performed to assess a right ureteral stone 55 months after the operation. The morphological findings were similar to those of the cecal tumour, accompanied by strong α-SMA and h-caldesmon immuno-expressions. Both lesions were positive for MDM2, CDK4 and S-100, and showed amplification of the *MDM2* gene on FISH analysis.
Conclusion: Based on these pathological features, we made the final diagnosis of dedifferentiated liposarcoma with the leiomyosarcoma phenotype. Within the searchable range, we identified no well-differentiated components. Retrospectively, our present cecal tumour might have originated from the subserosal layer or the peritoneum, and then progressed to involve the muscularis propria. In conclusion, from the therapeutic perspective, it is worth considering the possibility of well-differentiated/dedifferentiated liposarcoma in retroperitoneal and intraperitoneal mesenchymal neoplasms even when the histology is not typical.
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E-PS-06-044

Glomangioma of stomach mimicking GIST: case report

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Background & objectives: Glomangioma of stomach is an extremely rare entity and can clinically present with gastrointestinal bleeding. A case of glomangioma of distal stomach with haematemesis, clinically suspected as a GIST tumour of stomach is documented.
Methods: A 58-year-old female presented with haematemesis. CT scan revealed a distal stomach mass with features suspicious of GIST. A partial gastrectomy performed showed a submucosal tumour in the distal stomach, measuring 31x22x26mm. The lesion was soft, fleshy and lobulated. Rest of the stomach was unremarkable. Routine H&E and IHC studies were carried out to document the nature of the tumour.
Results: H&E sections showed a well delineated submucosal tumourous lesion exhibiting uniform, diffuse distribution of monotonous appearing cells with relatively scanty cytoplasm and dense nuclei, without any atypia. Tumour cells were arranged in small and large groups and nests, surrounding small and a few ectatic blood vessels, with scant intervening oedematous stroma. The tumour was infiltrating into the upper third of muscularis propria. IHC studies showed a strong expression for SMA, CD34 with total lack of expression for CD117, Chromogranin, Synaptophysin and pan CK. Ki 67 showed a very low proliferative index of 2%. Morphological features and further IHC studies confirmed a benign glomus tumour(glomangioma) of distal stomach.
Conclusion: Glomangioma of stomach can mimic GIST or neuroendocrine tumour and present with GI bleeding. An entity of submucosal lesion of stomach should include the rare entity of glomangioma in the differential diagnosis and IHC studies are warranted in such cases for further accuracy, and documentation. The benign or malignant nature of the glomangioma aids in further management of the case.

E-PS-06-045

HPV-associated mucoepidermoid carcinoma of the anal canal: a case report

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Background & objectives: Mucoepidermoid carcinoma (MEC) of the anal canal is rare. This type of tumour was first described in 1954, and a total of 58 cases have been reported. We herein report another case and emphasize on the immunohistochemical and molecular features.
Methods: A 68-year-old woman reported defecation difficulties and self-discovery of an intra-anal swelling. Rectal ultrasound endoscopy revealed an hypo-echoic lesion of the anorectal junction measuring 17 mm in thickness with infiltration of the vaginal wall. The lesion involved the upper part of the anal canal and the internal sphincter. The patient had chemo-radiotherapy and an abdomino-perineal amputation was performed.
Results: Microscopic examination revealed an infiltrative tumour composed of squamoid, mucin-producing, and intermediate-type cells, with a solid growth pattern. Tumour cells had large nucleoli with high grade atypia. There were no necrosis. Mucin was objectified by PAS, mucicarmin and Alcian blue stains. On immunohistochemistry, tumour cells expressed p63, p40, CK5/6, CK7 and p16. There was no expression of CK20, CDX2 and SATB2. In situ hybridization revealed the presence of high risk Human papillomavirus (HPV) RNA. The patient had adjuvant chemotherapy and relapsed after 6 months of surgery.
Conclusion: Anal MEC is extremely rare and is characterized by the same phenotypical features aas MEC of other sites. This case report emphasizes the role of HPV in the oncogenesis of MEC. The prognosis remains poor despite the progress in the treatment of anal cancer.

E-PS-06-046

Assessment of MMP9 expression in inflammatory bowel diseases (IBD) and microscopic colitis (MC) as a prognostic factor and a possible therapeutic target

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Background & objectives: Extracellular matrix remodelling through changes in the activity and expression of matrix metalloproteinases has known implications in the pathogenesis of inflammatory bowel disorders. We aim to review the correlation between MMP9 expression and disease severity in IBD and MC.
Methods: This retrospective study included 20 cases out of which 6 with Crohn's disease, 4 with ulcerative colitis, 8 with collagenous colitis and 2 with lymphocytic colitis. The MMP9 marker expression was evaluated based on positive lymphocytes from the inflammatory infiltrate in the lamina propria and the intraepithelial compartment using a four-tiered system: 0-none, 1-weak, 2- moderate and 3-strong positivity.
Results: Out of the 10 cases with IBD, 33% had severe active disease with a mean positivity of 2,66 in the lamina propria and 2,33 in the intraepithelial lymphocytes and 25% had moderate active disease, the mean score being 2 in the subepithelial compartment and 1,5 in the glandular and surface epithelium. The rest of 42% had minimally active or inactive disease with a mean expression of 1,25 in lamina propria and 1,6 in the epithelium. Concerning the MC, the mean scores for the inflammatory infiltrate in lamina propria were 1,125 as opposed to 1,5 in the columnar epithelium in collagenous colitis and 1,5 versus 2,5 in patients with lymphocytic colitis.
Conclusion: Etiology and pathological sequences in inflammatory bowel disorders are not fully understood, thus, emerging studies focus on different approaches as to predict the evolution and unveal personalized therapies. Stronger MMP9 expression in patients with IBD compared to MC, along with greater scores within higher severity cases than minimal or inactive stages of disease, strongly support the therapeutic potential of this marker and the use of its inhibitors for impeding aggravation or progression to adenocarcinoma, as suggested by other recent research.

E-PS-06-047

Cystic mesothelioma of the peritoneum: a case report of an unusual tumour and litterature review

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Background & objectives: Cystic mesothelioma of the peritoneum is an uncommon, benign abdominal tumour. There have been fewer than 130 cases reported in the literature today. The diagnosis of this pathology is difficult and based on histological findings. We present a new case of this entity.
Methods: We report the case of a 54-year-old women presented with abdominal pain and constipation. Abdominal examination was marked by diffuse abdominal distension, and tenderness. Computed tomography showed a large spherical multi-loculated cystic mass in the abdomen. Laparotomy was done. The mass and some of the free-floating cysts were carefully harvested. Benign cystic mesothelioma was revealed in the pathology report.
Results: 12 years later, she was operated on for gallbladder lithiasis. Intraoperative examination showed a cystic mass in the peritoneum. There was a significant peritoneal thickening, and a peritoneal effusion, with many cystic lesions that makes dissection and resection very difficult. Gross examination showed Cysts filled with serous fluid and mesured 2,5x0, 5 cm. Microscopic examination revealed a numerous small cysts lined by a single layer of bland, flat to cuboidal cells. This cysts were separated by scant loose to collagenous stromal septa. No infiltrative invasion of underlying tissues. Chronic inflammation and haemorrhage common. Immunohistochemistry stain showed that the tumour cells were positive for calretinin and WT1.
Conclusion: Establishing a diagnosis of cystic mesothelioma of the peritoneum is a challenging task, given rarity of the disease and the small number of reported cases in the literature. This tumour is known for local recurrence. It's agreed that surgery is the only effective treatment.

E-PS-06-048

Paneth cell carcinoma: a rare subtype of gastric carcinomas

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Background & objectives: Paneth cell carcinoma is one of the rare histopathological subtypes of adenocarcinomas arising from gastrointestinal tract. Several cases have been reported as individual case reports in the literature.

Methods: A 44-year-old male presented with a 10-month history of weight loss, epigastric pain, inability to eat and vomiting. In endoscopic examination, an ulcerated mass lesion of 7-8 cm in diameter in the antrum was detected. The endoscopic biopsy was reported as adenocarcinoma and total gastrectomy was performed.
Results: In the gastrectomy specimen, an ulcerated tumour (Borrmann Type III) measuring 8x6.5x1.7 cm was observed in the antrum on the lesser curvature. Histologically, the tumour was composed of differentiated areas with glandular structures and poorly differentiated areas consisting of individually infiltrating malignant cells. The cells in both components have abundant cytoplasm containing eosinophilic coarse granules and centrally located nuclei. The cytoplasm of tumour cells was strongly immunoreactive for lysozyme and showed dPAS positivity. The findings were compatible with Paneth cell carcinoma. The tumour was staged as pT4aN3a with metastasis in 11 lymph nodes. The patient did not receive adjuvant treatment and has been living disease-free for 10 months.
Conclusion: Although rare, Paneth cell carcinoma has unique histopathological features. One should be aware of this rare gastrointestinal adenocarcinoma subtype to diagnose. Because of its rarity, its pathogenesis and prognostic features are still needed to be established by larger series.

E-PS-06-049
A rare case of synchronous gastrointestinal stromal tumour and primary peritoneal mesothelioma - coincidental or not?
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Background & objectives: Gastrointestinal stromal tumour (GIST) represents the most common mesenchymal neoplasm of the digestive system and is frequently diagnosed with other types of primary malignancies. Nonetheless, primary peritoneal mesothelioma (PPM) occurs rarely even individually, thus a synchronism with GIST is exceptional.
Methods: We present the case of a 78-year-old female patient without relevant medical or occupational history, who presented to our clinic with complaints of diffuse abdominal pain and weight loss. After careful clinical and imagistic examination, the suspicion of GIST with diffuse peritoneal metastasis was raised. Patient underwent surgery where the gastric growth and a fragment of peritoneal tumour were excised.
Results: By means of histopatologic and immunohistochemistry analysis, we confirmed the diagnosis of gastric GIST that developed strong positivity for CD34, c-kit and DOG1 and was classified within the second prognostic group (with a 1.9% chance of progressive disease). The peritoneal growth surprised us from the beginning, as it did not share any morphological features with the gastric counterpart. The histology revealed a proliferation composed of epithelioid and spindle cells suggesting a carcinoma with sarcomatoid differentiation. The tumour tested positive for calretinin, WT1, caldesmon, CK 5/6, CK 7 and podoplanin, which was consistent with the diagnosis of biphasic peritoneal mesothelioma.
Conclusion: Primary peritoneal mesothelioma, although infrequent, is a diagnosis that must be acknowledged, because it has a different therapeutic management as compared to peritoneal metastasis. There are very few cases in literature that report similar associations between GIST and mesothelioma, one of them actually suggesting VEGF as a possible factor linking these divergent malignancies. Standardized research on other molecular interactions between co-existing tumours could change our whole approach on this matter.

E-PS-06-051
Histopathological evaluation of gastrointestinal stromal tumours
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Background & objectives: Gastrointestinal stromal tumours (GIST) are rare tumours that account for less than 0.2% of all gastrointestinal system tumours. We aimed to investigate the histopathological and clinicopathological features and survival of GIST cases in our archive of the last 6 years.
Methods: Demographic, histopathological and clinicopathological data of cases diagnosed with primary GIST in Istanbul Medipol University Faculty of Medicine Department of Pathology between 2016-2022 were evaluated retrospectively.
Results: Seventy eight primary GIST cases were evaluated. Forty two (53.8%) of the cases were male and 36 (46.1%) were female. The mean age at the time of diagnosis was 59 (range: 33-91). Fifty of the tumour cases (64.1%) were located in the stomach. The mean number of mitosis was 7.1 in 50 high magnification fields, 48 cases with ≤ 5 and 30 cases with >5 were detected. The mean Ki-67 proliferation index was 6.4%. Liver metastasis was detected in 7 of the cases with primary diagnosis, and lymph node metastasis was detected in 2 of them.
Conclusion: Standardization of histopathological reporting is of great importance for risk assessment in GIST cases.

E-PS-06-052
Evaluation of mismatch repair status in colorectal carcinoma
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Background & objectives: Colorectal carcinomas are among the most common malignancies in terms of morbidity and mortality worldwide. This study aims to analyse the mismatch repair (MMR) status and histomorphological features of cases with colorectal carcinoma.
Methods: Patients with a histological diagnosis of colorectal carcinoma in our hospital in the last 6 years were included in the study. Immunohistochemical techniques for the expression of MMR proteins (MLH-1, MSH2, MSH6, and PMS-2) were performed. MMR status and histomorphological features of the cases were analysed.
Results: Nuclear expression was observed in DNA mismatch proteins in 167 (89.7%) of the cases, while nuclear expression was lost in 19 (10.2%) cases. In the mismatch deficient group, 12 cases showed nuclear loss of MLH-1 and PMS-2, 5 cases showed nuclear loss of MSH-2 and MSH-6, and 2 cases showed nuclear loss of PMS-2. It was observed that the right colon involvement was prominent, including 15 of the 19 cases in the mismatch deficient group, right colon, 3 left colons, and 1 transverse colon tumour, but cases with left colon involvement were also seen.
Conclusion: It is known that mismatch deficient tumours are associated with a better prognosis. We think that the routine application of mismatch deficient immunohistochemical examination to all colorectal carcinoma cases may be important in terms of clinical guidance for cases without clinical and histomorphological features.

E-PS-06-053
Morphometric parameters of esophageal mucous in young people with gastroesophageal reflux disease and autoimmune thyroiditis

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Background & objectives: Gastroesophageal reflux disease (GERD) takes one of the leading positions in internal organs` pathology with comorbidity. Objective of our work was evaluation of morphometric parameters of the esophageal mucous membrane in young people with GERD and autoimmune thyroiditis (AIT).
Methods: Patients with GERD and AIT (main group) and 45 people with isolated GERD (comparison group) matched for age, gender, and social status were examined. The mean age in the groups was 21.9 ± 2.7 and 21.2 ± 2.4 years. Morphometric parameters were obtained (total thickness of the epithelium, basal layer thickness, the height of connective tissue papillae, and intercellular space).
Results: The histological study showed that in patients with GERD and AIT all the morphometric parameters studied had a significantly more severe course and exceeded similar indicators of the group with isolated GERD: epithelium total thickness 319.3±9.1 μm against 286.1±8.2 μm ($p<0.01$), epithelium basal layer thickness 79.6±3.2 μm versus 49.7±2.1 μm ($p<0.01$), connective tissue papillae height 224.8±7.3 μm against 172.7±4.6 μm ($p<0.01$), intercellular space 1.55±0.11 μm versus 1.12±0.09 μm ($p<0.01$). Considerable aggravation of the deviations in patients with AIT may reflect the involvement of an additional autoimmune inflammatory component in the pathological process.
Conclusion: GERD and euthyroid AIT comorbidity in the student population is accompanied by statistically more pronounced disorganization of esophageal mucosal epithelium compared with isolated GERD. The obtained data allow us to consider concomitant AIT as an unfavorable prognostic factor in the progression of GERD in the student population.

E-PS-06-054
Did the COVID-19 pandemic impact the presentation and management of colorectal cancer in a Tunisian population?
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Background & objectives: The implemented measures during the COVID-19 pandemic disrupted health care access, especially in low income countries. We aimed to determine the impact of the COVID-19 pandemic on management and presentation of colorectal cancer (CRC) in a Tunisian population.
Methods: We selected two groups of patients with newly diagnosed and treated CRC in Salah Azaiez institute, in the pandemic era (1 March 2020-1 December 2021) and in a corresponding time interval of the prepandemic era (1 March 2020-1 May 2018). Clinicopathological data were retrieved from pathological reports and compared between the two groups.
Results: The number of newly diagnosed CRCs was lower in the pandemic era (49 cases versus 82 cases). These patients presented at a significantly ($p<0.01$) younger age and with a greater tumour size (median age of 58 versus 62 and tumour size of 40 mm versus 30 mm). Among patients prescribed neoadjuvant treatment, 78% accessed it in the pandemic interval versus 70% in the second group. Lymph node involvement was significantly higher in patients of the prepandemic interval (51% versus 30%, $p=0.02$). There was no difference in T stage presentation ($p=0.2$), lymphovascular invasion rates ($p=0.3$) and tumour regression rates ($p=0.1$) between the two cohortes.
Conclusion: Although the demographic characteristics of patients with CRC diagnosed in the pandemic era were worse, there was no difference in histopronostic factors and health care access. With limited resources, tunisian health care system seemed to resist COVID-19's pandemic impacts.

E-PS-06-055
Tumour budding: a strong and reproductible prognostic marker in stage II colorectal carcinoma
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Background & objectives: StageII colorectal carcinoma is a heterogeneous group with a 5-year survival ranging from 32,3% to 66,5%. Recently, tumour budding (TB) has been recognized as a strong prognostic factor to select a subset of patients who may benefit from adjuvant therapy
Methods: 172 stage II colorectal carcinoma (CRC) patients with known outcome have been identified between 2007 and 2014. TB was defined as single tumour cells or clusters of <5 cells at the invasive tumour front. It was assessed by two different pathologists using the hot spot method. A score using a 3-tier system and a grade were finally attributed.
Results: 47 (27,4%) carcinomas had high and 125 (72,6%) had low budding scores. High grade budding was associated with an infiltrative growth pattern ($p<0,001$), lymphovascular invasion ($p=0,011$), neural invasion (0,002) and intratumoural lymphocyte infiltrate ($p=0,003$). Five-year cancer-specific survival was significantly poorer in high compared with low budding groups: 68% versus 80% ($P=0.023$). Multivariate analysis demonstrated tumour budding to be an independent prognostic factor (hazard ratio=2,33, $P=0.012$). Interobserver agreement was moderate for both score and grade: 74,4% agreement ($k=0.4$) versus 66,9% agreement ($k=0.23$), respectively.
Conclusion: In view of these findings, the use of TB as a reproductible and independent prognostic marker, easily assessed on hematoxylin and eosin slides, to identify a subset stage II CRC patients at high risk of recurrence and who may benefit from adjuvant therapy, had been advocated.

E-PS-06-056
A retrospective study investigating how common serrated adenocarcinomas are and whether it is possible to identify from morphology and immunohistochemistry
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Background & objectives: Sessile serrated adenocarcinoma is a challenging subtype that is rarely used in pathology reports. In previous studies the CK7+/CK20+ pattern of expression is displayed in serrated adenocarcinomas. In this project we tested such an expression retrospectively.
Methods: Haematoxylin and eosin (H&E) analysis on 100 cases of primary CRC samples identified serrated morphology on 37% of cases. Immunohistochemistry (IHC) staining using CK7 (clone: SP52; pre-diluted; ROCHE Diagnostics, Switzerland) and CK20 (clone: SP33; pre-diluted; ROCHE Diagnostics, Switzerland) antibodies was carried out via Ventana automatic Immunostainer (BenchMark Ultra IHC/ ISH System).
Results: CK7+/CK20+ pattern of expression was present in 21% of cases. 11% of CRC cases studied displayed general CK7+/CK20+ expression, as well as that same pattern in both serration and tumour components specifically. This evidence supports Hirano, et al., 2019 findings in which it is considered that the

serrated carcinoma pathway is estimated to account approximately for 10–30% of all CRCs.
Conclusion: Establishing the fact that serrated adenocarcinomas can be distinguished from traditional CRCs, we propose that CK7 and CK20 IHC analysis alongside adequate sampling of the tumour & adjacent non-neoplastic colorectal mucosa should be implemented when handling specimens. Increasing awareness in the scientific community in the reporting of serrated lesions, may consequently benefit patients with their likely prognosis and treatment.

E-PS-06-057
Neuroendocrine tumour arising from a Meckel's diverticulum: a rare entity
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Background & objectives: Meckel's diverticulum (MD), a vestigial remnant of vitelline duct, represents the most common abnormality of the gastrointestinal tract. Its malignant transformation is an unusual event. Herein, we report a case of a neuroendocrine tumour arising in the setting of MD.
Methods: We report the case of a 86 years-old man, with a history of peptic ulcer disease, who presented with symptoms of bowel obstruction. Blood tests showed a biological inflammatory syndrome and radiological exams concluded to a complicated MD. He underwent a cuneiform resection of the MD with uneventful post operative follow-up.
Results: Histological examination revealed the presence of a 0.8 cm well-differentiated neuroendocrine tumour invading the mucosa and the sub-mucosa. Tumour cells displayed an insular pattern and were focally arranged in rosettes. The tumour cells were monotonous, had an eosinophilic granular cytoplasm and small round nuclei with 'salt and pepper' chromatin. No mitotic figures were seen. Immunohistochemically, these cells were positive for synaptophysin and chromogranin A. The Ki-67 was expressed in less than 1% of tumour cells. Surgical margins were negative. The diagnosis of well-differentiated neuroendocrine tumour (Grade I) arising in a Meckel's diverticulum was established.
Conclusion: Eventhough it's scarce, neuroendocrine tumours should be taken into account when dealing with Meckel's divrticulum. Despite its small size, it is frequently associated with nodal and liver metastasis. An optimal surgical management and a close follow-up are advised.

E-PS-06-058
Adenosquamous carcinoma of the colon: study of 5 cases
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Background & objectives: Adenosquamous carcinoma (ASC) is an extremely rare subtype of colo-rectal cancer (CRC) with an incidence lower than 0.1% of all CRC. ASC shows an admixture of both adenocarcinoma and squamous cell carcinoma. We aim to describe clinico-pathological aspects of ASC.
Methods: We performed a retrospective study of 5 cases of patients diagnosed in our department with ASC collected in our institution over a period of 20 years from 2000 to 2020.
Results: Our study included 5 males. Patient's age ranged from 17 to 68years with an average of 50years. One of the patients had family history of CRC and personal history of high-grade conventional adenoma. ASC were widely disbursed throughout the colon with primary sites including the caecum (2cases) and the sigmoid (2cases), followed by the rectum (1case). Histologically, most ASC were of low-grade (4cases) and presented as stage III (3cases). Stages II and IV were identified each in 1case. All patients received adjuvant chemotherapy. One patient relapsed with local and metastatic forms. Three patients died and two were lost at follow up. The follow up average duration was estimated to 6.4months.
Conclusion: The clinical features are similar to other subtypes of adenocarcinoma. Treatment is based on surgery since the benefit of chemotherapy and radiotherapy is not well established. Because of the rarity of this subtype and its generally aggressive nature, no specific prognostic features have been identified. Few series have been reported including a small number of patients. The overall prognosis is worse than adenocarcinoma NOS of the colon across all stages.

E-PS-06-059
Ulcerated colonic lipoma mimicking a gastrointestinal stromal tumour in Von Recklinghausen's disease
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Background & objectives: Von Recklinghausen's Disease (VRD) predisposes to the development of various tumours, ranging from benign neurofibromas to malignant peripheral nerve sheath tumours. Among this spectrum, Colonic lipomas are extremely rare. Herein, we discuss clinico-pathological features of a tumour with misleading presentation.
Methods: A 29-year-old women with VRD presented with melena and symptoms of intermittent bowel obstruction. Computed tomography and colonoscopy were performed and suspected a gastrointestinal stromal tumour in the ascending colon. Considering the patient's background and an inconclusive biopsy, she underwent a right colectomy with uneventful post-operative course.
Results: Gross examination revealed the presence, of a 4 cm well-circumscribed exophytic mass in the caecum. The tumour was covered by an ulcerated mucosa. Cut section showed a homogenous, fatty appearance. Histologically, the tumour was composed of lobules of mature adipocytes with cellular fibrous septa. The spindle cells in the septa were negative to PS100, C-Kit, Dog 1 and SMA stains. The remaining mucosa showed a mild chronic inflammation. The final diagnosis concluded to a lipoma of the colonic mucosa.
Conclusion: It is still unknown whether the coexistence of colonic lipoma with VRD was a mere coincidence or an intrinsic association; and to our knowledge, only one case has ever reported this occurrence. Due to the variable expressivity of VRD and its systemic manifestation, a multi-disciplinary approach should always be considered.

E-PS-06-061

A rare case of extra genital non gestational choriocarcinoma of the jejunum

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Background & objectives: Choriocarcinoma is a highly invasive and metastatic neoplasm that affects young women. Non-gestational choriocarcinoma is an uncommon type of choriocarcinoma that develops from intrauterine gestational trophoblastic cells. Only 18 cases of choriocarcinoma of the small bowel have been reported.
Methods: A 34-year-old woman with gravida 2, para 2 who had her last delivery six years ago and had never had an abortion, was admitted for acute abdominal pain with melena. Gynaecological exam was normal. Her blood tests showed a markedly elevated β-hCG. Computed tomography scanning of the abdomen-pelvis revealed proximal jejunal bleeding. The patient underwent a surgical resection.
Results: The pathological examination revealed the presence, of a 5cm, red, haemorrhagic, round nodular masse of the jejunum. Microscopic examination revealed a proliferation of cytotrophoblasts and multinucleated syncitiotrophoblasts cells in an haemorrhagic background. Immunohistochemically, tumour cells stained positive for β-hCG.
The patient had a cataclysmic haemorrhage with haemorrhagic shock, which was complicated by an unrecovered cardiac arrest despite resuscitation attempts.
Conclusion: To date, the pathogeny of extragenital gastrointestinal tract choriocarcinoma is not elucidated. It is not easy to determine the primary or secondary nature of the tumour and this is why we must look for a history of genital bleeding or abortion in order to exclude the possibility of a molar pregnancy or a metastatic uterine choriocarcinoma which spontaneously disappear. Although extragenital choriocarcinoma in the small intestine is rare, it should be included in the differential diagnosis of small intestinal neoplasm.

E-PS-06-062

Granular cell tumour of cecum: a case report

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Background & objectives: Granular cell tumours are rare soft tissue neoplasms arising possibly from Schwann cells and found throughout the human body, most commonly in skin and subcutis. We herein present a case appearing as polypoid mass protruding inside the cecum.
Methods: During the investigation of anaemia in a 62-year old female patient, colonoscopy was implemented. A polypoid mass, measuring 1,5 cm, was found inside the cecum, excised and sent for histopathological examination. The rest of the colon was unremarkable endoscopically.
Results: Microscopic examination revealed a submucosal neoplasm composed mainly of polygonal and in a lesser extent of spindly cells organized in syncytium formations. Their nuclei displayed only mild atypia and anisonucleosis, while the surrounding cytoplasm was plump, eosinophilic and granular. No mitotic figures were observed. Immunohistochemistry stained the neoplastic cells for S-100 and CD68 markers, whereas CD117, SMA, CD34 and desmin were negative. Mitotic index Ki-67 was calculated 1-2%. Overall, the examination resulted in the diagnosis of a benign granular cell tumour.
Conclusion: Inferentially, our case highlights the importance of clinical awareness for granular cell tumours and their inclusion in the differential diagnosis of polypoid masses inside the cecum and the gastrointestinal tract in general. This is underlined by the fact that they possess about a 2% potential of malignant transformation.

E-PS-06-063

ARID1A expression as a possible marker of gastric precancerous lesions

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Background & objectives: AT-rich interactive domain-containing protein 1A (ARID1A) is a tumour suppressor, which functioning as pleiotropic gene expression inhibitor through regulation of chromatin conformation. ARID1A loss occur in 30% of all gastric adenocarcinomas, especially in MSI and EBV-associated molecular subtypes.
Methods: Gastric mucosa specimens were collected from 43 stomachs with gastric adenocarcinoma. Adenocarcinoma specimens and gastric mucosa fragments taken distant from a border of tumour growth (1 cm or more, distant zone group) were observed. Immunohistochemical ARID1A nuclear staining score was evaluated as proposed (Sakuratani T. et al., 2021). The Mann-Whitney U-test and Wilcoxon matched pairs test were used for comparing.
Results: Marked level of heterogeneity and variability in marker expression was found in the stomach cancer group. Semiquantitative assessment of ARID1A immunohistochemical staining demonstrated that ARID1A nuclear expression score in adenocarcinoma group was lower (median and interquartile range - 4 [2-6]) then in distant zone group (5 [3-6]). This difference was statistically significant ($p = 0,0447$) when applying Mann-Whitney test. However, interquartile range of distant zone group lies within interquartile range of adenocarcinoma tissue group and there was no statistically significant difference ($p = 0,0697$) between matched pairs according to Wilcoxon test.
Conclusion: Absence of difference according to Wilcoxon matched pairs test allows us to consider that distant zone is reflection of field cancerization. It can be assumed that in case of involvement of pathways leading to ARID1A loss in particular gastric cancer it takes place during early steps of gastric carcinogenesis. The study results indicate that ARID1A protein expression can be considered as a possible marker of risk assessment for gastric cancer and would be useful for early diagnosis of gastric adenocarcinoma.

E-PS-06-064

An essential and efficient combination of immunohistochemical profiling for an accurate diagnosis and subclassification of extra mammary perianal Paget diseases

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Background & objectives: Extra mammary perianal Paget disease (EMPPD) is clinicopathologically challenging, due to the risk of misdiagnosis/underdiagnosis, ambiguous origins and recurrence. Our aim is to identify an immunohistochemical panel that improve EMPPD diagnosis and subclassification (skin adnexal vs associated with visceral malignancies).
Methods: Twenty-nine EMPPD cases (biopsies) were studied; no prior skin or visceral malignancies were known. Histomorphology and a combination of ancillary tests (CK7, CK20, CDX2, GATA3, GCDFP15, P40, S100 and Melan-A) were reviewed/ performed.
Results: All EMPPDs were diagnosed/confirmed by immunohistochemistry: CK7+ 100% (29/29); CK20+ 68.2% (15/22); CDX2+

73.7% (14/19); GATA3+ 46.7% (7/15); GCDFP15+ 90% (9/10); P40, S100 and Melan-A all negative (21/21, 24/24 and 20/20). However, 5 visceral-EMPPDs were previously misdiagnosed as skin origin when CDX2 was not accessed, 1 of them with invasive mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) component that required additional chemotherapy treatment. Four skin-EMPPDs were originally called viscerally-originated when GATA3 was not accessed. Adding GATA3 and CDX2 to the most used CK7/CK20 panel illustrated true disease origins (skin versus visceral) and impacted clinical courses. GCDFP15 was less sensible than CK7 to identify EMPPD. P40, S100 and Melan-A show no diagnostic value.
Conclusion: EMPPDs have underrecognized malignant potential. The immunohistochemical panel CK7/CDX2/GATA3/CK20 that we propose refines EMPPD diagnosis by highlighting its origin(s), therefore providing new opportunities for patients' stratification and clinical management.

E-PS-06-065
A rare case of concomitant RAS and BRAF mutation in colon adenocarcinoma
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Background & objectives: Colorectal cancer is one of the most common cancers worldwide. RAS and BRAF are key oncogenes in the RAS/RAF/MAP-kinase pathway. RAS mutations are predictive of resistance to anti-EGFR drugs. RAS and BRAF mutations are generally recognized to be mutually exclusive.
Methods: An 87-year-old man presented to the emergency service with complaints of breathlessness, fatigue and anaemia. During the hospitalization, a colonoscopy was performed. An exophytic and ulcerative tumour was found in the right colon. Biopsies were performed and the diagnosis of a colic adenocarcinoma was made. The multidisciplinary tumour board decided to perform a right hemicolectomy.
Results: On gross examination, a tumour with 6.8x5.2cm which obliterated the colic lumen was described. Histologically it had a tubular and glandular architecture, with a mucinous component that represented 60% of the neoplasia. One, out of thirty one, lymph nodes was metastasized. Loss of MLH1 and PMS2 was detected by immunohistochemistry, MSH2 and MSH6 expression was maintained. The pathological stage was T3N1M0. The mutational status of the RAS and BRAF genes was studied by PCR. The mutation p.Gly12Ala/p.Gly12Val(G12A/V, c.35G>C / c.35G>T), was detected in codon 12 of the NRAS gene. In the BRAF gene the mutation V600E/D(c.1799T>A; c.1799_1800delinsAA/c.1799_1800delinsAC) was detected.
Conclusion: A concomitant BRAF and RAS mutation is very rare, with an estimated incidence of 0.05%. As a rare event not much is known about the appropriate treatment and prognosis of these patients, which seems variable. Prospective studies in a large cohort are needed to fully understand the characteristics of this subset of patient with colon cancer.

E-PS-06-066
Clinical and pathological features of the major duodenal papilla lesions
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Background & objectives: Ampullary carcinomas are a rare entity accounting for 0.2% of gastro-intestinal cancers. They arise from adenomatous lesions presenting each a different malignant potential. The aim of our study was to determine the characteristics of ampullary lesions in our population study.
Methods: Clinical, endoscopic, radiological and pathological features of 47 Patients who underwent upper GI endoscopy with biopsies of the major papilla or surgical resections (pancreaticduodenectomy) over the last 20 years were collected and statistically analysed.
Results: Mean age was 62.65 years. Side-viewing endoscopy identified an irregular protrusion in lumen in most cases (27.7%). ERCP identified bile duct invasion in 8.5% of cases. Three patients had metastatic disease. Lesions were adenocarcinomas in 74.5% of cases, adenomas in 17% of cases, among them 65.2% high grade. Unspecific inflammation was found in 8.5% of cases. Pancreaticobiliary type represented 36.3% of adenocarcinoma, 5% were intestinal type, 31% of mixed type adenocarcinoma, one case of mucinous carcinoma and one patient had an undifferentiated carcinoma with giant osteoclast-like cells. Tumours were well differentiated in 73.5% of cases. 65.5% of tumours were stages I/II.
Conclusion: Ampullary lesions are dominated by adenocarcinoma and most of them are stage I/II. In fact, ampullary carcinomas are generally symptomatic at an early disease stage, thus, withholding a better prognosis than other periampullary cancers. Early management of ampullary neoplasms can prevent malignant transformation.

E-PS-06-067
Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1 – a case report
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Background & objectives: Constitutional mismatch repair deficiency (CMMRD) syndrome is a childhood cancer predisposition syndrome that results from biallelic germline mutations in one of the MMR genes. The tumour spectrum is very broad and the benign manifestations can mimic neurofibromatosis type 1 (NF1).
Methods: A 15-year-old boy, with no recorded family medical history, presented with multiple café-au-lait macules, mainly localized on the anterior abdominal wall, and severe iron-deficiency anaemia. During the hospitalisation, his condition worsened experiencing gastro-intestinal symptoms with signs of intestinal intussusception. A priori detailed examination led to a right colectomy being performed.
Results: Macroscopic examination of the resected specimen revealed four polyps (4mm, 15mm, 30mm, and 40mm, respectively). Histologically, they all represented tubular/tubulo-villous adenomas, out of which the three largest presented high-grade dysplasia; foci of carcinoma in situ/intramucosal adenocarcinoma were observed in the 40mm polyp. Consequently, immunohistochemical stains for the MMR proteins (MLH1, MSH2, MSH6 and PMS2) were performed, which demonstrated a loss of PMS2-protein in both tumour and non-neoplastic tissue. The technique was repeated yielding the same results. The patient's young age, the NF1-like features and the large tubulo-villous adenomas featuring carcinoma in situ were consistent with CMMRD. Moreover, a NF1 germline mutation was not detected, and further genetic analysis is expected.
Conclusion: Despite the very low frequency of CMMRD, one should keep in mind the possibility of this diagnosis, as shown herein. Since skin café-au-lait spots are typically associated with NF1, a more frequent syndrome, CMMRD could be overlooked

leading to possible misdiagnosis. Careful interpretation of MMR proteins, notably for PMS2 in absence of positive internal controls, was paramount for the accurate assessment. A correct diagnosis is of utmost importance, given the high CMMRD mortality rate, and the necessity of genetic counselling.

E-PS-06-068

Gastrointestinal "juvenile-like (inflammatory/hyperplastic) mucosal polyps" as specific gastrointestinal manifestation of neurofibromatosis type 1 (NF1) – a case report

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Background & objectives: Neurofibromatosis type 1 (NF1) is a common syndrome that exhibits variable phenotypic expression. Gastrointestinal juvenile-like (inflammatory/hyperplastic) mucosal polyps (JLIHMPs) have been proposed as a NF1-specific gastrointestinal (GI) manifestation and only a few cases were reported so far.
Methods: We report a case of a 78-year-old female featuring JLIHMPs in clinically/genetically proven NF1. A thoroughly examination was carried out due to an iron-deficiency anaemia. The colonoscopy revealed two pediculated polyps located in the right colon (15mm and 23mm, respectively) and one in the left colon (60mm). Following polypectomies, microscopic examination and genetic analysis were conducted.
Results: Histologically, the two right-sided polyps showed juvenile-like features such as superficial ulceration and granulation tissue, dilated/distorted crypts separated by abundant, markedly inflamed stroma, rich in eosinophils and mast cells. Vascular changes (i.e. wall thickening) were present in the polyps axes. Additionally, squamous metaplasia was noted. The left-sided polyp exhibited similar characteristics; however, unlike the other two polyps, it presented foci of low-grade dysplasia. On IHC, performed on one of the right-sided polyps, CD117 staining showed numerous mast cells, stromal cells were CD34− and S100 staining did not show Schwann cells/neural alterations. Moreover, DNA analysis did not reveal any PDFRA or any specific mutations. The polyps characteristics were consistent with JLIHMPs.
Conclusion: Considering the poor characterisation of this entity, the diagnosis is non-trivial. Although usually not prominent, both juvenile and fibroid polyps (IFPs) features may be found in JLIHMPs. The lack of specific mutations sustained our diagnosis. As mast cells are deregulated in NF1, a heavy inflammation with numerous mast cells suggests a possible pathogenetic role of these leukocytes. Our findings add to the current knowledge on this particular entity as it may be recognised as specific gastrointestinal manifestations of NF-1.

E-PS-06-069

Mismatch repair protein status in gastric cancer: implications for diagnosis, prognosis and management

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Background & objectives: Discordant results were reported about the benefit of neoadjuvant chemotherapy (NChT) for patients harboring gastric cancer (GC) with mismatch repair protein (MMR) deficiency. Aim: to evaluate if MMR-status is related to survival and/or response to NChT in GC patients.
Methods: 116 operated GC patients with (n=46) or without (n=70) NChT were retrospectively selected from two institutions (2004-2015). Clinicopathological features were analysed. Tumour morphology was assessed according to WHO and Laurén classifications. Tumours were classified as MMR-proficient (MMRp) or deficient (MMRd) by immunohistochemistry. IBM-SPSS was used for statistical analysis. For survival analysis (Kaplan-Meier). Stage IV GC patients were excluded.
Results: 73/116 cases (62.9%) were MMRp and 43/116 (37.1%) were MMRd. MMRp-status was associated with poorly-cohesive (WHO) / diffuse (Laurén) histopathological subtype (n=26/73, 35.6%), while MMRd-status was associated with high-grade tubular (solid) morphology (WHO) (n=12/43, 27.9%) and indeterminate Laurén subtype (n=24/43, 55.8%) - p=0.003 (WHO) and p<0.001 (Laurén). Overall survival (OS) was not related to MMR status (p=0.735). There was no difference in OS in patients treated with surgery alone or NChT, as assessed in the whole series (p=0.161) and separately in MMRp (p=0.381) and MMRd (p=0.251) subgroups.
Conclusion: Histopathological assessment may be important in the identification of MMR-status in GC. Particularly, in this series, high-grade tubular (solid) morphology, according to the WHO classification (Laurén: indeterminate; Japanese Gastric Cancer Association: por1), identified 27.9% of MMRd cases. In line with some studies, MMR-status was not related to OS, either in patients submitted to direct surgery or NChT. These results are relevant, since over 60% of Western GC patients are diagnosed at an advanced stage and would perform NChT.
Funding: Institutional grant from Luz Saúde

E-PS-06-070

A case of clear cell sarcoma of the jejunum

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Background & objectives: Gastrointestinal clear cell sarcoma is a rare neoplasm, with neuroectodermal differentiation and associated to gene fusion translocation involving EWSR1. It has a poor outcome and often it has metastasis at presentation.
Methods: A 53-year-old woman presented to the emergency department with complaints of weight loss, anorexia and fatigue for the last three months. In the CT scan there was a suspicion of a jejunal mass, which was confirmed by enteroscopy. Jejunal resection was performed. During the surgery, the presence of peritoneal carcinomatosis was noted.
Results: On gross examination, the tumour had 4x3.5x3.5cm, with mural growth and lumen obliteration, with focal mucosa ulceration. On cut section, it was tanned, solid and lobulated. Histologically, it had a multinodular growth pattern and it was a predominantly solid neoplasm with focal areas of alveolar, glandular and papillary patterns, composed of uniform and clear cells.
Immunohistochemically the cells were immunoreactive for SOX10, synaptophysin and S100, and negative for panCK, p53, Cromogranin, DOG1, MelanA, HMB45, PAX8 and MITF. Gene fusion involving EWSR1 was confirmed by FISH, thus giving the final diagnosis of a gastrointestinal clear cell sarcoma/malignant gastrointestinal neuroectodermal tumour
No recurrence or progression was reported after 5-months.
Conclusion: Gastrointestinal clear cell sarcoma/malignant gastrointestinal neuroectodermal tumour is a rare neoplasm. Although uncommon, it should be considered on the differential diagnosis for melanoma metastasis in the bowel, because of

the overlapping immunohistochemical and morphology. The demonstration of EWSR1 gene rearrangement is the key for the definite diagnosis.

E-PS-06-071
Colonic diaphragm disease as a rare cause of large bowel stenosis
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Background & objectives: The leading cause of large bowel obstructions in adults is a stricture secondary to malignancy. Colonic diaphragm disease (CDD) is a rare aetiology of stenosis, occurring mostly in the ascending colon of older women on long-term non-steroidal anti-inflammatory drugs (NSAIDs).
Methods: We present a classic case of CDD with radiology, endoscopic and pathological correlation.
Results: A 74-year-old woman with a monoclonal B lymphocytosis presented at an emergency department with a severe postprandial abdominal pain. The CT-scan showed an ascending colon circumferential stenosis and the colonoscopy showed an irregular and friable lesion, which was biopsied and consistent with an ulcer edge. Our multidisciplinary team proposed a right colectomy due to subacute intestinal obstruction symptoms. Examination of the specimen confirmed a single diaphragm-like stricture, conditioning a 70% lumen stenosis, with signs of proximal dilatation. Microscopic examination showed a plica with submucosal fibrosis compatible with CDD. The patient had multiple NSAIDs prescriptions.
Conclusion: CDD is a rare condition associated with a common use drug. This case illustrates a typical case of a concentric stenotic lesion in the ascending colon presenting in an older woman medicated with NSAIDs. CDD is an important differential diagnosis of a colorectal neoplasm that pathologist and clinicians must be aware of.

E-PS-06-072
Esophageal schwannoma: a rare case report
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Background & objectives: Esophageal schwannomas are extremely rare, comprising ~2% of esophageal tumours and affect more frequently women between the 4th-6th decade of life. They are most often located in the proximal oesophagus. They are usually asymptomatic but sometimes can cause dysphagia.
Methods: We present a 47-year-old female who was referred for dysphagia with a history of an operation for diaphragmatic hernia and stenosis 20 years ago.
Results: Biopsies from the lower oesophagus were sent for histopathological examination and revealed a mesenchymal neoplasm composed of spindle-shaped cells with a fascicular pattern of growth and showing palisading of the nuclei. Immunohistochemically, the cells stained positive for S-100 protein and SOX10 but were negative for CD117, CD34 and Melan A. The mitotic index was low (1%).
Conclusion: The prognosis for schwannoma is good since schwannoma is most often a benign tumour with a very low recurrence potential. Malignant transformation is exceptionally rare. The therapeutic management of esophageal schwannoma depends on several factors, such as clinical complaints, tumour size and pathological data (malignancy, mitotic index). Thus, most of the studies recommend surgical resection as treatment of choice.

E-PS-06-073
Clinical and morphological approach in developing a decision support system for patients with autoimmune gastritis
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Background & objectives: Autoimmune gastritis associated with a high risk of gastric atrophy, stomach cancer and neuroendocrine tumours. Development of a decision support system would be helpful to determine the diagnosis and observation of patients for timely detection of gastric precancerous changes.
Methods: In pilot cross-sectional comparative study, 60 patients (30 patients with autoimmune gastritis and 30 - H.pylori-associated) were examined to identify informative diagnostic stimuli. General clinical investigation, upper endoscopy with OLGA-based staging of gastritis, IHC for neuroendocrine cells, antibodies to parietal cells and von Castle intrinsic factor, cyanocobalamin, ferritin, iron and folic acid levels were assessed.
Results: Pathognomonical clinical findings of autoimmune gastritis patients were comorbidity with other autoimmune diseases (25 patients in the main group), cyanocobalamin deficiency (17 patients) and iron deficiency (13 patients). Endoscopy findings identified an endoscopic atrophic grade cutoff point of O3 on the Kimura–Takemoto classification (area under the curve [AUC]: 0,84). All patients in the core group were predominantly afflicted fundic glands and detection of extensive intestinal and/or pseudopyloric metaplasia/SPEM. The most common finding was a combination of intestinal metaplasia I and II types (AUC:0,86). All patients were reported linear and/or micronodular neuroendocrine cell hyperplasia (AUC:0,92). Microcarcinoids was found in 5 patients, 4 had at least 1 neuroendocrine tumour.
Conclusion: Based on the priority obtained, the initial diagnostic approach may be based on primary selection of a cohort of individuals with suspicion on autoimmune gastritis with an additional assessment of presence of autoantibodies to parietal cells and Castle's factor, with the subsequent upper endoscopy in NBI mode and investigation of all the focuses of neuroendocrine hyperplasia. More research is needed to develop a mathematical model for medical decision support system.

E-PS-06-074
Intestinal neuroendocrine tumours: prognostic particularities
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Background & objectives: Neuroendocrine tumours (NETs) account for 2% of all gastrointestinal system malignancies and are most commonly observed the small bowel followed by the rectum and the appendix. This study aimed to investigate the pathologic characteristics and prognostic factors of intestinal NETs.
Methods: It is a retrospective study collecting all cases of intestinal NETs over a twenty-year period between April 2002 and January 2022 diagnosed in the pathology department of Habib Thameur Hospital, Tunis. All histopathological reports and clinical data were reviewed.
Results: There were 35 intestinal NETs. Thirty (86%) were in the appendix, three (9%) in the small intestine and two in the rectum (5%). The mean age was 40,8 years. The mean tumour size was 10.3 mm [2-40 mm]. The tumour grade was G1 in 27 cases, G2 in

7 cases. One rectal tumour was G3. All appendiceal NETs were classified pT1 or pT2 according the 2019 TNM classification. Concerning ileal tumours, 2 were pT3 and one pT4. The diagnosis of the two rectal NET was made in biopsy. Metastasis were present in 3 cases (2 rectal tumours and one small intestine tumour) and they were in the liver.
Conclusion: Contrary to many studies, the appendix is by far the most common location of NETs in this study. All appendiceal NETs were G1 and G2 and pT1 or pT2. Small intestine and rectal NETs were associated with metastasis and adverse prognostic factors (high grade and stage). We have confirmed the previously published findings that appendiceal NETs are associated with a good prognosis whereas small intestine and rectal tumours are frequently diagnosed at an advanced stage of metastatic disease.

E-PS-06-075
Pre-operative staging of rectal neoplasia - a 8-year series of anatomopathological and imagiolocical correlation
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Background & objectives: The therapeutic approach to rectal neoplasia is highly dependent on the clinical and radiological TNM staging (T-tumour, N-node, M-metastasis), where magnetic resonance plays a central role in the staging. This study evaluates the concordance between magnetic resonance and anatomopathological assessment.
Methods: We performed a retrospective review of all cases of rectal neoplasias (n=212) evaluated in our institution between January of 2014 to February of 2022. All patients with imagiological evaluation by magnetic resonance and lack of neoadjuvant therapy were considered (n=51). The anatomopathological staging and the imagiological staging were compared and classified as concordant, parcially concordant or discordant.
Results: All 51 cases were adenocarcinomas. The average age of the patients was 66,7 years (between 36 - 85 years old), divided into 30 males and 21 females.
The overall TNM staging concordance between the anatomopathological and imagiological pre-operative assessment was 35,3% (18 cases). The majority of cases (53,0%, 27 patients) demonstrated a partial concordance. Discordance was present in 11,7% (6 cases) of patients. When evaluating the staging components separately, the tumour depth of invasion (T) was concordant in 72,5% (36 cases). Regarding the evaluation of lymph nodes (N), there was concordance in 51,0% of cases (26 patients).
Conclusion: The results regarding the isolated evaluation of each staging component were similar to the previously described in literature. Concerning tumour depth of invasion, magnetic resonance imaging presents as an accurate, non-invasive method for staging rectal neoplasias. However, in half the cases the nodal status was not correctly evaluated. The physicians should remain aware of the limitations of pelvic magnetic resonance appraisal, especially in the detection of tumour nodal involvement.

E-PS-06-076
A rare case of duodenal mass revealing an unknown hepatocellular carcinoma
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Background & objectives: Hepatocellular carcinoma (HCC) tends to metastasize to extrahepatic organs. Stomach and duodenum involvement has been seldom reported. We report a case of duodenal metastasis revealing an unknown HCC in a male patient
Methods: A 74-year-old man, presented with atypical epigastric pain, asthenia and anorexia. Clinical examination did not reveal any abnormalities. Laboratory tests showed a microcytic hypochromic anaemia. The patient underwent an upper gastrointestinal endoscopy which revealed an ulcerative mass of the duodenal bulb, measuring 3 cm. Multiple biopsies were performed.
Results: Microscopic examination revealed a carcinomatous proliferation, within the duodenal mucosa, arranged in solid and trabecular pattern. Tumour cells were polygonal, with abundant eosinophilic granular cytoplasm, nuclear atypia and brisk mitotic activity. The stroma was sparsely inflammatory. Immunohistochemically, tumour cells stained positive for Hep Par 1. The diagnosis of bulbar metastasis of CHC was made and the patient was recalled for more investigations.
Conclusion: Gastrointestinal metastases from HCC are rare, with few cases reported in the stomach and duodenum. The suggested mechanism of metastasis is mainly direct invasion of a tumour contiguous with the GI tract. Herein we described a novel case of duodenal metastasis from HCC which presented as GI bleeding

E-PS-06-077
Tumour-stroma ratio on the prognosis of colorectal cancer
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Background & objectives: Tumour–stroma ratio (TSR) is a histological feature that reflects the value of the stromal component that surrounds cancer cells and represents a potential prognostic factor. This study aimed to investigate the association between TSR and survival in colorectal cancer.
Methods: The TSR was evaluated in patients diagnosed with colorectal adenocarcinoma.The analysed variables were age, gender, and pathological features according to the WHO classification. The TSR was categorized into 2 groups: ≤50%- low stroma and >50%- high stroma.The association between categorized TSR and survival was analysed using the nonparametric Kaplan-Meier method. Associations between pathological features and overall survival were also verified.
Results: A total of 158 patients participated in this study, of which 40% had lymph node metastasis (regional disease). Tumour budding was observed in 22% of patients. Overall survival was associated with the presence of tumour budding (p-value=0.019) and lymph node metastasis (p-value=0.034), with lower survival for these patients. In the analysed sample, 53.8% of colorectal adenocarcimas fall into the high stroma category, and this group corresponded to the death outcome. The survival of patients in the ≤ 50% - low stroma category was higher when compared to patients in the > 50% - high stroma category.
Conclusion: The tumour-stroma ratio (TSR) is a promising prognostic biomarker in colon and rectal cancer, represents an independent prognostic factor, such as lymph node metastasis and tumour budding. Stroma-rich colorectal cancers show a lower survival rate compared to low stromal tumours.

E-PS-06-078
Prognostic value of immunoscore in colorectal carcinomas
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Background & objectives: Immunoscore (IS), based on the evaluation of the immune infiltrate in the centre of the tumour and its invasive margin, is reported to be related to colorectal carcinomas (CRC) progression. Our study aimed to assess its prognostic value in CRC.
Methods: A total of 104 tumour specimens from patients after curative resection were reviewed. An immunohistochemical study (anti-CD3, anti-CD8) was carried out in the areas of "Hot Spot" in the centre of the tumour and its invasive margin. IS was calculated by the method described by Galon et al. The prognostic value was assessed through a survival study.
Results: The mean age of patients was 61.6 years. IS was I0 in 19.2%, I1 in 15.4%, I2 in 26%, I3 in 16.3% and I4 in 23.1%. Two groups were identified: low IS (≤ 2: I0-I2) and high IS (>2: I3 and I4). A predominance of low IS (60.6%, n= 63) was noted. Our study had shown that low IS significantly deteriorates overall survival while high IS enhances survival significantly ($p < 0.001$). We found a correlation between low IS and advanced pT stage ($p = 0.026$) but IS was not correlated with age, tumour size, tumour grade, vascular emboli, perineural invasion, metastasis and pTNM stage.
Conclusion: Increasing evidence demonstrates that the evolution of CRC is strongly dependent on the complex tumour microenvironment, particularly the immune system cells. Immunoscore is, therefore, a potential prognostic factor for time to recurrence, overall and disease-free survival in CRC together with its predictive value of response to chemotherapy particularly in stage III. Its reproducibility and reliability allow its introduction into daily practice for a better therapeutic management.

E-PS-06-079
Skeletal metastases as first clinical manifestation of malignant tumours of digestive system – a single centre experience
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Background & objectives: Skeletal metastases are the most frequent malignant bone tumours. The aim of our study is to determine frequency of skeletal metastases as first clinical presentation of malignant tumours of digestive system.
Methods: All biopsies taken at the Institute for Orthopedic Surgery "Banjica", Belgrade over the 10-years period (2010-2019) were reviewed using histopathology reports from the files of the Institute of Pathology, Faculty of Medicine, University of Belgrade. Selected histological slides were re-examined. Clinical data were also analysed.
Results: A total of 110 cases of skeletal metastases of digestive tumours were analysed. The vast majority of patients were males (77.3%). The average age of patients was 62.8±9.8 years. Most of the patients had skeletal metastases as first sign of malignant disease (91,82%). Different imaging methods confirmed solitary skeletal lesions in 65.4% cases. Metastases of digestive tract carcinomas were localized in the axial skeleton in 42.1%, appendicular skeleton in 46.7%, in both localization in 10,2%. The most common clinical presentation of skeletal metastases were pain (75.4%), mobility difficulties (28.2%) and pathological fracture (24.5%). Duration of symptoms before diagnosis was between 4-12 months (37.4% of patients).
Conclusion: Skeletal metastases of visceral carcinomas are common. In our study skeletal metastases were the first sign of malignant tumours of digestive tract in the vast majority of patients. It is unusual finding that patients had no preexisting gastrointestinal symptoms. This finding is very important because skeletal metastases are accepted as poor prognostic indicator. Early diagnosis through screening programs is highly important in future management and treatment decisions.

E-PS-06-082
Gastric epithelial dysplasia (intraepithelial neoplasia): from an impression to an algorithm
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Background & objectives: Epithelial dysplasia/intraepithelial neoplasia refers so-called marked gastric precancerous lesions. In the last revision of the WHO classification (2019), the term «dysplasia» was reintroduced, the terms indefinite dysplasia, intramucosal carcinoma and suspicion for invasive carcinoma are also used.
Methods: In order to evaluate an agreement level of specialists in the practical use of the WHO-2019 studies were carried out with group of pathologists with international participation. Selection of diagnostic patterns are identified by examining the biopsy material for the identification of three diagnostic signs of gastric epithelial dysplasia: epithelial atypia, differentiation gradient disorder (cell maturation) and histoarchitectonic disorganization.
Results: The agreement level was carried out using the Cohen's kappa (k). Verbal designation of patterns was accompanied by demonstration of images, discussion of the expert consent criterion, evaluation of the level of reproducibility of identification of patterns from the position of personal assessment in a face-to-face and remote mode, as well as the calculation of individual indicators in group training in comparison with reference variant. A poor level of interexpert agreement was found: general $k = 0.2$. After comments and discussion (master class) the expert consent criterion increased dramatically: general $k = 0.83$. However, this level of agreement reflected, rather, «diagnostic conformism» - experts reproduced the opinion of the moderator.
Conclusion: A schematic representation of diagnostic patterns, the application of which is described by the algorithm of actions, is support in making a diagnostic decision. The testing of the pictograms and algorithm allowed to reach a good level of agreement ($k = 0.65$). Usage of the proposed combinations of tissue and cellular patterns makes it possible to increase the accuracy and, most importantly, the reproducibility of diagnosis. Such approach probably reflects the new education standard for practical usage.

E-PS-06-083
Crohn's disease discovered through a herpetic superinfection: about a case
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Background & objectives: Herpetic viral superinfection in patients with chronic inflammatory bowel disease (IBD) is rare and responsible for outbreaks of IBD. This study aims to highlight the anatomo-clinical particularities of the association of IBD and herpes viral infections of the digestive tract.
Methods: We report a case collected in December 2011 in the Pathological Anatomy department of La Rabta Hospital.
Results: The patient was female, 21 years old and hospitalized for the first time in gastrology department due to liquid diarrhea

and weight loss. During the exploration, entero-CT scan has revealed extensive thickening of the entire right colon, as well as luminal collapse and presence of lymphadenopathy at the ileocecal junction. Histological examination revealed a disorganized architecture of the colonic and ileocecal mucosa with elongated, sinuous and distorted crypts. In addition, we noted the presence of multinucleated cells presenting a muriform aspect, with faded nuclei, voluminous and nucleolated in places. The chorion was inhabited by a rich inflammatory lymphocyte infiltrate mixed with neutrophils. neutrophils were in exocytosis producing crypt abscesses.
Conclusion: Herpes simplex virus (HSV) is a known cause of gastrointestinal infections, especially in immunocompromised patients. A few rare cases of colonic herpetic lesions in patients with IBD have been reported. With immunocompromised individuals, HSV regains higher pathogenicity and higher ease of dissemination. Therefore, it would be wise to search for HSV in immunocompromised patients with IBD. The gold standard of diagnostic tests is the search for HSV by PCR and immunohistochemistry on biopsies.

E-PS-07 | E-Posters Digestive Diseases Pathology – Liver / Pancreas

E-PS-07-001
EBV associated Lymphoepitelioma-like cholangiocarcinoma: case report and literature review

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Background & objectives: Lymphoepitelioma-like cholangiocarcinoma (LELCC) is an unusual type of cholangiocarcinoma first report in 1996 by Hsu et al. LELCC EBV+ is a neoplasm with better prognosis than conventional cholangiocarcinoma (CC), and female and young predominance.
Methods: We present a 49 years old male with history of primary sclerosing cholangitis, obesity, IBD and ischemic cardiopathy. An abdominal CT scan revealed two nodules in right hepatic lobe (18 & 24 mm) and pathologic regional lymph nodes. Liver needle biopsy was performed. Liver biopsy was diagnosis of poorly differentiated carcinoma, so surgery was indicated.
Results: Patient underwent surgery with right liver excision, cholecystectomy and regional lymph nodes dissection. Histologically tumour was composed by poorly differentiated cells arranged in nest, cords or lobules with focal glandular differentiation. Between neoplastic cells, there was a dense lymphoid infiltrate with lymphoid follicles. That reactive lymphoid infiltrate obscured the malignant epithelial cells. Lymph nodes were positive. Malignant cells were IHC positive for CK7 & CK19, and negative for Hepar1. EBV was demonstrated by ISH. No loss of MMR was demonstrated, EGFR and KRAS were WT, and PDL1 expression (SP142) was high. 3 months after surgery the patient is alive although he is on QT because of remain loco regional disease.
Conclusion: LELCC is a rare variant of CC with strong association with EBV and distinctive clinical behaviour and pathological features (no more 65 cases published). There is marked female predominance, although our case is a male and young age. The clinical outcome for EBV associated LELCC is better than CC, may be due to the dense lymphoid infiltration, which is a host defence against the tumour. LELCC has higher expression of PDL1 and this could have implications for potential treatment strategies.

E-PS-07-002
Unusual association of primary high grade neuroendocrine tumour and large cell neuroendocrine carcinoma of the liver – a case report

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Background & objectives: Neuroendocrine neoplasms in the liver are usually metastatic and primary hepatic neuroendocrine neoplasms are rare, representing about 0.3% of all neuroendocrine neoplasms, with, to our knowledge, 153 cases reported in the English literature.
Methods: This case concerns a 44-year-old man, previously healthy, who presented to the emergency department for abdominal pain, vomiting, and watery diarrhea. An abdominal CT-scan was performed and revealed a 12 cm large, heterogeneous hepatic mass, located in segment IVb. Preoperative fine needle biopsy of the mass suggested a well-differentiated (grade 2) neuroendocrine tumour.
Results: Grossly, the left enlarged hepatectomy specimen was almost totally replaced by a heterogeneous solid mass. Histologically, the tumour presented two components: a well differentiated one with organoid architecture and cells presenting a "salt and pepper" appearance, associated with a poorly differentiated component made up of large cells. Necrosis was evaluated to 50%. Both components demonstrated immunoreactivity for synaptophysin, chromogranin and INSM-1. Mitotic count was higher than 20 mitosis/2mm2, with a proliferative index, evaluated by Ki67, of 23%. Cells in the poorly differentiated area over-expressed p53, which was confirmed by molecular study. Primary hepatic tumour, associating a grade 3 neuroendocrine tumour and a large cell neuroendocrine carcinoma diagnosis was made.
Conclusion: The concurrent occurrence in the liver of a high grade neuroendocrine tumour and a neuroendocrine carcinoma has, to our knowledge, never been reported in the English literature. Primary hepatic neuroendocrine neoplasms are slow growing tumours that usually present at advance stage; their diagnosis remains challenging and should be made after elimination of other possible primitives. The results from our molecular analysis suggest that the neuroendocrine carcinoma component developed from the neuroendocrine tumour component after TP53 mutation.

E-PS-07-003
Medullary carcinoma of the pancreas: a case report and review of the literature

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Background & objectives: Medullary carcinoma of the pancreas is a rare tumour with a five-year survival rate of approximately 13%. Previously, this entity was regarded as a subset of poorly differentiated ductal adenocarcinomas, however, they have a distinctive morphological and molecular characteristic.
Methods: The aetiology and pathogenesis are not clearly understood however several studies have shown strong associations with a first degree relative with previous cancer and hereditary nonpolyposis colorectal cancer. Medullary carcinoma does not respond well to chemotherapy making surgery the first line treatment. It is important to differentiate from poorly differentiated adenocarcinoma with Epstein-Barr Virus infection as this mimics medullary carcinoma.

Results: We report the case of a 69-year-old male with a mass in the head of pancreas initially thought to be a neuroendocrine tumour. On resection, morphology showed solid sheets of cells with abundant eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli with a diffuse infiltration of tumour lymphocytes. Tumour borders were pushing with a dense chronic inflammatory infiltrate in surrounding stroma. Immunohistochemistry showed positivity for CAM5.2, EMA and CDX2 but was negative for MUC2, MUC4, CK7, Napsin, CA19.9 and EBV. Ki-67 proliferation index was over 80%. The tumour displayed loss of expression of the mismatch repair genes MLH1 and PMS2. Further mutational analysis revealed no KRAS, NRAS or BRAF variants.
Conclusion: Medullary carcinoma of the pancreas is a rare entity associated with microsatellite instability, mismatch repair defects, colorectal adenocarcinoma and familial syndromes. Our case demonstrates classical morphological features including dense tumour infiltrating lymphocytes, poorly differentiated epithelial cells with syncytial growth and pushing borders. Following diagnosis, genetic counselling should be considered to exclude Lynch syndrome as this may be the first sign of an inherited cancer syndrome. The case highlights the range of next generation techniques required to maintain best patient care.

E-PS-07-004

An extraordinary case of epithelioid/glandular malignant peripheral nerve sheath tumour arising between the ampulla of Vater and the pancreatic head

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Background & objectives: Glandular MPNSTs are extremely rare neoplasms with only a few cases reported in the literature. To the best of our knowledge this is the first case arising in the anatomic location of the ampulla of Vater and the pancreatic head
Methods: A 63-year-old male without signs of Neurofibromatosis-1 underwent Whipple's procedure for a 10.8cm tumour assumed to be a "GIST". He had no remarkable clinical history and never received Radiotherapy. CT-scans revealed no evidence of disease elsewhere. Microscopically, the tumour was composed of highly mitotic and pleomorphic spindle cells with a marbling appearance and to a lesser extent of epithelioid/glandular areas with cribriform, solid and glandular patterns. Rare foci of squamous and heterologous osteoid elements were also noted.
Results: By immunohistochemistry, the sarcomatoid areas of the neoplasm were focally and weakly positive for S-100.The epithelioid areas were strongly positive for CkAE1/AE3 and BerEp4. All GIST markers (CD117, DOG1, CD34) as well as PDGFRA molecular testing were negative along with melanocytic markers (Melan-a, HMB-45, SOX-10), smooth muscle markers (SMA,desmin), markers of lipomatous lineage(MDM2, CDK4), neuroendocrine markers (chromogranin, synaptophysin), mesothelial markers (calretinin, D2-40), STAT6 and TLE1. Moreover there was immunohistochemical loss of nuclear H3K27me3 and complete loss of p16 indicative of CDKN2A gene silencing mutation. Tumour cells tested negative by FISH for gene fusions characteristic of synovial sarcoma (SS18-SSX1, SS18-SSX2, SS18-SSX4). Considering the morphology, the immunohistochemical and molecular results, we diagnosed the tumour as a sporadic High-Grade MPNST with malignant epithelial component.
Conclusion: Our case highlights the potential of MPNSTs for divergent differentiation. Interestingly enough,the epithelioid component of the tumour had metastasized to one peripancreatic lymph node. A high level of awareness is required by the pathologist to accurately diagnose this extremely rare group of neoplasms. It is essential that all other entities in the differential diagnosis have been excluded first. In our case we focused especially on biphasic synovial sarcoma, primary or metastatic sarcomatoid carcinomas and carcinosarcomas, dedifferentiated liposarcoma and even malignant mesothelioma, leiomyosarcoma and melanoma.

E-PS-07-005

Endophilin A3 expression in pancreatic ductal adenocarcinoma

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Background & objectives: Endophilin A3 (SH3GL3), is a BAR domain protein involved in transmembrane trafficking. EndoA3 can favor distinct tumoral phenotype, hyperproliferative or prometastatic effect. Our study aimed to evaluate SH3GL3 expression and to correlate it with clinicopathological features in pancreatic ductal adenocarcinoma.
Methods: Archival specimen from 67 cases diagnosed with PDAC in "St. Spiridon" University Hospital were stained using anti-SH3GL3 antibody. The cases were assessed semi-quantitatively based on the intensity of rection and percentage of positive cells, resulting a two-tier classification: negative and positive EndoA3. A statistical analysis was performed.
Results: SH3GL3 immunostaining was positive in 53 cases and negative in 14 cases. In tumour epithelial cells the marker presented a diffuse cytoplasmic pattern usually with week or moderate intensity levels, focally with granular perimembranous condensations. Within the SH3GL3 positive group, we recorded 2 cases staged as pT1, 29 as pT2, 21 as pT3 and 1 as pT4. The tumours were graded as follow: 8 cases were G1, 44 were G2 and 1 case G3. Statistical analysis revealed significant differences between SH3GL3 expression and tumour stage ($p=0.018$), tumour grade ($p=0.001$).
Conclusion: Overall, our data support that SH3GL3 expression could be considered as prognostic marker, indicating an aggressive behaviour of PDAC.

E-PS-07-006

Pancreatic mucinous cystic neoplasm with Leydig cells and co-existent multifocal low grade pancreatic intraepithelial neoplasia

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Background & objectives: Mucinous cystic neoplasm (MCN) of the pancreas is a cyst forming neoplasm of the pancreas with mucinous lining and characteristic ovarian-type subepithelial stroma. Despite the presence of ovarian-type stroma, the presence of Leydig cells is not well established in MCN.
Methods: A 60-year-female presented to the OPD with non-specific abdominal fullness, and on work-up had a mass lesion in the body of pancreas. Distal pancreatectomy and splenectomy were performed.
Results: The resected pancreas measured 13x6x4cm and spleen measured 12x6x5.5cm and weighed 340 grams. A cyst measuring 5x5x4cm was noted in the body of the pancreas. On microscopy, the cyst was lined by mucinous epithelium, and the subepithelial tissue showed ovarian-type stroma with nests of Leydig cells,

which were confirmed by immunohistochemistry. The rest of the pancreas showed multifocal low grade pancreatic intraepithelial neoplasia (PaIN)

Conclusion: Presence of Leydig cells in the ovarian-type stroma of MCN has not been widely reported. This finding suggests that the 'ovarian-type' stroma may in fact actually be ovarian stroma, which further supports the theorized pathogenesis of this tumour, that the ectopic ovarian stroma incorporated in the pancreas during embryogenesis may become activated in the setting of hormonal imbalance. Presence of multifocal PaIN in the case also support possible common mutations and genetic pathway.

E-PS-07-007

Caveolin-1 and p21 induction in aggressive pancreatic neuroendocrine neoplasms

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Background & objectives: Research data denotes Pancreatic Neuroendocrine Neoplasms (pNENs) to represent genetically different entities, tumours (pNETs) and carcinomas (pNECs) with different malignant potential. Current study explores senescence associated marker p21 and senescence regulator Caveolin-1 expression profiles between the two subtypes.

Methods: Both protein expression profiles were studied immunohistochemically in paraffin-embedded pancreatic lesions and normal adjacent tissues (NAT) from 24 pNEN patients (13 pNETs and 11 pNECs mean-age: 59.69±3.2 and 61.18±3.2 respectively). Staining intensity scores were calculated by multiplying intensity (negative to high: 0-3) with the immunoreactive score: 0-10%=1, 11-50%=2, 51-80%=3, 81-100%=4) and data were statistically analysed using SPSS 26.

Results: Immunostaining of senescence marker p21 was increased in both cancer epithelium and stroma (pNEC) compared to NAT corresponding elements (p=0.048 and p=0.04 respectively). Induced p21 expression was also detected in pNEC patients both epithelium and stroma when compared to pNET patients (p=0.002 and p=0.024 respectively). In between pNEN groups caveolin-1 expression was also more prominent in pNEC patients' epithelium. Still within pNEC patient group loss of caveolin-1 expression in their epithelium was observed in those with positive lymph nodes metastasis (p=0.034). In the pNET a reduction in the expression of caveolin-1 was observed in the presence of inflammation (p=0.03).

Conclusion: Based on p21 expression, induced senescence seems a common feature of pNENs although more prominent in pNECs and with caveolin-1 concomitant expression in pNEC epithelium to promote senescence. A role of caveolin-1 protein in tumour progression was also apparent, as loss of expression in pNECs epithelium with high metastatic potential was observed. Additionally, loss of stromal caveolin-1 upon the presence of inflammation in pNETs was observed potentially associated with caveolin-1 mediated senescence due to release of SASP factors.

E-PS-07-008

Mucoepidermoid carcinoma of the liver: a rare, diagnostically challenging case

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Background & objectives: Mucoepidermoid carcinoma (MEC) is a malignant epithelial neoplasm that arises most common in major salivary glands. It occurs rarely in liver. To now there have been less than 20 cases reported. We report a case of primary MEC of liver.

Methods: Our patient was a 70-year-old female. A mass of approximately 65x55 mm in size, located in the liver segment 5 was detected. It was evaluated as a possible primary liver malignancy. Then the patient was taken liver segmentectomy operation. In macroscopic examination an ill-defined lesion was detected.

Results: Histology of the lesion revealed that the tumour was composed of tumour cells that coalescing as glandular structures and solid nests in some areas as well. On non-cirrhotic background there was a tumour that consisted of the mixture of squamous, mucinous and intermediate cells to varying degrees. Histomorphologic and immunohistomorfologic evidence were interpreted as mucoepidermoid carcinoma. Any possible primary focus was not detected by additional imaging methods, so the tumour was diagnosed as MEC which is an uncommon subtype of intrahepatic cholangiocarcinoma.

Conclusion: MEC is the most common malignant epithelial neoplasm of salivary glands in adults and children. It rarely occurs in other organs. MEC of the liver is extremely rare. First case in liver was presented by Pianzola and Drut in 1971. Due to its relative infrequency in liver, the pathogenesis has not been elucidated. Primary MEC of the liver is a highly aggressive tumour with the overall survival shorter than 6 months.

E-PS-07-009

Solid pseudopapillary neoplasms of the pancreas, a study of 4 cases

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Background & objectives: Solid Pseudopapillary Neooplasms (SPNP) of the pancreas are rare and low grade pancreatic neoplasms, seems dominantly in females. We aimed to evaluate retrospective data analysis, clinical, macroscopic and microscopic features of our SPNP cases and compare them with the literature.

Methods: Here we presented four cases of SPNP which were diagnosed between 2012-2022 years in Sivas Cumhuriyet University Pathology Department. We reassessed our cases and compared our findings with the literature.

Results: All the patients were female. Their ages ranged from 18 to 58 years with an average of 42. The tumours were located in various parts of the pancreas and the average size was 5 cm. Macroscopically, all lesions had shown cystic and solid areas. The youngest patient had a history of pituitary adenoma and suspicion of Lynch syndrome due to PMS-1 heterozygosity. None of the patients had metastatic lesion. Microscopically none had lymphatic invasion and two patients were assessed as pT3 due to peripancreatic adipose tissue invasion. All of the SPNP cases had heterogeneous pattern with solid and pseudopapillary structures and showed haemorrhagic and pseudocystic changes in various areas.

Conclusion: When the clinical, microscopic and macroscopic features of our cases were evaluated, they were found to be compatible with the literature. In addition, although a few cases of other pancreatic tumours incidentally associated with Familial Adenomatous Polyposis Syndrome have been reported in the literature, there is no definite data about the association of pancreatic tumours with Lynch syndrome as probably suspected in one of our cases. Additional studies are needed to elucidate this issue.

E-PS-07-010

Mixed acinar neuroendocrine tumour: a rare case of pancreatic tumour

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Background & objectives: Acinar cell carcinomas are rare tumours, representing 1-2% of all pancreatic adult tumours. We present a case of acinar pancreatic carcinoma and short review of the literature
Methods: A 81-year -old male patient presented with abdominal pain and weight loss. CT-imaging revealed a well demarcated tumour measuring 4.5 cm in greatest diameter at the pancreatic body. On sectioning the tumour was totally encapsulated, solid, tan with fleshy consistency.
Results: On low power microscopic examination, the tumour was cellular and macronodular with fibrous strands. On higher magnification it had an acinar, trabecular, and solid growth pattern. The neoplasm consisted of a mixture of small-sized cells with hyperchromatic nuclei and medium-sized cells with distinct nucleolus and eosinophilic granular cytoplasm PAS(+), PASD(+), AB(-) on histochemical examination. There was increased mitotic activity (15-20mitosis/10HPF) and spotty necrosis. The immunohistochemical analysis revealed a CKAE1/AE3(+), CK7(+), CK19(+), CK8/18(+), Trypsin diffusely (+), Chromogranin-A diffusely (+), Synaptophysin(+) , NSE(+), CD56(+), Vimentin (-), MUC5AC(-), TTF1(-), PAX8(-), CDX2(-), Ki-67 25% phenotype. The diagnosis was consistent with acinar carcinoma with extensive neuroendocrine markers expression, corresponding to mixed acinar- neuroendocrine carcinoma subtype.
Conclusion: Mixed pancreatic carcinomas include all combinations of ductal, acinar, or neuroendocrine differentiation, commonly a mixture of predominant acinar and neuroendocrine component. In case of a discrete neuroendocrine component accounting >30% of the tumour, the neoplasm is designated MiNEN. Alternatively, they can show extensive mixture of acinar and neuroendocrine cells, whereupon they are designated as acinar carcinoma, mixed subtype. They share the same prognosis as pure pancreatic acinar carcinoma.

E-PS-07-011

A singular case of primary hepatic extra gastrointestinal stromal tumour (EGIST)

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Background & objectives: A primary hepatic GIST is an exceptionally rare, barely reported entity, of which we report a singular case.
Methods: A 65-year-old female patient with symptomatology and clinical features of a solitary hepatic mass lesion was worked up, with investigations culminating in an ultrasonography-guided biopsy which was examined histologically and subjected to ancillary testing. A structured differential diagnosis was established and each entity/group of lesions was excluded systematically, until a conclusion was attained.
Results: This biopsy showed a morphologically non-committal lesion, which on concerted diagnostic effort, utilising a broad-based immunohistochemistry panel, which also included GIST determining markers, CD34, c-Kit and DOG-1: was diagnosed as a hepatic extra gastrointestinal stromal tumour (hepatic EGIST). The possibility of secondary hepatic involvement was incontrovertibly discounted clinically.
Conclusion: GISTs predilect the stomach and small intestine, but these tumours can occur anywhere in the gastrointestinal tract. Extra gastrointestinal stromal tumours [EGISTs] have been reported in the omentum and a slew of cases elsewhere. Our case underpins the importance of a non-dogmatic, broad-based analytic approach in dealing with a morphologically obscure hepatic neoplasm, which may well turn out to be the rare primary hepatic GIST / EGIST. The management implications of a precise diagnosis, in this situation, cannot be overemphasised.

E-PS-07-012

Low-phospholipid associated cholelithiasis syndrome - a case report and literature review

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Background & objectives: Low-Phospholipid Associated Cholelithiasis (LPAC) syndrome is a genetic disease associated with a mutation of the ABCB4 gene which codes for protein MDR3, a biliary carrier. It is characterized by the development of biliary lithiasis with no excess of cholesterol secretion.
Methods: We report a case of a 54-year-old female with clinical criteria for LPAC syndrome and ABCB4 gene mutation. She had a complex history of cholangitis/pancreatitis recurrence despite cholecystectomy and treatment with ursodeoxycholic acid. Hepatectomy was performed based on imagiologic findings consistent with cholangiocarcinoma.
Results: The gross examination revealed three specimens of hepatic tissue, weighing 97,5 gr, the largest measuring 87x40x60 mm. On the cut surface, there were some ill-defined, withish and firm areas; the remainder of the parenchyma was homogeneous and tanned. Histologically, there was no malignant lesion but some signs pointing to biliary duct obstruction were found: mild portal fibrosis, sometimes with “onion bulb” pericanalary pattern, ductular proliferation and mononuclear moderate chronic portitis. Few epitheloid granulomas and multinucleated giant cells with cholesterol crystals were also identified. After surgery, the patient developed an abdominal abscess that was successfully managed with antibiotics and drainage. The patient is alive and well, three months post surgery.
Conclusion: LPAC syndrome is defined by two of the following criteria: age < 40 years at onset of biliary symptoms, recurrence of biliary symptoms after cholecystectomy, and intrahepatic hyperechogenic foci detected by ultrasound. This case reports LPAC syndrome in a female with two diagnostic criteria and mutation of the ABCB4 gene. Histologically there are no pathognomonic lesions, but variable findings related to intrahepatic lithiasis may be seen. This report emphasizes the importance of pathological examination and multidisciplinarity in LPAC syndrome.

E-PS-07-013

Hepatic epithelioid hemangioendothelioma: a case report

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Background & objectives: Report of the clinicopathological features of a hepatic epithelioid hemangioendothelioma This entity is an extremely rare, often multifocal, malignant vascular tumour with difficult diagnosis due to the clinical and pathological similarities with other hepatic neoplasms, especially the angiosarcoma.
Methods: An 82-year-old man presented with icteric skin and generalized oedema. The abdominal Ultrasound and the Computed Tomography showed a multinodular and heterogeneous liver that was biopsied.

Results: Histology showed malignant epithelioid cells with eosinophilic cytoplasm and moderate nuclear pleomorphism within a myxohyaline stroma. No mitotic figures or necrosis were present. Tumour cells expressed positivity for vascular markers (CD 34, CD31 and Factor VIII) and were negative for cytokeratins. Both WWTR1-CAMTA1 and YAP-TFE3 gene fusions are characteristics of this neoplasm. WWTR1-CAMTA1 gene fusion, resulting from a t(1;3)(p36;q25) translocation, is found in as many as 90% of cases. However, this tumour did not express these molecular alterations. The patient died in the following month of the diagnosis from terminal hepatic insufficiency.
Conclusion: Hepatic epithelioid hemangioendothelioma is a rare tumour with immunoreactivity for keratins in many cases, potentially leading to confusion with carcinomas. The differential diagnosis are metastatic or primary carcinomas and angiosarcoma. The latter is the most common primary malignant liver mesenchymal tumour in adults, and therefore, it is important for pathologists to be familiar with the immunohistopathological features of this hepatic entity.

E-PS-07-014
A rare case of primary signet ring ampullary carcinoma
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Background & objectives: Signet-ring cell subtype of ampullary carcinoma is a rare occurrence with only than 49 cases reported in the literature. We present a case of a 68-year-old woman diagnosed with signet-ring cell ampullary carcinoma.
Methods: 68-year-old woman complaining of chronic upper abdominal pain diagnosed with duodenal ulcer after multiple endoscopic examination, presented to the emergency room with worsening of abdominal pain and sudden onset of jaundice. A CT scan was performed describing an ampullary lesion suggestive for a benign process, with no secondary lesions present.
Results: The patient was transferred to our gastroenterology department and underwent an endoscopic retrograde cholangiopancreatography demonstrating occlusion of the common bile duct by a large, ulcerated lesion of the ampulla of Vater. Multiple biopsy fragments were taken from the affected area. The histopathologic examination revealed an ulcerated malignant proliferation of discohesive cells with signet-ring features, infiltrating the submucosa and expanding the lamina propria and villi. The diagnosis was supported by the special stains and immunohistochemistry markers performed. On small superficially obtained samples or ulcerated biopsy fragments, in the absence of clinical suspicion of a malignant proliferation, the diagnosis can be easily missed in the early stages.
Conclusion: Signet-ring cell ampullary carcinoma is a rare entity and it may be difficult to diagnose. The patients usually present with jaundice and some of them with abdominal pain and it usually presents as an expansive ulcerated lesion with malignant features but there are cases when the endoscopic or CT aspects may not suggest a malignant process. Literature studies show that extensive sampling and biopsy fragments obtained from the depth of the lesion are needed for accurate microscopic diagnosis.

E-PS-07-015
Pancreatic carcinoma: primary or metastatic? A case report
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Background & objectives: Pancreatic metastases are rare with reported incidence 1.6% to 11% in autopsy studies. We report a rare case of renal cell carcinoma (RCC) metastatic to the pancreas, clinically suspected as a new primary tumour and a brief literature review.
Methods: A 78-year-old female with a prior radical nephrectomy in 2002 for renal cell carcinoma was consulted for atypical abdominal pain. CT-imaging showed a multilobulated mass measuring 4.5cm in greatest diameter at the pancreatic tail. A distal pancreatectomy was performed.
Results: On microscopic examination the tumour was composed of clear cells with distinct membrane and pronounced nucleolus arranged in a solid and alveolar pattern. There were extensive areas of necrosis. Immunohistochemical examination revealed a [CKAE1/AE3(+), Cam5.2(+), EMA(+), Vimentin(+), CD10(+), RCC weekly (+), CK7(-), CD117(-), Chromoganin A(-), Synaptophysin(-)] phenotype. The morphological and immunohistochemical findings were consistent with metastatic clear cell renal carcinoma, in agreement with the past medical history.
Conclusion: Among the metastasis to the pancreas, renal cell carcinoma is the most common. Despite this fact the clinical and radiological differential diagnosis of the metastasis remains a challenge. Histological examination is paramount for the accurate diagnosis.

E-PS-07-016
Collision of low-grade hepatocellular carcinoma and low-grade chondrosarcoma
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Background & objectives: Collision tumours of the liver are rare. The commonest variant is collision of hepatocellular carcinoma (HCC) and cholangiocarcinoma. Chondroid differentiation may occur in sarcomatoid HCCs which are high grade tumours. We report the collision of low-grade HCC and low-grade chondrosarcoma.
Methods: A 65-years-old man with liver cirrhosis and history of treated viral C hepatitis presented with hepatic focal lesion (4x4.3cm) in segment VIII with elevated alpha-feto protein (AFP) and portal vein thrombosis. Patient started Sorafenib therapy and lesion pursued a stationary course for 18 months, with drop of AFP and recanalization of portal vein. Right hepatectomy was done.
Results: The received surgical specimen revealed two adjacent nodules of tumour with well demarcated borders on a background of micronodular cirrhosis. Histologically, one tumour consisted of mildly pleomorphic polygonal hepatocytes arranged in thick trabecular and pseudoacinar patterns. The other tumour showed mildly pleomorphic malignant chondrocytes in lacunae embedded in chondroid stroma.
Immunohistochemically, the epithelial tumour was positive for HepPar-1, Glypican-3, and Arginase-1 confirming hepatocellular nature, while the mesenchymal tumour was positive for S100 and negative for epithelial markers. Molecular analysis is being performed.
Post-operative 18F-fluorodeoxyglucose (FDG) PET/CT revealed clear operative bed with no FDG avid skeletal or soft tissue lesions. Six-months post-operative, the patient is event-free.
Conclusion: The presence of chondroid matrix in HCC is not conclusive to high-grade sarcomatoid tumours, as collision of HCC and chondrosarcoma exists. Collision tumours of the liver are extremely rare and should always be reported and molecular

analysis should be encouraged to better understand the underlying mechanisms by which they develop.

E-PS-07-017

Audit of key pathological parameters in pancreaticoduodenectomy specimens performed for pancreatic ductal adenocarcinoma in a national centre over an 11-year period

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Background & objectives: Pancreaticoduodenectomy(PD) is the mainstay of curative treatment for pancreatic ductal adenocarcinoma(PDAC), however, the approach to pathological examination varies widely. Our aim was to assess the rate of microscopic margin involvement(R1) and nodal involvement(N1) in PD specimens performed at our institution.
Methods: Pathology reports from PDs performed for PDAC were retrieved from our laboratory database between 2011-2021. Margin status, number/name of involved margins, number of positive lymph nodes and the correlation between nodal positivity and R1 status were assessed. Patient age, sex, neoadjuvant treatment status, tumour grade and stage were also recorded.
Results: A total of 272 PD specimens were received. The majority were in males(55%) and the median age was 69. 63% were grade 2. The median number of nodes retrieved was 18 with 67% showing N1 status. 35% of specimens had a final R1 status. Of these, 59% had a single involved margin, 41% had multiple involved margins. The facing superior mesenteric vein(SMV) dissection margin was the most commonly involved(51%). The pancreatic neck transection margin was involved in 15%. 29% of the cases had prior neoadjuvant treatment. The R1 rate in the neoadjuvant cases was 20%. 83% of R1 cases had metastatic disease to lymph nodes(N1).
Conclusion: Using the Royal College of Pathologists criteria for positive margin status in PD specimens (<1mm to inked margin), the rate of R1 status in our cohort has averaged at 34% (11%-64%) over 11 years. The margin most often involved was the facing SMV dissection margin. Neoadjuvant cases had a low rate of R1 status(20%). Margin involvement was associated with lymph node involvement in 83% of cases, in keeping with international data.

E-PS-07-018

Intraductal oncocytic papillary neoplasm of the pancreas associated with invasive carcinoma: case report

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Background & objectives: Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is an uncommon type of cystic pancreatic tumour. Additionally, although rarely reported, association with invasive carcinomas has been established but its long-term behaviour hasn't been fully described.
Methods: A 62-year-old was programmed for endoscopic ultrasound after an incidental finding of a pancreatic cyst. The study revealed a multiloculated cyst with thick septs and a single solid nodule inside, suggestive of a mucinous neoplasm. The lesion was associated with asymmetric dilation of the principal pancreatic duct. Patient underwent pancreatoduodenectomy, and excised tissues were sent to pathology.
Results: The excised tissue showed a multiloculated cyst with a 2 cm diameter. Histopathological study of the resection revealed an intraductal papillary growth from a pseudostratified epithelium of cuboidal cells with big nucleus, prominent nucleolus, and increased eosinophilic cytoplasm (oncocytic); associated with occasional goblet cells. They are arranged in focal, cribriform and cystic structures, which morphologically correspond to IOPN. In addition, adjacent to the main cyst formation, foci of irregular glandular structures made up of oncocytic epithelium are found, surrounded by desmoplastic stroma, revealing an associated invasive carcinoma. HepPar-1 and CK-7 were positive in both the invasive and intraductal components, and Ki-67 was expressed in 30%, conferring a high proliferation rate.
Conclusion: IOPN has been historically considered a subtype of intraductal papillary mucinous neoplasm (IPMN). Nonetheless, recognized recently as a distinct entity from IPMN, also determined as a precursor of invasive carcinoma. The association of background invasive carcinoma and its postresection surveillance have not been fully described, and ranges from 20-60%; occasionally associated with completion of pancreatoduodenectomy. Consequently, there's a need to report cases, for further characterization and development of adequate protocols for long-term management

E-PS-07-019

Correlation of endosonography-guided fine needle aspiration cytology, and needle biopsy in the diagnosis of pancreatic lesions, at Fundación Santa Fe de Bogota, Colombia

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Background & objectives: Diagnosis of pancreatic lesion is challenging. Endosonography-guided aspiration (EUS-FNA) and biopsy (EUS-FNB) are useful as a diagnostic tool. This study aims to define the correlation between eco-endosonograpy-guided fine needle aspiration cytology, and through-the-needle biopsy diagnosis of pancreatic lesions.
Methods: This is a cross-sectional study of patients who underwent EUS-FNB and EUS-FNA as part of the diagnosis of pancreatic lesions. Diagnostic correlation for the two most common diagnosis: ductal adenocarcinoma (PDCA), and neuroendocrine tumour (pNET), with the two tests was evaluated using hypothesis test, correlation coefficient, and prevalence of diagnosis.
Results: One hundred-seventeen patients were evaluated, 59(50.43%) male, and 58(49.57%) female. Seventy patients (70) were diagnosed with PDCA, and nineteen (19) patients with pNET. Other diagnoses included autoimmune pancreatitis, necrotizing granulomatous disease, and mucinous neoplasms among others.
There was a good correlation between cytology and biopsy diagnosis for PDCA (chi2 P=0,0001), and (kappa-Cohen 0.7844; IC(0,5356-1,0332). Surgical specimens' information was available for 17 patients. Diagnostic correlation of cytology and surgical specimen was (0.736; IC(0,3872-1,085)). A total of 41(58,57%) patients, presented with advanced, inoperable, PDCA. For 19 patients with pNET, no correlation between cytology and biopsy specimens was found (p=<0,21). All pNET tumours were small, under 2 cm in diameter.
Conclusion: There is a correlation between cytology and biopsy diagnosis of PDCA, making both tests comparable. For pNET, no correlation was found, although the number of cases was limited, and most cases were small and challenging to access.

Cytology and biopsy diagnosis for advance inoperable disease in PDCA is highly useful, allowing anatomopathological diagnosis for chemotherapy and radiotherapy treatment decisions. Accuracy measurement of the two tests requires a larger series that include surgical specimen diagnosis as a gold standard.

E-PS-07-021

First presentation of amyloidosis diagnosed in a gallbladder specimen

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Background & objectives: Amyloidosis is caused by extracellular deposition of insoluble fibrillar proteins. Two major types are AL-primary,myeloma associated and AA-secondary amyloidosis. Common sites include kidneys,heart,liver, nervous system and gastrointestinal tract. We present a rare case of gallbladder amyloidosis discovered incidentally after cholecystectomy.
Methods: An 83-year-old male without significant medical history presented with fever and upper right quadrant pain. Clinical findings were consistent with acute calculous cholecystitis. A cholecystectomy was performed.
Results: Grossly, the gallbladder wall was thick (0,7 cm), focally perforated, the mucosal surface was granular and brownish and the lumen contained one gallstone. On histology, ulcerated follicular cholecystitis and pericholecystitis were observed. In addition, eosinophilic amorphous depositions were observed in the lamina propria and the wall of small blood vessels. The amorphous material was diastase-PAS(+), blue in Masson trichrome and Congo Red(+) with mild apple-green birefringence under polarized light. Immunohistochemically it was positive for serum amyloid P-SAP(+) and negative for SAA(+).
Conclusion: Gallbladder amyloidosis is extremely rare, with fewer than 20 cases reported. It is suggested that ischemic damage and loss of wall contractility caused by amyloid deposition may be a significant driving factor for inflammation. If found incidentally in an otherwise healthy patient, as in our case, further examination is required to discover the underlying aetiology. In the present case, follow up information was scant but there was clinical suspicion of multiple myeloma, indicative of AL- amyloidosis.

E-PS-07-022

Pancreatic cavernous haemangioma – a welcome diagnosis for a pancreatic mass

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Background & objectives: Pancreatic haemangioma is a very rare entity with fewer than 30 cases reported in the English literature. It has an unspecific clinical presentation usually being asymptomatic or presenting with abdominal pain.
Methods: In this case report we present the case of a 73-year-old male with inflammatory bowel disease with complaints of left abdominal flank pain. A CT-scan was performed showing a caudal pancreatic nodule. The lesion was hypodense with central hypervascularization raising the hypothesis of a neuroendrocrine neoplasia or an adenocarcinoma. The patient underwent a distal pancreatectomy and splenectomy.
Results: The gross examination showed a well circumscribed lesion with expansive growth. It was 6x4,3x3,9 cm and had a yellowish cut surface with haemorrhagic areas. Histology revealed a proliferation of dilated vascular spaces lined by typical endothelium with multiple thrombi and recanalization areas. The lesion was encapsulated by a fibrous bland tissue. The remaining pancreatic parenchyma exhibited signs of chronic obstructive pancreatitis – severe fibrosis, acinar atrophy and Wirsung duct dilation. Twenty-two peripancreatic, perisplenic and celiac lymph nodes showed no tumour cells.
Conclusion: Although a rare entity in the pancreas cavernous haemangioma is histologically similar to haemangiomas arising in other locations. Its diagnosis may be obscured by its rarity, but it should be a part of the differential diagnosis regarding hypervascularizated lesions on CT-scan and entities with vascular differentiation microscopically as it has a very favourable prognosis.

E-PS-07-023

Pancreatoblastoma: a case report

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Background & objectives: Pancreatoblastoma(PB) is a rare malignancy of childhood. Although the primary treatment is surgical resection, a standardized chemotherapy/radiotherapy protocol does not yet exist. Herein presented a case of PB who underwent surgical resection to emphasize clinicopathological features in these rare tumours.
Methods: Pathological examination was performed by routine hematoxylin-eosin and immunohistochemical staining.
Results: In a 6-year-old boy, post-traumatic abdominal imaging incidentally revealed a solid lesion in the body and tail of the pancreas. In addition, metastatic masses were detected in the retroperitoneum. Histopathological examination revealed a tumour tissue consisting of epithelial cells forming solid areas admixed with squamous epithelial cell islands consistent with PB. The patient was treated with neoadjuvant chemotherapy (Carboplatin and Doxorubicin). In the resected specimen following regression of the tumour, solid epithelial areas observed in the pretreatment tumour biopsy were predominantly replaced by epithelial cells forming gland-like structures, and the number of squamous epithelial cell islands decreased. The patient did not experience any recurrence or metastasis (24 months).
Conclusion: The case presented here supports the findings that PB can be observed incidentally in young males on a non-syndromic basis. Although further cases are required to conclude, it also emphasizes the beneficial effect of neoadjuvant therapy in PB treatment.

E-PS-07-024

Cholangiocarcinoma: fusions in FGFR2 detected in liquid biopsy

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Background & objectives: Cholangiocarcinoma constitutes a heterogeneous group of malignant tumours originating in the biliary tree. The absence of an early diagnosis, intra-intertumoral variability, and chemoresistance, lead to a disappointing prognosis.
Methods: We present a 59-year-old male patient with a history of chronic hepatitis B with undetectable viral load. In 2017, a previously unknown lesion in segment VIII was diagnosed by imaging

tests. For this reason, an MRI with contrast was indicated, which showed a lesion radiologically compatible with a cholangiocarcinoma. Therefore, a surgical resection was recommended in a multidisciplinary committee.
Results: The surgical specimen showed a hepatic parenchyma infiltrated by glandular structures with a tubular pattern, composed of atypical cells immersed in a desmoplastic stroma. It showed positive staining for Q7, for low molecular weight (CAM5.2) and high weight (34Be12) keratins. Diagnosis was peripheral intrahepatic cholangiocarcinoma.
Previously treated with first-line chemotherapy, in 2021 genetic variations on DNA and fusion genes on RNA were studied with the use of an expanded NGS panel. Mutations and amplifications on DNA results were negative, while results on RNA were not evaluable. Therefore, a liquid biopsy was performed, detecting fusions of FGFR2-TACC2. In this instance, the patient benefited from a newly targeted therapy: FGFR2 inhibitor, Pemigatinib.
Conclusion: Preservation and viability of the RNA is tough and decisive for appropriate/accurate analysis. Since FGFR2 partners are usually partially included in the commonly used NGS panels, plus the fact that the detection of fusion genes is technically hard, we conclude that this process is challenging. The role of liquid biopsy opens a new possibility to ensure the study of fresh material in order to improve the outcome of diagnosis.

E-PS-07-025
A very rare tumour in gallbladder: coexistence of large cell neuroendocrine carcinoma and intracholecystic papillary neoplasm
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Background & objectives: Neuroendocrine carcinomas(NEC) of gallbladder account for 0.5% of all NECs, 4% of all gallbladder malignancies. Large tumours often extend into liver and/or metastasize. Herein, we report an extremely rare case of NEC involving liver and gallbladder, accompanying intracholecystic papillary neoplasm(ICPN).
Methods: We report a 62-year-old male patient presented with jaundice and abnormal liver tests. A solid mass involving liver and gallbladder was detected radiologically. PET/CT scan revealed also lung and skin metastases besides liver mass (SUVmax=16.3). His past medical history and physical examination was otherwise nonspecific. Partial hepatectomy with cholecystectomy was performed.
Results: Grossly, a tumoral mass with the largest diameter of 13.5 cm, extending between gallbladder and liver parenchyma was detected. A polypoid lesion in the mucosa was residing next to the tumour that was protruding into lumen. Histopathologically, main mass had solid-trabecular pattern, and composed of large atypical epitheloid cells with hyperchromatic irregularly-shaped nuclei, prominent nucleoli and granular cytoplasm. Geographic necrosis and frequent atypical mitotic figures were striking(21/10HPF). Tumour diffusely expressed synaptophysin and chromogranin with very high Ki67 staining(90%). Besides, mucosal polypoid lesion revealed a tubulopapillary growth exhibiting high-grade cytologic atypia. The main mass and the concomitant lesion were diagnosed as large cell NEC and ICPN with high-grade intraepithelial neoplasm.
Conclusion: There are few publications in literature reporting NECs originating from gallbladder/biliary duct. However, another rare pathology, ICPN, was reported to have an increased association with NECs of gallbladder. In our case, though the tumour bulk of NEC was in the liver, presence of ICPN in close proximity with the tumour mass in the gallbladder raised a suspicion that the tumour may have originated from gallbladder. We thought the type of concurrence in our case is worthy of attention.

E-PS-07-026
Solid pseudopapillary neoplasm of the pancreas in children: two cases of a rare entity
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Background & objectives: Solid pseudopapillary neoplasm (SPN) is a low-grade malignant tumour with a predilection for adolescent girls and young women. Although rare, it accounts for 60 to 70% of all paediatric pancreatic tumours, and usually has an excellent prognosis after surgical resection.
Methods: Herein, we report the clinicopathological features of two cases of solid pseudopapillary neoplasm, along with a brief review of the literature.
Results: Case 1 refers to a 13-year-old boy with a pancreatic head tumour and case 2 to a 14-year-old girl with a pancreatic uncinate process tumour, both presenting with abdominal pain. Cephalic duodenopancreatectomy was performed after a presumptive diagnosis and confirmatory cytology, respectively. Grossly, tumours were 9cm and 3,6cm, well-demarcated, haemorrhagic, with solid and cystic areas. Microscopically, they were composed of poorly cohesive epithelial cells forming solid and pseudopapillary structures, positive for β-catenin(nuclear), CD10, progesterone receptors and negative for chromogranin. No lymph node or distant metastasis were identified. Patient 1 is alive and disease-free for 6 months. Patient 2 developed a Wirsung duct stenosis, is alive and disease-free for 4 years.
Conclusion: SPN is a rare low-grade malignancy often found incidentally or presenting with unspecific abdominal discomfort or pain. Awareness for this entity in the paediatric population and in males, along with the recognition of its morphological and immunophenotypical features are essential to confirm the diagnosis. As in the adult population, an excellent prognosis solely with surgery is described for paediatric patients, even in the presence of metastatic disease.

E-PS-07-027
Two cases of hepatic epithelioid hemangioendothelioma with unusual TFE3 immunopositivity
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Background & objectives: Hepatic epithelioid hemangioendothelioma (HEHE) is a malignant vascular tumour of the liver. There are 2 subtypes, conventional variant with WWTR1-CAMTA1 fusion and recently characterized variant with YAP1-TFE3 fusion which is extremely rare.
Methods: We report two cases of HEHE which have striking morphologic features consistent with so-called YAP1-TFE3 fusion subtype, nuclear TFE3 expression and negative CAMTA-1 reactivity on immunohistochemistry. A 66 years old male and a 26 years old female with hepatic masses which were confirmed as HEHE on trucut biopsy.
Results: Both patients have been treated with liver transplantation. Histological examination of the liver explant materials confirmed the presence of HEHE. Both had the unique histological features of

YAP1-TFE3 fused subtype. Immunohistochemistry also supported the YAP1-TFE3 fused variant, by CAMTA1 negativity and TFE3 positivity. First case had metastatic lesions on the C2-C3 vertebral level and multiple lesions on the liver in the MRI after 2 years of follow-up. The hepatic lesions were confirmed as HEHE by biopsy. He received medical oncological therapy. Two and a half years after the transplantation patient died of hepatic failure. Second case has no distant metastasis or recurrence after 3 months of follow-up.
Conclusion: Hepatic epithelioid hemangioendothelioma with YAP1-TFE3 fusion is an extremely rare, recently described malignant vascular tumour. Awareness of this variant's morphologic features are important during differential diagnosis and to avoid misclassification.

E-PS-07-028
Adenomyoma of the ampullary region: a malignancy mimicker
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Background & objectives: Adenomyoma and adenomyomatous hyperplasia in the gastrointestinal tract are commonly benign lesions, usually found in gallbladder. Rarely, they occur in the ampullary region and cause serious complications. Herein, we describe the clinicopathological features of an adenomyoma of the Vater's ampulla.
Methods: A 61-year-old woman presented with obstructive jaundice and mild abdominal pain. Blood tests showed conjugated hyperbilirubinemia. Duodenoscopy revealed a bulging ampulla with normal overlaying mucosa. Radiological examinations reported no further extension. Endoscopic biopsy was inconclusive and couldn't exclude malignancy. Seeing it was symptomatic and suspicious of malignancy, a cephalic pancreaticoduodenectomy was performed with uneventful post-operative course and follow-up.
Results: Gross examination showed a 6mm, white, firm lesion of the ampullary wall. Histologically, it consisted of an admixture of benign epithelial and mesenchymal elements: proliferating benign glands of various size lined by columnar cells and separated by disorganized fibromuscular tissue. The overlying mucosa was unremarkable. Peripancreatic, hepatic pedicle's and superior mesentery lymph nodes were free of tumour. The gallbladder, which was conveyed with the surgical specimen, displayed chronic cholecystitis.
Conclusion: Since the vast majority of ampullary adenomyomas present suspicious symptoms and mimic malignant tumours, its preliminary diagnosis could be very challenging. Due to the serious clinical implications of over-treating a benign lesion; a careful endoscopic, radiological and pathological assessment are mandatory in order to ensure an accurate pre-operative diagnosis, especially that these screening modalities are nowadays, more accurate to fulfill this purpose.

E-PS-07-029
Liver solitary fibrous tumour with simple biliary cyst: a radiological and histological diagnostic challenge
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Background & objectives: Primitive solitary fibrous tumour of the liver is an extremely rare mesenchymal tumour with uncertain biological behaviour, only a few cases reported in the literature, no definite criteria of malignancy and whose preoperative diagnosis can be very challenging.
Methods: We report the case of a 68-year-old man who presented with dyspepsia and had no history of previous neoplastic disease. Ultrasound, MRI and CT scan showed a mass forming lesion of 10 x 7,5 x 9,5 cm, partially cystic with a solid component of 5 x 6 cm, involving the IV hepatic segment, vascularized from the left hepatic artery.
Results: At gross examination, a left hepatectomy showed a 11 x 8 x 10 cm neoplasm, mostly solid with a cystic part not communicating with the biliary tree. At microscopy, the solid part was made of storiform spindle cells organised in bundles, with focal myxoid and fibrotic changes, involving the peribiliary tissue, sparing the porto-biliary peduncle; focal ischaemic necrosis occurred. The cyst was covered by a biliary epithelium with pseudopyloric metaplasia. Neoplastic cells were strongly and diffusely immunoreactive for CD34, STAT6 and BCL2, negative for S100, CD117, DOG1, ERG, PR, inhibin, calretinin and WT1. The mitotic count was 4 mitoses/10 HPF and Ki67 was 15%. Lymph nodes were free of neoplasia.
Conclusion: A diagnosis of primary hepatic solitary fibrous tumour adjacent to a simple biliary hepatic cyst was provided. No similar cases are reported in the literature. Since it is a very rare primitive liver neoplasm, no criteria are available for prognosis and therapy. We decided to apply the score proposed by Demicco and Colleagues (Modern Pathology 2017; 30,1433–1442) and the neoplasm was considered as an" intermediate risk" lesion. The patient is currently free of neoplasia, undergoing close follow up.

E-PS-07-030
Invasive adenocarcinoma arising from an intraductal papillary mucinous neoplasm of the pancreas: a case report
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Background & objectives: Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing cystic lesions that involve the pancreatic ductal system. A subset of IPMNs will progress to invasive carcinoma. This study aims to present a case of malignant transformation of an IPMN to better understand this entity
Methods: We report a case of a 60-year-old female without past medical history who presented with signs of mixed pancreatic insufficiency: recent diabetes and steatorrhea associated with weight loss and anorexia. The radiological exploration concluded with a tissular lesion of the head of the pancreas with dilatation of the main and secondary pancreatic ducts. The patient underwent a cephalic pancreaticoduodenectomy.
Results: On gross examination, serial sectioning showed an ill-limited whitish mass with a myxoid change, reaching the duodenum without infiltrating it. The tumour measured 8,5x 6,5cm. The Wirsung duct was dilated, containing a friable whitish material. Histology examination showed intestinal-type IPMN that involves both the main and the secondary ducts. The tumour contained also foci of invasive adenocarcinoma, which were also found in the surgical sections, Lesions of chronic atrophic autoimmune pancreatitis were also found. The patient underwent a totalisation of its pancreatectomy and adjuvant chemotherapy was also indicated.
Conclusion: IPMNs are rare and are characterized by a risk of malignant transformation. Histologically, IPMNs are divided into three subtypes: intestinal, gastric, and pancreaticobiliary. IPMNs can occur anywhere in the main pancreatic duct and/or

its branches. Clinical symptoms include chronic pancreatitis, weight loss, diabetes mellitus, and jaundice. The differential diagnoses of IPMNs include other pancreatic intraductal neoplasms, mucinous cystic neoplasms, and retention cysts. IPMNs without an invasive carcinoma are often curable. The prognosis for IPMNs with invasive carcinoma is significantly worse

E-PS-07-031

Undifferentiated embryonal sarcoma of the liver (UESL), arising in mesenchymal hamartoma: report of two adult cases

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Background & objectives: Embryonal sarcoma of the liver is a malignant neoplasm, composed of heterogeneous undifferentiated mesenchymal cells. About 50% of cases occur in children between 6 and 10 years of age and rarely occurs in adults. It occasionally arises in mesenchymal hamartoma.
Methods: CASE 1:19-years-old male presented with abdominal pain and weight loss. Examinations revealed elevated liver enzymes and a cystic liver mass measuring 14 cm. CASE 2:33-years-old male patient with a history of surgery for hydatid cyst of liver one year ago, presented with recurrence of complaints. Imaging studies showed heterogeneously contrasting, lobulated solid 16 cm tumour on the right liver lobe.
Results: Right hepatectomy was performed on both patients. On gross examination: first patient had 13.5x9x8.5 cm solid & multicystic, partly oedematous tumoral lesion; second patient had 16.5x9.5x13 cm solid, lobulated tumour with extensive necrosis. On histopathologic examination, cellular component was composed of medium to large spindled or stellate cells with marked nuclear pleomorphism. Occasional PAS positive eosinophilic hyaline globules were seen. With extensive sampling and serial sections, focal areas compatible with mesenchymal hamartoma were found in both tumours. Immunohistochemically, tumour cells were vimentin, CD56, BCL2, pancytokeratin and alpha-1-antitrypsin positive. As a result of morphological and histopathological findings, both cases were reported as "Undifferentiated Embryonal Sarcoma associated with mesenchymal hamartoma".
Conclusion: UESL is a challenging diagnosis. Due to the rarity of UESL in adults, these patients are often misdiagnosed as hepatic abscess, haemorrhagic cystic tumour, or hydatid cyst, as in the second case. It should always be included in the differential diagnoses of large liver masses, regardless of patient age. In addition, sampling and microscopic examination are very important as it can be associated with mesenchymal hamartoma.

E-PS-08 | E-Posters Endocrine Pathology

E-PS-08-001

Case report: secondary paraneoplastic hyperparathyroidism with brown tumour of the femur

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Background & objectives: The diagnosis of neuroendocrine tumour (NET) has serious implications concerning treatment and prognosis. In addition, paraneoplastic hyperthyroidism should always be considered in the differential diagnosis in a severely symptomatic patient with no evidence of abnormality in the parathyroid glands.
Methods: We describe a 39-year-old female with 2 weeks right leg pain preventing her from ambulating; on imaging she had a 10 cm lytic lesion of femur and associated pathologic fracture. The patient presented with a 6 month-long history of nausea, vomiting, and weight loss. At admission, she endorsed significant polyuria, polydipsia, chronic abdominal pain, constipation, reflux and notable memory difficulties.
Results: Lab investigations showed hypercalcemia (13.1 mg/dl) and extremely elevated PTH (>2000 pg/ml). The differential diagnosis included primary hyperparathyroidism, parathyroid carcinoma, or ectopic PTH production. Additional imaging studies revealed a large lytic lesion in the femoral metaphysis and a well-circumscribed homogenous nodule in the right lower lobe. A lung biopsy was done and showed a well-differentiated neuroendocrine neoplasm, while a bone biopsy was suggestive of brown tumour. The profile suggested a well differentiated neuroendocrine tumour, grade 2 (4.0 cm greatest dimension) with focal necrosis. The histology and immunohistochemical features were consistent with atypical carcinoid, which was focally positive with Chromogranin, Synaptophysin and CD56.
Conclusion: Actively hormone secreting NET have been described in the literature, but NET secreting PTH and causing secondary hyperparathyroidism with brown tumour of long bones are very rare; some of the more common paraneoplastic syndromes seen in lung tumours, especially in small cell carcinomas and adenocarcinomas, are: hypercalcemia, inappropriate ADH secretion, hyponatremia, ectopic Cushing's syndrome, carcinoid syndrome, hypoglycemia. This is a rare and interesting case that required a multidisciplinary approach and illustrated the importance of correlating laboratory with imaging and histology,

E-PS-08-002

Reclassification of papillary microcarcinoma (PMC) according to the "Porto proposal" criteria

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Background & objectives: PMC is a variant of papillary carcinoma that measures≤1cm with an excellent prognosis.Recently, a proposal has been advanced to use the designation of papillary mirotumour (pMT) for PMCs with no risk factors. In this study, we aimed to reclassify pMCs according to the Porto-proposal (Pp)criteria.
Methods: We have retrospectively collected 29 cases of PMC diagnosed in our pathology department (2012-2022). Clinical and pathological parameters have been retrieved from pathological reports. They included: age, sex, discovery circumstance, location, size, subtype, presence of psammomas, presence of tumour capsule, tumour capsule invasion, angioinvasion, extension to thyroid pseudo-capsule, multifocality, other concurrent thyroid pathology and state of the patient. We have evaluated and reclassified all cases following the Pp. We have briefly compared the clinical outcomes in both groups.
Results: Mean age of patients was 46, 6-years-old (17-67) with a female predominance (sex ratio=2,2) .23 cases of PMC were incidentally discovered during lobectomy for benign conditions (9 cases), for PC of the ipsilateral or contralateral lobe (14 cases). In 6 cases, TIRADSV-thyroid nodule was discovered during ultrasound-imaging. The mean size of the tumour was 5,2mm. Multifocality was observed in 5 cases. The histological variant was follicular(25cases), conventional papillary(3cases) and tall cell (one case). A tumour capsule was present in 7cases and showed features of invasion in 4cases.Minimal thyroid

capsule invasion was found in 5 cases. In one case, vascular invasion was reported. A total of 17cases could be classified as pMT according to the Pp. One patient developed pulmonary metastasis and local recurrence.
Conclusion: Although the use of the term of pMT could reduce the psychological stress among patients and clinicians, it doesn't seem to be of high interest in cases of concurrent ipsi or contralteral invasive papillary carcinoma since the patient's prognosis is that of the invasive tumour. Further studies with large sample size and molecular analysis are also needed in order to definitively validate and generalize the use of Porto proposal.

E-PS-08-004
Utility of intraoperative frozen section analysis on Bethesda category III-IV-V thyroid nodules and the effect of concurrent imprint cytology
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Background & objectives: Bethesda category III-IV-V thyroid nodules represent therapeutic difficulty. This study aims to determine the utility of frozen section analysis (FS) on Bethesda category III-IV-V thyroid nodules and to investigate the effect of concurrent imprint cytology on diagnostic performance of FS.
Methods: FS results and final diagnostic reports of all patients with Bethesda category III-IV-V nodule who underwent partial thyroidectomy or nodule resection with FS were scanned from hospital electronical database. Demographic information, size of the nodule and presence of concurrent imprint cytology were noted.
Results: There were 81 patients fulfilling the criteria, with mean age of 43,5 years, female/male ratio of 3,2:1 and mean nodule size of 21 mm. In 20 cases, concurrent imprint cytology was performed and evaluated during FS. The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FS was 71,4%, 95%, 83,3% and 90,4%, respectively, with a diagnostic accuracy of 88,8%. When cases were separated as those with and without concurrent imprint cytology; sensitivity, specificity, PPV and NPV of FS with imprint cytology were 80%, 93,3%, 80% and 93,3%, respectively. For FS without imprint cytology; sensitivity, specificity, PPV and NPV were 68,7%, 95%, 83,3% and 90,4%, respectively.
Conclusion: Bethesda category III-IV-V nodules have variable rates of malignancy and low concordance among pathologists, which causes difficulties in follow-up and treatment decisions. Use of FS is thought as a way to eliminate these difficulties. Overall, FS has low sensitivity for detecting malignancy in Bethesda category III-IV-V nodules. However, concurrent imprint cytology could help to increase the ability of FS to correctly identify malignancy. Larger studies regarding this aspect are needed.

E-PS-08-006
Update regarding the role of PD-L1 in oncocytic thyroid lesions on cytological samples
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Background & objectives: Few articles demonstrated a correlation between PD-L1 and papillary thyroid carcinoma (PTC) on thyroid fine needle aspiration cytology (FNAC). Its role in oncocytic thyroid lesions remains controversial, therefore we examined PD-L1 immunostaining in liquid-based cytology (LBC) of these lesions.
Methods: From January 2019 to March 2021, 114 thyroid lesions diagnosed by FNAC as lesions with a predominant oncocytic component, were evaluated with PD-L1 immunostaining on both LBC and histology samples. FNAC cohort included 51 benign (B, negative controls), 4 Atypia of undetermined significance/Follicular lesions of undetermined significance (AUS/FLUS), 57 follicular lesions (FN/SFN), and 2 suspicious for malignancy (SFM) cases.
Results: Fifty-four cases (11B, 2 AUS/FLUS, 39 FN/SFN and 2 SFM) had histological follow-up: 1B case resulted as an oxyphilic nodule in Hashimoto Thyroiditis (HT), 10 B as goiters, 2 AUS/FLUSs as oncocytic adenomas (OAs); 39 FN/SFNs included 27 OAs, 4 FA, and 8 oncocytic carcinoma (OC). The 2 SFMs were diagnosed as OAs. Increased plasma membrane and cytoplasmic PD-L1 expression were found in 47 LBC cases (41.2%). Among the histological series, 67.3% of OAs and 75 % of OC had PD-L1 expression, whilst negative PD-L1 was found in oncocytic cells in HT. A positivity in >30% of the neoplastic cells was found in 72.9% of the cases including six OC.
Conclusion: These data suggest that PD-L1 is expressed in oncocytic thyroid lesions. While weak PD-L1 expression failed to discriminate benign from malignant lesions, OC demonstrated more intense cytoplasmic and membranous expression.

E-PS-08-007
Papillary carcinoma of thyroid gland with CA 19-9 positivity. A case report
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Background & objectives: Elevated levels of carbohydrate antigen 19-9 (CA 19-9), serologically and immunohistochemically, usually present with worse outcome and prognosis, especially in malignant cases. Usually, elevated levels of CA 19-9 have been associated mainly with malignancy and with medullary thyroid carcinomas.
Methods: A 74-year-old female patient, presented with multiple suspicious thyroid nodules measuring 0.5-6 cm, in both lobes. Microscopically the nodules were multiple foci of papillary carcinoma, sclerotic and oxyphil type, with severe perithyroidal extension, necrosis, perineural infiltration and calcifications. Two lymph nodes had metastases from the carcinoma.
Results: Serological exams showed that the patient had increased levels of CA 19-9, thus indicating related immunohistochemical expression on the lesion. On IHC, it was confirmed a diffuse and widespread stain of CA 19-9 was confirmed. The lesions were also developed on the background of severe autoimmune thyroiditis.
Conclusion: CA 19-9 might be of importance in predicting the prognostic outcome of a thyroid lesion, either benign (e.g., thyroiditis, Hashimoto thyroiditis and Graves disease) or malignant (e.g., papillary carcinoma). More specifically, increased expression of this antibody has been shown to demonstrate higher mortality rate than the control group. Some studies have correlated this phenotype with the tumour size, multifocality, local and distant metastasis and also RET mutation.

E-PS-08-008
Clinico-morphologic characteristics of thyroid cancer with follicular morphology

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Background & objectives: Thyroid carcinomas are the most common endocrine tumours malignancies. Follicular thyroid carcinoma (FTC) and Hurthle (oncocytic) cell carcinoma (HCC) accounts for 15% of cases. The aim of this study was to identify the differences between the two entities.
Methods: The retrospective study comprised 56 consecutive cases of FTC (40 cases) and HCC (16 cases) was investigated during 2007-2020. All cases were reviewed by three independent pathologists in order to establish the histological variant and to reassess the main characteristics. Statistical correlations between FTC and HCC and various clinicopathological parameters were also performed.
Results: FTC presented: age (mean 52); female 75%; size 8-93 mm; minimally invasive (33 cases), widely invasive (5 cases), encapsulated angioinvasive (2 cases); collision tumour (8 cases); capsule invasion (13 cases); extrathyroidal extension (4 cases); lymph node metastasis (2 cases), lymphovascular invasion (30 cases), relapse (1 case); tumour stage T2-T4 (34 cases). HCC presented: age (mean 57); female 87.50%; size 21-80 mm; collision tumour (3 cases); capsule invasion (2 cases); extrathyroidal extension (1 case); lymph node metastasis (2 cases); lymphovascular invasion (15 cases); tumour stage T2-T4 (13 cases). All cases presented unilateral involvement and associated thyroid pathology. Significant differences were noted between FTC and HCC only with lymphovascular invasion (p= 0.038).
Conclusion: In thyroid carcinoma with follicular architecture, FTC versus HCC, parameter of aggression determined only by lymphvascular invasion, date obtained with statistically significant differences (p=0.038), in relation to the other classical clinicopathological features. As evidenced by the cases we present, HCC are tumours with aggressive clinical behaviour and high metastasis potential, compering to FTC.

E-PS-08-009

Poorly differentiated thyroid carcinoma, an unusual tumour in young patients. Report of two cases

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Background & objectives: Poorly differentiated thyroid cancer (PDTC) is a rare aggressive thyroid malignancy with a unique feature in morphology and behaviour. In young individuals it is a very unusual observation and its clinical feature, genetic mechanism and outcome is poorly understood.
Methods: In this study we report two cases of PDTC in a 31- and 34-year-old patients. Both patients were admitted to the surgical department of Mures County Emergency Hospital with a Bethesda 5, suspicious for malignancy thyroid cytology. A total thyroidectomy was performed and the specimens were analysed in the Pathology Department.
Results: On microscopic examination both tumours were encapsulated and had an insular, trabecular and/or solid tumour growth. One of the tumours, of 54 mm, had angioinvasion. Both cases met the Turin criteria for PDTC diagnosis: tumour cells were small, monotonous, with few cytoplasm and convoluted nuclei. Both tumours displayed necrosis and more than 5 mitoses per 10 HPF. No features of differentiated thyroid carcinoma were noticed. In one of the tumour, intermingled with the monotonous cells, pleomorphic giant tumour cells with bizarre features were noticed. In immunohistochemistry these cells expressed Cytokeratin, Thyroglobulin, TTF-1 and PAX 8, proving their follicular origin, and also their non-anaplastic character.
Conclusion: We should always keep in mind that PDTC may occur in young individuals. Its association with pleomorphic tumour giant cells do not always represent tumour dedifferentiation. As PDTC accounts for most fatalities from non-anaplastic thyroid cancers, a correct diagnosis is important for clinicians and oncologists to predict the prognosis.

E-PS-08-010

Pituitary neuroendocrine tumours and non-neoplastic adenohypophysis arising in ovarian teratomas: a likely under-recognised phenomenon

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Background & objectives: Recently, our group has identified and comprehensively characterized both non-neoplastic adenohypophysis and pituitary neuroendocrine tumours (PitNETs) occurring in ovarian teratomas. Our objective is to highlight the role of histochemical and immunohistochemical tools in recognizing and properly classifying these proliferations.
Methods: PitNETs and non-neoplastic adenohypophysis arising in ovarian teratomas were identified from our institutional records. Adenohypophyseal tissues were assessed using reticulin histochemistry and immunohistochemical biomarkers (pituitary transcription factors including PIT1, TPIT, SF1, ER-alpha, GATA3, adenohypophyseal hormones, alpha-subunit, CAM5.2, S100 and MIB1). All included cases were reviewed by both endocrine and gynecologic pathologists. Demographic and clinicopathologic information was recorded for each case.
Results: One of five teratomas was immature. Three PitNETs and two non-tumorous adenohypophyseal proliferations were identified (median patient age 26 years; range 16-67). The PitNETs were all of PIT1-lineage: 2 sparsely granulated lactotroph tumours (0.15 and 0.4 cm) and 1 mixed sparsely granulated lactotroph and densely granulated somatotroph tumour (0.15 cm). The MIB1 labelling index (LI) ranged from < 1% to 1.5%. Unlike the PitNETs, the two cases of non-tumourous adenohypophysis were composed of admixed PIT1, TPIT and SF1-lineage cells with a MIB1 LI < 1%, demonstrated interspersed S100-positive folliculostellate cells and showed no reticulin disruption.
Conclusion: Both non-neoplastic adenohypophysis and PitNETs occur in ovarian teratomas and may be mistaken for other neuroendocrine neoplasms. Reticulin histochemistry and immunohistochemical biomarkers are required to confirm adenohypophyseal cell origin, distinguish nontumourous elements from PitNETs, and subtype and prognosticate PitNETs, if applicable. Further epidemiological studies are needed to determine the prevalence of PitNETs and non-tumourous adenohypophysis in ovarian teratomas.

E-PS-08-011

Poorly differentiated thyroid carcinoma associated with pleomorphic tumour giant cells: report of a challenging case

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Background & objectives: Poorly differentiated thyroid carcinoma (PDTC) is a rare tumour type originating in the thyroid follicular cells. The presence of pleomorphic tumour giant cells in PDTC is always worrisome for the pathologist as they usually refer to anaplastic carcinoma.
Methods: We report the case of a 31-year-old female admitted to the hospital for a right thyroid macronodule, suspicion for follicular neoplasm in cytology. Total thyroidectomy was performed and the specimen was sent to the Pathology Department.
Results: On macroscopy, the left right lobe was almost entirely replaced by a whitish nodule of 54 mm. On microscopy, the nodule was surrounded by an irregular capsule, with suspicion of vascular invasion. The nodule was solid with large tumour nests/islands, separated by thin, fibrous septa. Small foci of endocrine-type necrosis were also present. The tumour was composed of monotonous tumour cells, with round-ovalar centrally placed nuclei, with prominent nucleoli. But focally pleomorphic giant cells with an abundant eosinophilic cytoplasm and large, irregular, sometimes frankly monstrous nuclei were seen. The mitotic index was 6 mitosis/10HPF. On immunohistochemistry the tumour cells and the pleomorphic giant cells expressed both thyroglobulin and TTF-1.
Conclusion: The immunohistochemical profile of the pleomorphic giant cells indicates not only their follicular origin but above all their differentiated nature. This case shows that pleomorphic tumour giant cells arising in PDTC do not always represent dedifferentiation and progression to anaplastic carcinoma. Distinction among these processes is critical as their treatment and prognosis are very different.

E-PS-08-012
Gamna-Gandy bodies: a rare finding in a papillary thyroid carcinoma
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Background & objectives: Gamna-Gandy bodies (GGB) are fibrous tissue coated by iron and calcium with unusual articulated and bamboo-like fibres. GGB are currently thought to be caused by minor haemorrhages, mostly in spleen and atrial myxomas, rarely reported in other locations.
Methods: A 46-year-old woman displaying multinodular goiter and primary hyperparathyroidism, underwent total thyroidectomy and parathyroidectomy. Gross and histological examination were performed, including additional histochemical techniques – Perls and Von Kossa (VK) stains.
Results: We report a case of a multifocal Papillary Thyroid Carcinoma (PTC), measuring 32mm in its largest dimension, in a background of a nodular hyperplasia. Sclerotic areas with mycelia-like appearance were found within the PTC. Perls and VK highlighted the iron and calcium encrusted fibres, compatible with GGB. So far, only rare cases of thyroid GGB have been reported, all of them associated with follicular adenomas and nodular hyperplasia, none associated with PTC. It is unknown if the coexistence of nodular hyperplasia has contributed to GGB formation in this case. The patient underwent radioiodine ablation and is alive with no evidence of disease 17 months after the surgery.
Conclusion: Knowing that the thyroid is a richly vascularized organ and that the haemorrhage process is the origin of GGB formation, it would be expected more cases of thyroidal GGB. Perhaps a low interest in GGB justifies the scarcity of this entity. With this case we intend to underline the importance of reporting GGB and carry out the review of cases of neoplasms associated with GGB, especially in thyroid, in an attempt to clarify their meaning and potential impact.

E-PS-08-013
Papillary thyroid microcarcinoma - tall cell variant arising in mature cystic teratoma of the ovary - a case report
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Background & objectives: Presence of malignancies in somatic parts of mature cystic teratoma (MCT) of the ovary is rare. We present a case of tall cell variant (TCV) of papillary thyroid microcarcinoma (PMC) arising in MCT of the ovary.
Methods: A 31-year-old female patient presented with a left ovarian cyst which on ultrasound scan showed measured 5.0 × 5.0 cm and was likely MCT. Laparotomy with cystectomy was performed. Grossly, it was an intact unilocular cyst with smooth surface, filled with tufts of hair and sebum (0.1 cm thick) with only small thickened area (1.0 x 0.8 x 0.6 cm).
Results: Microscopically, the cyst wall was lined by stratified squamous epithelium and contained mature tissues (skin, appendages, respiratory epithelium, cartilage and thyroid tissue). In the thickened area, there was a small focus of thyroid tissue; within which PMC (0.6 cm) was noted, composed of trabeculae and follicles of tall cells.
Diagnosis: PMC-TCV, arising from a small focus of thyroid tissue in MCT with maximum tumour size of 0.6 cm. The patient underwent US scan of the thyroid gland and computed tomography scan of the neck and chest with no clinical evidence of tumour metastasis. The patient has been on follow-up with for 4 years post-surgery with uneventful recurrence-free clinical course.
Conclusion: Our case is a PMC diagnosed in a small focus of thyroid tissue within MCT (not meeting diagnostic criteria for struma ovarii), different from two previously reported cases of PTC in struma ovarii. To our knowledge, this is the first case of PMC-TCV arising in MCT with conservative surgery. Such treatment modality may be an alternative to previously suggested more radical options. However, standardization of treatment protocols requires immediate reporting of secondary malignancies in MCTs and referral to large databases.

E-PS-08-014
Core-needle biopsy in the diagnosis of thyroid lesions - risky or diagnostically helpful?
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Background & objectives: Diagnosis of thyroid tumours is routinely based on an ultrasound guided fine needle aspiration biopsy (FNAB). In some cases, however, FNAB fails and CNB may be an alternative diagnostic tool.
Methods: The study was conducted over a period of 4 years, 2019-2022. Twenty-seven patients with thyroid tumours larger than 2cm, suspicion of malignancy and insufficient repeated FNAB, underwent CNBs of the thyroid at NIO-PIB in Warsaw.
Results: Diagnostic material was obtained in 24 patients, in remaining 3 cases CNB was performed twice to obtain material sufficient for microscopic examination, immunohistochemical and molecular tests (NGS). For one patient with suspicious Hodgkin lymphoma the final diagnosis required a surgical biopsy of the lymph node. There were 5 anaplastic carcinomas, 2 poorly differentiated carcinomas, 1 medullary carcinoma, 1 PTC, 5 metastatic carcinomas (2 SCC, RCC, HCC, mucoepidermoid carcinoma) 3

lymphomas, 5 follicular tumours, 1 sarcoma, 1 NUT carcinoma (with NSD3-NUTM1 fusion), 1 deep fibrohistiocytoma, 2 inflammatory lesions. Hematoma at the biopsy site was observed in two patients and the cancer cells seeding along the needle tract in one patient.
Conclusion: CNB of the thyroid lesions according to strictly defined indications in a hospital setting allows a confident diagnosis with a low risk of complications in cases of failure of a FNAB. This method can be particularly useful for the diagnosis of anaplastic/poorly differentiated and metastatic carcinomas.

E-PS-08-015
Predominantly necrotic but follicle-preserving pattern of a rectal cancer metastasis causing misinterpretation of cytological image from fine-needle aspiration biopsy of a thyroid tumour
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Background & objectives: Metastases to thyroid are uncommon, accounting for 1,4-3% of thyroid neoplasms. In a 68-year-old woman with rectal cancer in stage T3bN2Mx a PET/CT scan revealed a thyroid tumour in the right lobe, suggestive of a synchronous neoplasm with nodal metastases.
Methods: The ultrasound suggested a malignant tumour (22x18x30 mm; EU-TIRADS 5). FNAB showed numerous sheets of atypical epithelial cells without obvious differentiation in an abundant necrotic debris. PAX-8 positivity in a few cells was interpreted as confirming thyroid origin of the lesion. Anaplastic thyroid carcinoma, TBS VI was reported. A similar cytological picture was seen in FNABs from neck lymph nodes.
Results: Total thyroidectomy with lateral neck dissection was performed. On HE slides the tumour presented evidently glandular, with large, centrally necrotic cribriform and smaller tubular structures, as well as less differentiated single cells in a desmoplastic stroma, with normal thyroid follicles preserved in between. Necrosis constituted about 70% of the tumour. The tumour cells were positive for: CDX-2, SATB2 and CK20, and negative for TG, TTF-1 and PAX-8, with Ki67 index about 60%. There was angioinvasion and extrathyroidal extension with R1 margins, and additional small metastatic foci found in the left lobe and isthmus. There were also numerous and large metastases in the central neck compartment and right neck lymph nodes.
Conclusion: Differential diagnosis of high grade tumours can be challenging in cytology specimens. Positivity for PAX-8 in some cells should not result in prompt diagnosis of a lesion of thyroid origin, as follicular cells might be admixed to the cells of the metastasis depending on the pattern of the metastatic tumour growth. In the presented case of a rectal cancer metastasis, two contrasting elements led to an erroneous interpretation of the cytology image: abundant necrosis and preservation of some follicular structures.

E-PS-08-016
Epithelioid angiosarcoma of the adrenal gland: a rare case report
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Background & objectives: Angiosarcomas are aggressive malignant tumours originating from the blood and lymphatic vessel endothelium. It accounts for approximately 1% of all sarcomas. Although they are mostly seen in the skin and soft tissue, they rarely present with organ involvement.
Methods: We report on a 72-year-old man with an epitheloid angiosarcoma of the left adrenal gland. The patient had undergone cardiac bypass surgery for coronary artery disease and had chronic obstructive pulmonary disease. In routine screenings,a cystic bleeding mass with a diameter of 11cm was detected in the left adrenal gland in computed tomography.Clinically,the non-functional mass was evaluated as adrenal insidentheloma and operated.
Results: Histologically, the tumour is a vascular tumour consisting of epithelioid cells with vesicular nuclei and prominent nucleoli that occupies irregular vascular spaces and also forms solid areas, showing pleomorphism, necrosis, and viable mitotic activity. Immunohistochemical stain that revealed positive reactivity for cytokeratin, CD31, ERG, FLI-1. The case was diagnosed with primary adrenal epithelioid angiosarcoma, as there was only a lesion in the adrenal gland in the clinically and radiologically examinations. The differential diagnosis includes malignant vascular tumour, melanoma, poorly differentiated carcinoma, clear cell sarcoma, epithelioid sarcoma, and anaplastic large cell lymphoma.
Conclusion: Epithelioid angiosarcoma is a highly aggressive endothelial cell malignancy. Although it often occurs in deep soft tissue, it has been reported that it can occur in various tissues such as adrenal, thyroid, skin and bone. Early diagnosis of these tumours due to their aggressive behaviour is important for treatment and prognosis. Therefore, we aimed to present our case, which requires careful evaluation of histomorphological immunohistochemical examinations in the diagnosis due to its unusual location.

E-PS-08-017
Micromorphometric parameters of the adrenal cortex of rats under conditions of constant lighting and chronic alcohol intoxication
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Background & objectives: Excessive light exposure and chronic alcohol intoxication are characterized by the development of morphological changes in the adrenal glands. We examined the influence of constant lighting, chronic alcohol intoxication and their joint action on micromorphometric parameters of rat adrenal cortex.
Methods: The study was conducted on 160 male Wistar rats, which were divided into 4 groups and were kept for 3 weeks: control and I group – under fixed light regime, II and III group – under constant light regime, but I and III group received a 15-% water solution of ethanol. The width of the adrenal cortex zones was conducted.
Results: It was found that in animals of II group there was a decrease in the width of the cortex compared with the control, mainly due to the fascicular and reticular zones. In animals of I and III groups, an increase in the width of all zones of the cortex was observed, and in III group the increase in the glomerular and reticular zones was more pronounced than in animals of group I.
Conclusion: The conducted study indicates that constant illumination leads to a decrease in the thickness of the adrenal cortex, and the effect of ethanol, both separate and combined with constant illumination, leads to an increase in the width of the adrenal cortex.

E-PS-08-018
Anaplastic thyroid carcinoma: a 12-year observational retrospective study

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Background & objectives: Anaplastic thyroid carcinoma (ATC) is the most aggressive form of thyroid cancer, arising from the thyroid follicular cells. It accounts for the majority of deaths from thyroid carcinoma. This study aimed to evaluate the clinico-pathological and immunohistochemical features of ATC.
Methods: A retrospective-observational study was conducted over a 12-year period, between June 2009 and June 2021, including all patients diagnosed with ATC at the Emergency County Hospital from Timisoara. Medical records and histopathological features of tumour fragments, lobectomy and thyroidectomy specimens were analysed for all patients, as well as immunohistochemical markers (CK AE1/AE3, p53, Vimentin, Thyroglobulin, TTF-1, Ki-67) in some cases.
Results: Twenty-one patients were diagnosed with ATC. The average age at diagnosis was 70 years, and the female-to-male ratio was 9.5:1. On gross examination, the tumour was solid and partially encapsulated (57%), unencapsulated (19%) or not specified; the average maximal dimension was 5.5 cm. Histologically, all ATCs were hypercellular, with spindle or squamoid cells, marked nuclear pleomorphism, high mitotic activity and tumour necrosis. The growth pattern was infiltrative, with extrathyroidal extension (62%), lymphovascular (71%) and perineural (43%) invasion. Twelve cases associated foci of differentiated thyroid carcinoma. Immunohistochemically, ATC expressed heterogenous positivity for CK AE1/AE3, p53, Vimentin; absent or weak expression for Thyroglobulin and TTF-1; mean Ki-67 index was greater than 60%.
Conclusion: In our study, ATC affected older women more common. Most cases were diagnosed in the advanced form, with aggressive morphological features and loss of thyroid differentiation, which makes the diagnosis more challenging for pathologists as well as for clinicians. Due to the frequent association of foci of well-differentiated papillary or follicular thyroid carcinoma, ATC could represent a gradually dedifferentiation of pre-existing well-differentiated thyroid carcinomas. Recognition of these features is crucial for the therapeutic management of patients with anaplastic thyroid carcinoma.

E-PS-08-019

Lipoadenoma of the thyroid with bizarre nuclei and signet-ring cells: a case report

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Background & objectives: Variants of follicular adenomas include lipoadenoma, follicular adenoma with bizarre nuclei and signet-ring cell follicular adenoma. We report an exceptional case of lipoadenoma with bizarre nuclei and signet-ring cells and emphasize on pathological, immunohistochemical and molecular characteristics.
Methods: A 78-year-old woman presented with a left thyroidal nodule measuring 31 x 20 mm. It was classified EUTIRADS 5 on ultrasonography. Fine needle aspiration showed sheets of tridimensional cells with hyperchromatic nuclei. Cytology was reported malignant Bethesda VI suggesting poorly differentiated carcinoma. The patient underwent total thyroidectomy and lymph node dissection.
Results: Microscopically, the tumour presented micro-follicular and trabecular architecture with mixed adipose tissue. There were signet-ring cells associated to extracellular mucin. There were no vascular invasion and the tumour was well limited. Tumour cells had sparse marked anisokaryosis. Mitosis were rare (1/2mm²). Cells expressed TTF1, PAX8 and thyroglobulin. Adipose cells expressed PS100. Proliferative KI67 index was estimated to 1%. There were no expression of thyrocalcitonin, ACE, BRAF, Mammaglobin, GCDFP15, GATA3, TRK and SOX10. RNA sequencing detected an oncogenic PPARG-PAX8 fusion. Definitive diagnosis was bizarre nuclei lipoadenoma associating signet-ring cell. Lymph nodes were negative. The last follow up was in March 2022 and the patient had no evidence of recurrent disease.
Conclusion: This is the first case report of lipoadenoma with bizarre nuclei and signet-ring cells. The presence of bizarre nuclei and signet ring cells may lead to a misdiagnosis in cytology. The integrative pathology of morphology and immunohistochemical features led to the actual diagnosis.

E-PS-08-020

Adrenal "Pseudo-oncocytic?" "Rhabdoid?" pheochromocytoma in a male suffering from Li-Fraumeni syndrome: What is it? A case report

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Background & objectives: A rare variant of phaechromocytoma, 'oncocytic variant', has been described only 6 times in literature. It has relatively high malignant potential. However, 'Pseudo-oncocytic/ Rhabdoid' morphology/variant has never been described. Here we present case seen in pateint of Li-Fraumeni syndrome for discussion.
Methods: Clinical examination, blood investigations, computed tomography (CT) scan, I-metaiodobenzylguanidine (123I-MIBG) scintigraphy and surgery were performed. Macroscopy, microscopy (conventional hematoxylin and eosin staining and immunohistochemistry) and transmission electron microscopy(TEM) were performed. The Pheochromocytoma of the Adrenal gland Scaled Score (PASS score) was used to evaluate the malignant potential of the tumour.
Results: A 33-year-old patient, known with Li-Fraumeni syndrome had a right-sided adrenal mass found on CT in 2019. With a clinical diagnosis of pheochomocytoma, surgery was performed. Histology showed a pheochromocytoma, morphologically having oncocytic features but without increased number of mitochondria confirmed by Prohibitin immunohistochemistry and TEM, indicating a pseudo-oncocytic subtype. The cells could also be interpreted as 'rhabdoid'. Unfortunately, the final conclusion could not be taken about the variant, but more arrows are pointing to a pseudooncocytic type.
Conclusion: So far in literature 'Pseudooncocytic/Rhabdoid' subtype has never, to our knowledge, been described. Presence of Li Fraumeni syndrome makes this more special, however the exact incidence and nature of this variant is unknown. For that matter, actual 'Oncocytic variant' is also not clearly known because of paucity of cases. Therefore, further explorations are needed to label this variant and to contemplate its existence, if any.

E-PS-08-021

What is the name of this tumour: malignant thyroid teratoma or thyroblastoma?

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Background & objectives: Thyroid teratomas are extremely rare neoplasms mostly presenting in newborns and their grading is based on the quantity of immature neuroectodermal tissue. Thyroblastoma is a recently described embryonal neoplasm of adults resembling thyroid parenchyma within the first intrauterine trimester.
Methods: A 18-day-old female was delivered by a cesarean section at 36th gestational week due to ultrasonographically detected pleural effusion. At the time of birth, a palpable mass was observed in the neck. Computerized tomography revealed a neck mass, within the thyroid tissue. The patient underwent a left thyroid lobectomy after a FNAB diagnosis of an "immature teratoma".
Results: On H&E, thyroid was almost completely replaced by the tumour. Pseudostratified ciliated columnar, intestinal and squamous epithelium; smooth/striated muscle, adipous tissue, mature cartilage, neuroglial elements and immature neuroectodermal component (INEC) were present. TTF-1/PAX8 confirmed the presence of mature residual thyroid tissue around the tumour. GFAP was positive in the INEC and the glial tissues. B-HCG, CD30, Glypican3 and OCT3/4 were negative. Ki67 index was 70% in the INEC, which occupied 10 low-power fields (LPFs). It was diagnosed as a "malignant teratoma" (grade 3) according to 2017 WHO Classification of Endocrine Tumours which recommends grading tumours with more than 4 LPFs of INEC, mitoses, and/or pleomorphism as grade 3/malignant teratoma.
Conclusion: The last (2022) WHO Classification of Endocrine & Neuroendocrine Tumours states that thyroid tumours with more than 4 LPFs of INEC should be reclassified as thyroblastoma. However, thyroblastoma is defined as a tumour composed of foetal-type primitive-appearing thyroid follicles, and primitive spindle cells arranged into fascicles which are absent in this tumour. We want to emphasize that there are very rare thyroid tumours that are unaware of the fact that the WHO classification has changed.

E-PS-08-022
Next generation sequencing in follicular cell-derived thyroid carcinomas with poor prognosis
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Background & objectives: Despite the good overall prognosis, some thyroid cancer types may show unfavourable evolution (UE). Our objective is to determine the frequency and type of genetic alterations that can provide prognostic and therapeutic information in a series of cases with UE.
Methods: Retrospective observational study. Subjects: patients with differentiated thyroid cancer with unfavourable evolution, poorly differentiated and anaplastic carcinomas, treated at our institution between 2001 and 2019, both inclusive. Methodology: case identification, extraction of DNA, PCR, library preparation, purification and massive sequencing of optimal samples using AmpliSeq Focus Panel, AmpliSeq Library PLUS on MiSeq sequencer (illumina), bioinformatics analysis on Variant Interpreter (illumina).
Results: Seventeen cases with optimal samples could be studied: 3 papillary carcinomas (PTC) and 2 follicular carcinomas (FTC) with UE, 5 poorly differentiated carcinomas (PDTC), three of them with UE, 3 anaplastic carcinomas (ATC), all of them with UE, 1 PTC with a minor component of PDTC and good evolution, 1 PTC with a minor component of ATC and UE, and 2 PDTC with a minor component of FTC and UE. Ten cases had pathogenic/variant of unknown significance point mutations: 5 in NRAS (3 p.Gln61Arg and 2 p.Gln61Lys), 2 in BRAF (p.Val600Glu), 1 in EGFR (p.Arg297Cys), 1 in BRAF (p.Val600Glu) and PIK3CA (p.Glu545Lys), and 1 in NRAS (p.Gln61Arg) and BRAF (p.Asp594Asn).
Conclusion: Massive sequencing has provided information about pathogenic or variants of unknown significance mutations in 10 of the 17 cases studied, although in 7 of them the alterations detected could have been identified by simpler and cheaper methods, as they correspond to NRAS mutations and BRAF V600E mutation. In two cases more than one mutation could be detected. The meaning and clinical implications of these concomitant mutations need further investigation.
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E-PS-08-023
Adrenal gland composite pheochromocytoma – ganglioneuroma: a case report
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Background & objectives: Composite pheochromocytoma of the adrenal medulla is a rare neuroendocrine tumour that represents the 1-9% of pheochromocytomas. Little is known about its biologic potential, as only seventy cases have been reported previously in the literature.
Methods: We describe a case of adrenal composite pheochromocytoma -ganglioneuroma in a 66-year-old female patient. After surgery, the right adrenal gland specimen was processed and examined by standard H&E technique and immunohistochemistry. Cut surface showed a grey - brown lesion measuring 4 cm.
Results: Histologically, the tumour was composed of two distinct patterns. One pattern was composed of polygonal cells arranged in well-defined nests surrounded by a delicate fibrovascular stroma consistent with pheochromocytoma. The other pattern consisted of ganglion cells embedded in a schwannian stroma which was consistent with ganglioneuroma. Both components were positive for Chromogranin A and Synaptophysin but with variable intensities. Ganglion cells within the ganglioneuroma component and sustentacular cells within the pheochromocytoma component were positive for S-100 protein. Melan A, p504s, AE1/AE3 και Inhibin were negative. The mitotic index was <5%.
Conclusion: The frequency of composite adrenal-pheochromocytoma tumours has been reported as ranging from less than 3% of all adrenal gland neoplasms. They are treated in principle by complete surgical resection. An adequate clinical follow-up is advised for the potentially malignant neoplasms. It is difficult to predict the clinical behaviour. There are no absolute criteria for malignancy. However, features more frequently noted in malignant tumours are the presence of necrosis, vascular invasion and/or extensive local invasion, cytological atypia and high mitotic index.

E-PS-08-024
Papillary thyroid microcarcinoma: characteristics at presentation and evaluation of recurrence histological features
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Background & objectives: Papillary thyroid microcarcinoma (PTMC) is defined as a thyroid tumour measuring 1 cm or less and it usually

has an indolent course. This study aims to describe its epidemiological, histologic characteristics and to provide data on outcome after surgery.
Methods: We retrospectively analysed 31 consecutive patients with PTMC who underwent surgery at our institution between 2012 and 2021; 27 of them (87% of cases) were treated also with radioiodine therapy and followed for at least 1 year. The data on patients gender, age, morphological characteristics, extent of disease, therapy, locoregional and distant control were collected.
Results: There were 26 women and 5 men. The mean age was 53.5. Most of the PTMCs were diagnosed incidentally during pathologic examination. Median tumour size was 5.5 mm. 16% of PTMCs showed multifocality, with 3 cases of unilateral multifocal lesions and 2 cases with bilateral multifocal tumours. TNM stages were I in 30 patients (96.77%) and III in one patient (3.2%). A total of 18 cases (58%) had regional lymph node sampling and 3 of them were metastatic (9%). 25 patients (80.64%) underwent bilateral lobar resection. During the follow-up period, the recurrence was diagnosed in only 1 patient (locoregional recurrence one year later). There were no PTMC related deaths.
Conclusion: The prognosis for patients with papillary thyroid microcarcinoma in this serie was excellent, with a 100% survival rate and and a low rate of recurrence associated with PTMC. Nevertheless, approximately 3% of patients developed recurrent disease; aggressive treatment may be justified depending on the presence or absence of prognostic risk factors.

E-PS-08-025
Reliability of frozen section thyroid examination: through a series of 536 cases
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Background & objectives: Frozen section examination (FSE) of thyroid nodules is an essential step in guiding surgical procedures and aiming for optimal patient management.
The purpose of this study was to evaluate the reliability of FS according to definite histologic examination.
Methods: This was a retrospective study conducted on 536 thyroid resection specimens sent for FSE over a 4-year period. FSE's results were compared to the final microscopic examination (FME),. The diagnostic value of FSE was evaluated by calculating sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV). Delayed results were excluded from statistical analysis.
Results: The population included 452 women and 84 men (average age: 49.9 years). The 536 FS were benign in 284 cases (53%), malignant in 60 cases (11.2%) and the response was delayed in 192 cases (35.8%). The FME showed that among the 284 nodules considered benign, 224 were truly benign and 60 were malignant. Among the 60 malignant, 56 were carcinomas: papillary (52), vesicular(3) and undifferentiated(1) and 4 were benign. The delayed results were benign in 76 cases, malignant in 112 cases and lesions of uncertain malignancy in 4 cases. The Sp was 98.3% with a PPV of 93.3% and the Se was 48.3% with a NPV of 78.9%.
Conclusion: FSE is very reliable with a Sp approaching 100%. The rate of thyroid carcinomas reported varies from 4.5 to 26.3%, depending on the series. In our study, it was 11.2%. Most of series showed false positivity (FP) between 0.1 to 0.6% and Sp between 50 to 92% which is comparable to our series, where we found FP in 0.7% and Sp in 98.3%. The low Se was related to encapsulated vesicular lesions, technical problems, nuclear artifacts and difficulty of microcarcinoma's identification.

E-PS-09 | E-Posters Gynaecological Pathology

E-PS-09-001
Squamous cell carcinoma of the ovary associated with endometriosis: a case report
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Background & objectives: To analyse the clinical, therapeutic and pathologic features of a primary squamous cell ovary carcinoma case associated with endometriosis. This is a rare entity that accounts less than 1% of primary ovarian malignant tumours.
Methods: 52 years old woman presented to gynecological consult for abnormal vaginal bleeding and lower abdominal pain. She had no history of malignancies or relevant diseases. Physical examination and imaging showed several uterine nodules consistent with myomas and a torsion of the right ovary with central necrosis. The patient underwent surgery, performing total hysterectomy with left salpinguectomy and right adnexectomy.
Results: On microscopic examination, moderately differentiated squamous cell carcinoma of the ovary was seen displaying a diffusely infiltrative pattern with abundant keratinization and extensive necrosis. The cells had pleomorphic nuclei with conspicuous nucleoli and ill defined citoplasmic borders. Central areas showed abundant keratin formation with some calcifications. Isolated glandular formations without atypia were observed in the ovarian cortex consistent with endometriosis. The ovary was entirely submitted and did not reveal other lesions like teratoma or Brenner tumour. Surgical staging was performed showing a peritoneal implant. The patient received paclitaxel, carboplatin and bevacizumab. At the moment, she is disease-free after 14 months of follow-up.
Conclusion: Squamous cell carcinoma of the ovary is an infrequent tumour with few cases reported in the literature. It has poor prognosis and in most cases arises from mature cystic teratoma with malignant transformation or less frequently shows association with endometriosis or Brenner tumour. The pure form is not related with any of the conditions mentioned before. Optimal debulking surgery and adjuvant chemotherapy seem to be the best treatment option in advanced disease but further studies are needed.

E-PS-09-002
Malignant transformation of ovarian mature teratoma: a 20-year experience of Tunisian centre
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Background & objectives: Mature teratoma is the most common tumour of ovary. It is usually a benign germ cell tumours. Malignant transformation is extremely rare. The objective of our study is to highlight the clinico-pathologic characteristic of malignant transformation of ovarian mature teratoma.
Methods: A total of 6 cases of mature teratoma with malignant transformation at the Department of Pathology and Gynaecology of Farhat Hached University Hospital in Sousse, over a period of 20 years (from 2000 to 2019). A review of clinical, paraclinical, pathological and evolutionary data was performed in all cases.
Results: The prevalence of mature teratoma with malignant transformation was 0.12%. The average age was 57.5 years. The main clinical presentation was abdominal pain. The main tumour size was 15.1 cm. 3 tumours were in the right, one case were in the left and 2 were bilateral. Abdominal sonography was an essential exam for the diagnosis. There were 3 squamous carcinoma, one melanoma, one intestinal type adenocarcinoma and one vesicular

thyroid carcinoma. The main survival time for 3 patients varied from 1to 8 months. The other patients were lost.
Conclusion: Mature teratoma with malignant transformation are rare aggressive tumours that mostly occurs in post-menopausal age. It is characterized by a late stage diagnosis and poor outcome. Treatment is based on surgery and radio-chemotherapy. Immunotherapy and target therapy has been recently introduced to reduce mortality. The overall goals of management are palliation of symptoms, preventing recurrence or spread of disease and preservation of fertility.

E-PS-09-003
Expression of autophagy markers in ovarian cancer
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Background & objectives: Autophagy is a crucial cellular mechanism that coordinates various physiological processes. Many cancers can activate autophagy and make the tumour more aggressive. In this study, we analysed autophagy in ovarian cancers.
Methods: We included 122 patients with ovarian cancers. Tissue microarray was made for immunohistochemical analysis of p62, LC3, and Beclin1 expressions. Their expressions were correlated with tumour histology type, differentiation, and stage. The percentage of positive tumour cells was estimated from the total number of tumour cells. Samples with positive cells were stratified into three ranges of positivity: <10%; 10–50%; >50%.
Results: There was a strong positive correlation between p62 and LC3 expression, while both markers were in negative correlation with Beclin1. The expression of each analysed marker showed a statistically significant association with tumour histological type, stage, and differentiation ($p<0.001$). While p62 and LC3 were more prominently expressed in patients with high-grade serous ovarian cancer (HGSOC), Beclin 1 expression was lower in HGSOC and more prominent in other histology types. A higher expression of p62 and LC3 was observed in later tumour stages, while the opposite was observed for Beclin1 expression. Tumour differentiation positively correlated with p62 and LC3 expression, and negatively with Beclin1 expression.
Conclusion: The expression of p62 and LC3 was more prominent in HGSOC in comparison to other histology types, while Beclin1 expression was more prominent in carcinomas other than in HGSOC. While p62 and LC3 expression was associated with higher tumour stages and tumour grades, the opposite was found for Beclin1. Prominent p62 and LC3 expression in combination with weak Beclin1 expression in HGSOC indicate the potential for application of autophagy inhibitors in patients with this tumour subtype.

E-PS-09-004
Expanding the spectrum of GLI1-activated mesenchymal tumours – a high-grade uterine sarcoma harbouring a novel PAMR1-GLI1 fusion
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Background & objectives: GLI1-activated mesenchymal tumours comprise a group of seemingly unrelated entities, including pericytoma with t(7;12) translocation, plexiform fibromyxoma, gastroblastoma, malignant epithelioid neoplasm with GLI1 rearrangements and GLI1-amplified mesenchymal neoplasms. Herein we report an unusual GLI1-rearranged uterine sarcoma.
Methods: Clinical history:
A 57-year-old female presented with an abdomino-pelvic mass. MRI showed a myometrial mass extending beyond the serosa, with features of peritoneal involvement. The patient underwent oncologic resection. Gross examination revealed a perforated multi-nodular uterine tumour (21cm) with a firm white and soft fleshy cut surface, featuring haemorrhage and necrosis. An omental deposit (9cm) also displayed similar appearance.
Results: Histopathology:
The tumour was morphologically heterogenous, disclosing frankly sarcomatous areas composed of pleomorphic spindle and focally epithelioid cells, intermingled with a component of monomorphic spindle cells arranged in fascicles. There was a rich vascular network and zones of necrosis with peripheral amianthoid-like collagen plaques. Lymphovascular invasion and metastasis to lymph nodes and omentum were identified. The tumour was immunopositive for CD10 and cyclinD1, and negative for MNF116, ER, p16, CD117, DOG1, S100, smooth muscle and melanotic markers. ArcherTM Fusion Sarcoma Assay detected PAMR1(exon1)-GLI1(exon4) fusion, confirmed on RT-PCR and Sanger sequencing. The patient received adjuvant chemoradiotherapy however developed metastatic recurrence and demised 18 months post-surgery.
Conclusion: To the best of our knowledge, this forms the third report of GLI1-rearranged uterine sarcoma. Previous reports showed low-grade epithelioid morphology and harboured canonical fusions (ACTB-GLI1, PTCH1-GLI1). In contrast, this case shows high grade, predominantly spindled morphology and harbours a novel fusion, PAMR1-GLI1. The precise classification of these tumours, and their relation to other uterine sarcomas with high GLI1 expression, including a subset of HG-ESS and LMS, remain uncertain. Emerging GLI/Hedgehog inhibitors provide clinical relevance to recognising these tumours.

E-PS-09-005
Cervical carcinosarcoma: a rare case report
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Background & objectives: Uterine carcinosarcoma is an aggressive biphasic malignant neoplasm, composed of epithelial and mesenchymal elements. Cervical carcinosarcoma (CCS) is exceptionally rare with less than 70 cases described in the English literature.
Methods: We present a case of a 63-year-old woman with a sudden episode of high volume serous vaginal discharge. On physical examination there was a 5 cm exophytic flat friable mass in the cervix. A pelvic magnetic resonance imaging (MRI) showed an expansive lesion with 70x50x56mm in the endocervical canal that did not invade the uterine body.
Results: The biopsy revealed a malignant neoplasm with a predominant sarcomatous component without a specific morphological differentiation, and less than 5% of squamous cell carcinoma. Immunohistochemistry revealed positivity for cytokeratins (AE1-AE3; 34BE12; CK 8/18) and EMA in the squamous component; CK8/18 was heterogeneously positive in the sarcomatous component and p16 was diffusely positive in both components. Accordingly, the proposed diagnosis was cervical carcinosarcoma with homologous mesenchymal component. The patient was submitted to radical surgery and the final post-operative staging was FIGO (2018): IB3. Due to surgical complications adjuvant treatment was not performed.

Conclusion: CCS is rare and can be misdiagnosed in cervical biopsy due to the lack of identification of one of the tumour components. CCS is aggressive, being the tumour stage the single most important prognostic factor. CCS most frequently presents as a vaginal discharge, which in this case allowed the diagnosis in an early stage of the disease - FIGO (2018):IB3. Even though there were surgical complications, the patient recovered well, without evidence of disease during the 12-months follow-up.

E-PS-09-006

CD163 overexpression in serous ovarian carcinoma with calcification

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Background & objectives: CD163 is expressed by M2-macrophages in malignant neoplasms. M2-macrophages are tumour-associated macrophages of the immunosuppressive phenotype. They are predictors of unfavorable prognosis and contribute to the progression of the tumour process.
To study the CD163 expression in serous ovarian carcinoma.
Methods: We examined 30 samples of serous ovarian carcinoma with calcification (group 1) and 30 samples without calcification (group 2). A histological study was performed to verify the material and form groups. An immunohistochemical study was performed using CD163 Monoclonal Antibody. The immunohistochemical study was evaluated by counting CD163+ M2 macrophages in 6 fields of view (1 mm2) of each slice.
Results: CD163 expression in group 1 (with calcification) was higher (192.47±14.80 cells per 1 mm2) compared to group 2 (without calcification) (150.67±9.56 cells per 1 mm2, $p<0.05$, Student's t-test). CD163+ M2-macrophages were mostly localized in the tumour stroma, tumour cells, and around calcifications.
Conclusion: Overexpression of CD163 is detected in serous ovarian carcinoma with calcification. It indicates the involvement of M2-macrophages in the formation of tumour calcifications.

E-PS-09-007

An exceptional tumour of the vagina: case report

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Background & objectives: Vaginal adenosarcoma is an exceptional tumour arising from endometriosis.
We report through this case, the 8th in the literature and the first without endometriosis signs, the elements of the positive diagnosis and our experience in treatment of this rare tumour
Methods: A 34-years-old patient consulted for vaginal pain with a prolapse mass. She did not any clinical or radiological sign of endometriosis. Gynaecological examination showed a mass of vagina. Mass biopsy was performed. Pathology results were consistent with the diagnosis of a low grade adenosarcoma. The patient underwent hysterectomy with bilateral salpingo-oophorectomy without any neoadjuvant chemotherapy.
Results: Primary vaginal adenosarcoma is extremely rare. Only seven cases have been reported in literature. It was reported that vaginal adenosarcoma were considered to be arising from vaginal endometriosis. Our patient is the first in the literature without a sign of endometriosis. Anatomopathological examination is the gold standard for diagnosis.
Histological examination reveals a biphasic tumour with phyllodes-like architecture composed of benign endometrioid glands and stroma. Depending on stromal cytologic atypia, we distinguish low grade adenosarcomas with monotonous stromal nuclei with mild to moderate atypia and High grade adenosarcomas with pleomorphic and markedly atypical nuclei. Surgical exicion is the main management. Benefit of postoperative chemotherapy or radiotherapy is uncertain.
Conclusion: Vaginal adenosarcoma is an extremely rare biphasic neoplasm that is most often, but not necessarily, linked to endometriosis. The diagnosis is based on histological study because of non-specific clinical and radiological features. Treatment and prognostic factors have not been established yet.

E-PS-09-008

A combined high grade serous carcinoma and carcinosarcoma arising in mature teratoma in ovary: a report of a case

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Background & objectives: Carcinosarcoma is a rare type of malignant ovarian tumour, consists of both epithelial carcinoma and malignant mesenchymal tumour. Additionally, it is much rarer, coexisting with other types of ovarian malignancy.
Methods: We present a case of a 67-year-old postmenopausal woman with combined high grade serous carcinoma and carcinosarcoma arising in mature teratoma in the same ovary. The patient visited our hospital due to abdominal distension for a year and the computed tomography showed a 5cm-sized solid mass with ascites of whole pelvic cavity. She underwent explolaparotomy after pre-operative chemotherapy.
Results: Grossly, right ovary showed a solid and cystic mass with hair and cartilaginous components. Microscopiccaly, tumour was composed of an admixture of biphasic malignant tumour arising in mature teratoma. The malignant mesenchymal tumours consisted of chondrosarcoma, rhabdomyosarcoma, and undifferentiated sarcoma, while malignant epithelial components were squamous cell carcinoma and adenocarcinoma. Synchronously, high grade serous carcinoma with positivity of WT-1 and p53 coexisted in the same ovary. The patient died of the peritoneal seeding of malignant tumour 2 years after diagnosis, despite the postoperative chemotherapy.
Conclusion: Malignant transformation of a mature teratoma is associated with a poor prognosis. To our knowledge, this is a unique case, carcinosarcoma arising in teratoma coexisting with high grade serous carcinoma, which has not been reported previously.

E-PS-09-009

Alveolar rhabdomyosarcoma of adult uterine cervix: a rare case report

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Background & objectives: Rhabdomyosarcoma of uterine cervix is a very rare malignant tumour, especially in adults. Rhabdomyosarcoma is

classified into several subtypes, which are embryonal, alveolar, spindle cell/sclerosing, and pleomorphic.
Methods: We present the case of alveolar rhabdomyosarcoma in a 34-year-old woman with vaginal bleeding. Magnetic resonance imaging revealed a cervical mass with several enlarged iliac lymph nodes without distant metastasis. Malignant neoplasm was suspicious and total hysterectomy was done after hormone therapy.
Results: Microscopically, the cervical mass was composed of two distinct features; one with small discohesive cells and the other with larger cells with abundant eosinophilic cytoplasm. Immunohistochemical stains showed positivity for vimentin, myogenin, and myo-D1 at both different features, but in different patterns, suggesting the diagnosis of mixed alveolar and embryonal rhabdomyosarcoma. Fluorescence in situ hybridization (FISH) detected the FOXO1 translocation, supporting the diagnosis of alveolar rhabdomyosarcoma. The patient underwent the postoperative radiation and chemotherapy, but multiple node metastasis along para-aortic, mesenteric, aortocaval, and supraclavicular area was detected 6 months after surgery, and the patient died of the disease a year after surgery.
Conclusion: FISH playes an important role in distinguishing subtypes of rhabdomyosarcoma, and it is important to recognize these different subtypes due to difference of overall survival.

E-PS-09-010
Coexistence of mature cystic teratoma of the ovary with endometrioid adenocarcinoma arising from a site of endometriosis: a case report of an extremely rare combined ovarian lesion
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Background & objectives: Both endometriosis and mature cystic teratoma tend to occur very frequently at reproductive ages. However, their coexistence is extremely rare, particularly in postmenopausal patients. The incidence of a synchronous ovarian endometrioid adenocarcinoma has hardly ever been reported.
Methods: We report the case of a 63-year-old postmenopausal female with a history of non-Hodgkin's lymphoma, who presented with an ovarian mass as an incidental finding during a CT scan follow-up. Additional imaging tests described the mass as partly solid and partly cystic. The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy and a bilateral pelvic lymph node dissection.
Results: Macroscopic examination showed an ovarian lesion measuring 8x7x3.8 cm, composed of both a thin-wall cystic element and a solid counterpart. The cystic part was filled with white soft material, hair and blood, while the solid one appeared whitish and elastic. Microscopically, the lesion displayed three different pathologic entities; an endometriotic cyst, from which a well-differentiated adenocarcinoma arose, and a mature cystic teratoma. The neoplastic cells were positive for CK7, PAX8 and CK15.3 and negative for CK20. p53 appeared mildly to moderately positive (wild type).
Conclusion: To our knowledge, up until now there have been published only 4 case reports and one case series of simultaneous mature cystic teratoma and endometriosis since 1960, all of which occurred in women of reproductive age and not necessarily on the same ovary. Our case report contributes to the literature presenting an even rarer entity of a synchronous lesion coexisting unilaterally in the same ovary, raising questions about the succession of events and the pathophysiological mechanisms involved.

E-PS-09-011
Gallbladder carcinoma recurs as uterine metastasis
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Background & objectives: Metastases to the female genital tract are rare, with metastatic disease restricted to the uterus being even less frequent. The primary tumour is most often intra-genital rather than extra-genital. We present a case of uterine metastasis of a gallbladder carcinoma.
Methods: A 66-year-old woman was diagnosed with a 3,4cm lobulated mass, in the left parametrium, of mixed consistency, with no sign of endometrial tumour. There was no lymph node enlargement or ascites. Her past medical history was significant for gallbladder carcinoma, stage II, since 2,5 years, after laparoscopic cholocystectomy for symptomatic cholethiliasis. She underwent TAH & BSO omentectomy and umbilicectomy.
Results: On macroscopic examination the body of the uterus was occupied by a tumour mass measuring 3cm. In the left ovary there was a 1,9cm tumour, solid and cystic filled with serous-mucoid fluid and in the right ovary a cystic tumour of 1,8cm. The omentum had hard consistency of 6cm. In the left ovary a diagnosis of an adenosquamous carcinoma was made of billiary and intestinal type with squamous component of >25%, with areas of necrosis and LVIs and parasalpingeal extension. There was a full thickness infiltration of the uterine wall, of the right ovary, the omentum and umbilicus, by billiary type adenocarcinoma, consistent with metastasis from the gallbladder carcinoma (GBC).
Conclusion: Metastases to the female genital tract are rare. When metastases from extragenital primaries occur, the ovaries are affected the most. Metastatic localization in the uterine corpus accounts for less than 10%. Concurrent metastatic disease in the ovaries is found in 65%. Among extragenital primary tumours metastasizing to the uterine corpus is GBC in 4,8%. Dissemination of GBC has a propensity for distant spread. Uterine metastasis has to be excluded in women with uterine/parametrial mass and a personal history of GBC.

E-PS-09-012
Incidental primary (localized) extranodal ovarian follicular B-cell lymphoma (FL): a case report of a rare entity
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Background & objectives: Ovarian lymphomas are usually secondary and indication of disseminated disease. Primary ovarian lymphomas are rare and of better prognosis. We describe a primary ovarian follicular lymphoma in a 71-year-old woman who underwent surgery for a fibroma of the ovary.
Methods: We received the uterus with left fallopian tube measuring 6cm long and 0,3cm maximum diameter and left ovary whose dimensions were 4,5X3,5X2cm. On sections the ovary was almost fully replaced by a mass with smooth, lobulated surface with solid, vaguely nodular, tan-white appearance and sclero-elastotic consistency.
Results: Microscopic examination showed a B-cell proliferation arranged in follicular (75%) and diffuse distribution, consisting of numerous, variably-sized, non-polarized neoplastic follicles, with attenuated or absent mantle zones, expansile and typically arranged in a back-to-back fashion. Focal residual ovarian parenchyma was identified, confirming its ovarian origin. The neoplastic cells

by immunohistochemistry were expressing CD20, CD79a, CD3, PAX5, CD23, CIg, CD10, bcl-2, bcl-6 with Ki-67 proliferation rate 30-40% in the nodular areas and 0-5 centroblasts per high power field. No lymph nodal or bone marrow involvement was detected. Tumour markers were unremarkable. The final diagnosis was of a primary low-grade follicular lymphoma. Standardized first-line therapy for follicular lymphoma, with R-CHOP chemotherapy, was introduced.
Conclusion: Most ovarian lymphomas represent secondary involvement by a systemic disease. In comparison, primary ovarian lymphomas are rare and incidental but ovary is the most common site in the female genital tract to be involved by haematological malignancies. This case exemplifies the need to consider NHL in the differential diagnosis of unusual large solid ovarian tumours. Their prognosis is better than secondary lymphomas, which have to be excluded clinically. In our case the patient is free of disease one year later.

E-PS-09-013
Immunohistochemical markers for uterine fibroids recurrence prediction
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Background & objectives: Uterine leiomyoma is the most common neoplasms in the female reproductive tract. Myomectomy is selected to preserve the uterus, however, this neoplasm can recur after this surgical treatment. Consequently, we aimed to identify immunohistochemical markers of recurrent uterine fibroids.
Methods: Samples of 13 patients with primary diagnosed leiomyoma and 18 patients with recurrent one, who had been provided lapascopic reconstructive plastic surgery were recruited. Pathomorphological and immunohistochemical examination was carried out for leiomyoma. The expression of the proliferation marker (Ki-67), vascular endothelial growth factor (VEGF), progesterone (PgR) and oestrogen (ER) receptors, proto-oncogene p16 and anti-oncogene p53 was evaluated.
Results: It was found that Ki-67 level was higher in reccurent fibroids as to primary diagnosed tumours ($p = 0.031$), which may reflect the proliferative potential of the tumour most prone to recurrence. In studied groups there was significant difference between ER, PgR, p16 biomarkers. Increased VEGF expression was revealed in both leiomyomas compared to internal control (normal myometrium), but expression level in each group was not found to differ. Apparently, changes in p53 expression are not leading in the pathogenesis of uterine fibroids, since there were no statistically significant differences in the expression of this protein between patients groups.
Conclusion: Pathogenetic factors of recurrent uterine fibroids are high rates of Ki-67, VEGF, p16, ER and PgR in leiomyoma. These tissue-based markers seem to be usefull in routine practice to predict the recurrent potential of uterine fibroids.
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E-PS-09-014
Endometrial stromal nodule in pregnancy - an unsual presentation of exceedingly rare tumour
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Background & objectives: Endometrial stromal nodule is an exceedingly rare benign tumour, most often diagnosed in perimenopausal women, who complain of abnormal bleeding and local pain. In such cases, hysterectomy is recommended as clinical and imaging investigations cannot rule out malignancy.
Methods: We report the case of a pregnant 32 year old woman who a healthy, full-term baby by C-section. During the surgery, a well circumscribed, solid, yellow nodule measuring 6x4x3 cm was incidentally observed located on the maternal surface of the placenta. The tumour was surgically removed and underwent ample histopathological and immunohistochemical analysis.
Results: Microscopic examination revealed a well demarcated proliferation of polygonal to spindle cells with abundant eosinophilic cytoplasm and large nuclei with conspicous nucleoli, consistent with decidual reaction. The cells were arranged in fascicles, within a myxoid stroma. The mitotic activity was about 15/10 HPF. Immunohistochemical analysis demonstrated that the tumour cells stain intensely for CD10, SMA and WT1 and moderately for PLAP. Ki67 (MIB1) proliferation index was about 20%, which could be explained by the hormonal stimuli. Based on these results, the diagnosis of endometrial stromal nodule was established with decidualization.
Conclusion: Endometrial stromal nodules are among the rarest benign tumours of the uterus. Since these tumours usually affect perimenopausal women and preoperative investigations cannot establish the benign nature, hysterectomy is considered the standard treatment. The case we present is unique because, to our knowledge, there are only two reported cases of an endometrial stromal nodule associated with pregnancy. This association renders the histopathological diagnosis particularly difficult due to the unusual morphological features, reflecting hormonal changes.

E-PS-09-015
Combined small cell and large cell neuroendocrine tumour of uterine cervix - a case report
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Background & objectives: Neuroendocrine tumours of the female genital tract are aggressive neoplasms, developing most often in the uterine cervix (NECC) and accounting for 1.4% of all cervical cancers. The prognosis of NECC is poor and there is no standardized therapy.
Methods: A 39-year-old patient presented to our hospital for vaginal bleeding. She had a previous core needle biopsy from omentum who showed endometrioid carcinoma of ovary/endometrium (ER and PgR positive, WT-1 negative). Imaging showed frozen pelvis with a large right parametrial mass. Cervical and endometrial biopsies were performed in order to define the type and origin of the neoplasm.
Results: In both specimens the histoplathological examination revealed a high-grade neoplasm with neuroendocrine features, with a mixture of small cells and large cells, with cellular necrosis and brisk mitotic figures. Both specimens had the same immunophenotype. All the neoplastic cells were positive for Synaptophysin, Chromogranin A, CD56, ISL-1, p16 and CK7 and negative for ER, PgR, PAX-8, CDX-2, WT-1 and p40. The Ki-67 was positive in 80-90% of neoplastic cells. The endometrioid component was absent in both specimens. The diagnosis of high-grade neuroendocrine carcinoma with small and large cell morphology was made. The absence of tumour elsewhere based on MRI concluded that the primary tumour is from the cervix.

Conclusion: NECC is characterized by high incidence of lymphovascular invasion and distal metastasis. Women with NECC have a poor prognosis irrespectively of the treatments used.

E-PS-09-016

Endometrial carcinoma with multiple metastases to the central nervous system: a case report with a comparative NGS analysis of the primary and metastatic tumours

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Background & objectives: Metastasis from endometrial carcinoma to the central nervous system is rarely encountered. We report a case of a 34-year-old female with dedifferentiated endometrial carcinoma metastasizing to the brain which developed six months later.
Methods: There was a well-differentiated endometrial carcinoma, and a second component of poorly differentiated carcinoma, both were positive for PAX-8 immunostain. The CNS metastatic tumour is composed of sheets of undifferentiated tumour cells with islands of immature cartilage, with negative PAX-8 immunostain. These tumours were subject to analysis by NGS to verify the relationship between the different components.
Results: NGS of the well-differentiated endometrial carcinoma component showed a pathogenic KRAS mutation (c.35G>A, p.Gly12Asp) with an allele-variant frequency (AVF) of 53.5%, in addition to mutations in the PIK3CA and PTEN genes, as well as a mutation of an unknown significance in the PDGFRA gene. The poorly differentiated component showed a mutation profile similar to the well-differentiated component. However, it lacked the KRAS mutation and harboured two extra mutations in the NRAS (c.182A>G, p.Gln61Arg) and PIK3CA (c.1034A>G, p.Asn345Ser) genes, with an AVF of 33.4% and 32.7%, respectively. Interestingly, the metastatic brain tumour showed an almost identical mutation profile to the poorly differentiated component of the endometrial carcinoma.
Conclusion: This is a rare case of metastasizing endometrial carcinoma to the CNS. Molecular testing supported almost identical molecular profiles between the poorly-differentiated endometrial carcinoma, and the metastatic tumour in the CNS, indicating that the brain tumour had possibly originated from the poorly differentiated endometrial carcinoma component. This might have implications for the treatment of similar cases.

E-PS-09-017

Determination of microsatellite instability with the Promega™ MSI Analysis System and the Idylla™ MSI assay on 31 endometrial carcinomas with deficiency of DNA mismatch repair

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Background & objectives: Microsatellite instability (MSI) is due to deficiency of the DNA mismatch repair (MMRd) system. The aim of this study is to define the optimal approach for MSI testing and to clarify discrepancies with MMR protein expression in immunohistochemical analysis (IHC).
Methods: We selected 31 endometrial cancers (EC) with loss of expression of MMR proteins (MLH1, MSH2, MSH6 or PMS2) to compare two MSI tests, Promega™ and Idylla™. Both recognize mutations in short sequences of specific genes (BAT-25, BAT-26, NR-21, NR-24 & MONO-27 and ACVR2A, BTBD7, DIDO1, MRE11, RYR3, SEC31A & SULF2) to classify endometrial cancers as unstable (MSI-H) or stable (MSS).
Results: Loss of MMR proteins were distributed in 22 MLH1-PMS2, 4 MSH2-MSH6, 3 MSH6, 1 PMS2, and 1 MSH2-MSH6 & PMS2. With Promega™, ten EC were classified as MSS, five as doubtful and sixteen as MSI-H. With Idylla™, two EC cancers were classified as MSS and twenty-nine as MSI-H. Concordance between molecular testand IHC were 51,6% for Promega™ and 93,5% for Idylla™. Concordance between Idylla™ and Promega™ was 58.1%. Four of ten MSS cases in Promega™ presented isolated losses of MMR proteins (3 MSH6 and 1 PMS2). The carcinoma with isolated loss of PMS2 was also MSS with Idylla™.
Conclusion: Idylla™ MSI assayshows higher sensitivity than Promega™ MSI analysis, in detecting MSI-H in MMRd EC. Promega™ misses isolated losses of MMR proteins. Probably, the selection criteria for MSI-H in Promega™ (more than one gene mutated) is the reason of the low agreement. The discordance between IHC and molecular tests could be explained by sample features, MSS or MSI-low cases with MMRd and because Idylla™ was developed to analyse MSI in colorectal carcinomas with different range of instability.

E-PS-09-018

Ovarian teratoma associated with anti-N-methyl-D-aspartate receptor encephalitis

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Background & objectives: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is often accompanied by an ovarian teratoma. A prevailing theory suggests that generation of autoantibodies to NMDAR on neurons in the central nervous system is triggered by neuroglial tissue in the associated teratoma.
Methods: A 15-year-old female presented with a 6-days history of psychological symptoms of mental disorientation for time, person, and place. She had no history of medical or psychiatric problems. Brain computerized tomography (CT) results were unremarkable. A pelvic CT revealed a 3.0-cm, well marginated, heterogeneous, calcified mass in the right ovary with fat components. The patient underwent a right ovarian cystectomy.
Results: The cystic ovarian mass measured 2.4x 2.2x 1.8 cm in size. The cut surface showed multiple cysts filled with yellowish gelatinous material and some hairs. Microscopically, the mass revealed a mature cystic teratoma showing foci of neuroglial tissue with lymphoid aggregates containing germinal centres. Mature neurons were rare, but showed degenerative features including smudged nuclei, cytoplasmic vacuolation, and eosinophilic deposits. Astrocytes were focally hypercellular. Anti-NMDAR encephalitis associated with teratoma was considered. Cerebrospinal fluid was positive for Anti-NMDAR antibody. The patient suffered from paraneoplastic neurological syndrome, which included impaired awareness, dysphagia, slurred speech, and dysphoria due to autoimmune encephalitis. The patient slowly improved with a moderate residual cognitive defect.
Conclusion: Here we report a rare case of ovarian teratoma associated with anti-NMDAR encephalitis. The presence of colocalized neuroglial tissue with lymphoid aggregates containing germinal centres and degenerative features within neuroglial tissue in ovarian teratomas should be clinically considered as anti-NMDAR encephalitis.

E-PS-09-019

Serous cystadenofibroma and mature cystic teratoma. A rare case of collision tumours of the ovary

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Background & objectives: Collision tumour is coexistence of adjacent neoplasms in the same organ without histological intermixing. Collision tumours have been reported in various organs but are relatively rare in the ovary. We report a case of coexistent serous cystadenofibroma and cystic teratoma.
Methods: A 39-year-old patient underwent salpingo-oophorectomy. On macroscopic examination the ovary was replaced by a cyst measuring 7.5cm in greatest diameter with smooth outer surface. Cross section revealed two adjacent cysts. One cyst with sebaceous material, hair and a small solid nodule in the inner wall. The other cyst containing clear fluid, with a small papillary area 2,5cm in greatest diameter.
Results: Microscopic examination of the wall of the ovarian cyst revealed a mixture of mature benign tissues, like stratified squamous epithelium associated with keratinous material, dermal adnexa, respiratory epithelium, fatty tissue and bone marrow with medullary space. The adjacent cyst was lined by benign serous (ciliated/ cuboidal) epithelium. The small papillary excrescences and the glands within the fibrotic stroma were also lined by benign serous epithelium. Based on the histological features a diagnosis of collision tumour of the ovary comprising a serous cystadenofibroma and mature cystic teratoma was made.
Conclusion: Various combinations of collision tumours of the ovary have been reported, although quite rare and with not well understood pathogenesis. They are only diagnosed post-operatively after histopathological examination and their recognition is very important as accurate diagnosis of each component is paramount for proper management, depending on the individual biological characteristics of each of the tumour components. In case of malignancy, the most aggressive component and stage of the tumour will determine the prognosis.

E-PS-09-020

The immunohistochemical validation of Bcl-2 family proteins in ovarian cancer

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Background & objectives: The Bcl-2 family proteins are well-characterized regulators of the mitochondrial (intrinsic) pathway of apoptosis. In this study, using immunohistochemical approach we estimated the level of both pro-apoptotic (Bak, Bax, Bid, Bim) and anti-apoptotic (Bcl-2, BclxL) proteins in ovarian cancer samples.
Methods: The level of Bcl-2 family of proteins was estimated as Q-score that takes into account the intensity and percentage of positively-stained cells. The Q-score distribution of each protein was evaluated according to clinicopathological parameters such TNM stage, lymphatic invasion and tumour grade. The Wilcoxon-Mann-Whitney non-parametric test and Spearman correlation was used for statistical analysis.
Results: In current study 58 cases of ovarian carcinomas were included. According with clinical and pathological data, 14 (24%) were classified as T1-2 (TNM classification), 44 (76%) as T3-4, and 42 (72%) were characterized as high-grade carcinomas. The Q-scores of Bcl-2 protein was significantly lower than Q-scores of other members Bcl-2 family proteins. Moreover, about 20% of tumours did not express Bcl-2 (Q-score was 0) in the epithelial component. The Q-scores of Bcl-2 were statistically significantly higher in T1-2 group than in T3-4 [p=0.007]. It was observed that the Q-scores of Bcl-2 was less in high-grade tumours [p=0.046], while the same parameter of Bim was higher in high-grade tumours [p=0.001].
Conclusion: Immunohistochemical analysis of the ovarian carcinoma samples demonstrated that Bcl-2 expression was significantly lower than expression of other members of Bcl-2 family proteins and negatively correlated with the size and grade of primary tumour. These observations could indicate a suppressive role of Bcl-2 in progression of ovarian tumours.
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E-PS-09-021

Clinicopathological presentation and outcome of adult-type granulosa cell tumours of the ovary: a retrospective study of 24 patients

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Background & objectives: Granulosa cell tumours (GCT) of ovaries are rare neoplasms originating from sex-cord stromal cells. They are characterized by their long natural history and tendency to recur years after initial diagnosis. Our aim is to evaluate clinico-pathological findings in Tunisian women.
Methods: We collected, during 11 years, 24 cases of adult GCT of the ovaries, diagnosed in the department of pathology of Habib Bourguiba Hospital within the period lasting from January 2011 to December 2021.
Results: Median age was 46,8 years. The most common symptom was menorrhagia (11cases). Tumours median size was 14,6 cm. Microscopically, microfollicular patterns were the most common patterns (13 cases). Call-Exner bodies were seen in 18 cases. Moderate atypia were seen in 7 cases and marked atypia in one. Mitoses were ≥ 5 mitoses/10 HPF in 7 cases. Eight cases had necrosis. Immunohistochemically, Inhibin was positive in 100% tumours. Three cases recurred after 3, 8 and 20 years. One patient was lost of sight. The two other had an incomplete surgical resection of the residual tumour with adjuvant chemotherapy. One patient had regression of the residual tumour. The second developed hepatic metastasis.
Conclusion: GCT are the most frequent hormono-secreting tumours of the ovary. They have a low malignancy potential and generally have a good prognosis. Mitotic index and residual tumour disease are the most valuable prognostic factors. Complete tumour resection should always be attempted. Chemotherapy can be effective in recurrent cases.

E-PS-09-022

CD34 as a predictive marker for the effect of autologous platelet rich plasma and autologous endometrial cells in treating infertile women with thin endometrium

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Background & objectives: To evaluate the endometrial immunophenotype of patients treated with hysteroscopically controlled injections of autologous platelet rich plasma (PRP) and autologous endometrial cells as a treatment for infertile women with thin endometrium for prognosis of the treatment outcome.
Methods: To evaluate the endometrial immunophenotype of patients treated with hysteroscopically controlled injections of autologous platelet rich plasma (PRP) and autologous endometrial cells as a treatment for infertile women with thin endometrium for prognosis of the treatment outcome.
Results: PgR expression in successfully pregnant patients: in glands Me =300,0 (Q1-Q3: 267.5-300.0), stroma: Me =300,0 (Q1-Q3: 267.5-300.0); in non-pregnant patients: in glands Me =300,0 (Q1-Q3: 180.0-300.0), in stroma 297.0 (Q1-Q3 294.0-300.0), p=0.437 for glands, p=0.247 for stroma. ER expression in successfully pregnant patients: in glands Me =300,0 (Q1-Q3: 260.0-300.0), stroma: Me =300,0 (Q1-Q3: 240.0-297.5); in non-pregnant patients: in glands Me =297.0 (Q1-Q3: 230.0-300.0), in stroma 294.0 (Q1-Q3 260.0-300.0), p=0.611 for glands, p=1 for stroma. CD34 expression in successfully pregnant patients: Me =3.0 (Q1-Q3: 2.0-4.0); in non-pregnant patients: Me =4.0 (Q1-Q3: 3.0-4.0) (evaluated only in stroma). p=0.035.
Conclusion: We applied a novel approach for infertility treatment in patients with refractory thin endometrium. Injections of PRP into basal layer of endometrium facilitate the reconstitution by enhancing cell proliferation and angiogenesis. The effect can be predicted with CD34 expression in endometrial stroma which can help to stratify patients effectively before the treatment procedure.
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E-PS-09-024
Mixed ovarian yolk sac tumour with mucinous carcinoma and ganglioneuroma in a postmenopausal female: a case report
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Background & objectives: Ovarian germ cell tumours in postmenopausal patients are rare. They have a poorer outcome compared with those in young women. We report a case of mixed ovarian yolk sac tumour with mucinous carcinoma and ganglioneuroma.
Methods: A 55-year-old nulliparous lady presented with change in bowel habits and an abdominal mass was palpable on examination. CT scan revealed a multiloculated solid-cystic mass in the pelvis. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and omentectomy. Macroscopic examination showed a ruptured 20cm solid-cystic tumour replacing the left ovary, with large areas of haemorrhage and necrosis.
Results: The tumour comprised three separate components of different lineages, namely a germ cell tumour (yolk sac tumour), an epithelial tumour (mucinous carcinoma) and a tumour of neural crest origin (ganglioneuroma). The mucinous carcinoma merged with the yolk sac tumour, but was a distinct separate component as shown by their contrasting immunohistochemical profile. One of the postulations was that this tumour may be a mixed germ cell tumour with a component of yolk sac tumour and a teratoma, from which the epithelial neoplasm and ganglioneuroma grew. The behaviour of this tumour appeared to be driven by the yolk sac component, as evidenced by metastatic disease composed solely of yolk sac tumour.
Conclusion: The prognosis of ovarian germ cell tumour in postmenopausal women is poor, even for patients with early-stage disease. Our patient died of her disease at 6 months after diagnosis, which is in accordance with other similar cases reported in the literature. The rarity of germ cell tumour in postmenopausal women can cause initial diagnostic uncertainty to the unwary. It is important to reach the accurate diagnosis as most of the cases have an aggressive clinical course.

E-PS-09-025
Primary peritoneal psammocarcinoma: a case report and review of literature
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Background & objectives: Psammocarcinoma is a rare form of low-grade serous carcinoma originating in the ovaries or the peritoneum. The primary peritoneal psammocarcinoma (PPP) is even rarer. We present a rare case of fortuitous discovery of a PPP and review of literature.
Methods: A 74-year-old woman was admitted to the surgery department to undergo cholecystectomy for gallbladder lithiasis. At laparoscopy, we discovered peritoneal nodules that were biopsied. Subsequently, a hysterectomy, bilateral adnexectomy and omentectomy were performed. Bibliographic research, using the term "Primary Peritoneal Psammocarcinoma", was performed at Pubmed databases from 1990 to 2019.
Results: Biopsy's pathological examination showed small epithelial nests under 15 cells with low-grade cytological features invading surrounding structures with extensive psammomatous bodies. Pathologic examination of the later specimen revealed no invasion of the ovarian stroma. Our case fulfilled all the criteria defined by Gilks and modified by Chen et al for the diagnosis of PPP. The decision of medical staff was to complete by adjuvant chemotherapy after surgery. Up to date, fewer than 30 cases of PPP have been reported in the English literature. The mean age was 54 years old, and the most common clinical presentation was an incidental discovery. Most institutions recommend optimal debulking followed by adjuvant chemotherapy.
Conclusion: The PPP has morphologic diagnostic criteria that distinguish it from other epithelial serous neoplasms. The behaviour of this tumour is unclear, and the treatment is not standardized because of its rarity and lack of long-term follow-up. More cases need to be studied for better understanding and improvement of the management protocols.

E-PS-09-026
Solid mature teratoma associated with gliomatosis peritonei: a case report
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Background & objectives: Gliomatosis peritonei (GP) is the presence of benign peritoneal implants of mature glia tissue, with unclear origin. It's generally found in patients with immature ovarian teratoma. Less than 100 cases of mature ovarian teratoma with GP were reported.
Methods: We report the case of a 9-year-old girl with abdominal distension and pain. CT-scan identified an adnexal tumour with peritoneal dissemination. Alpha-fetoprotein and CA-125 serum levels were: 42,56 ng/mL,165,2 U/mL. CEA and β-HCG were normal. A salpingo-oophorectomy, omentectomy and parietal peritoneum excision was performed. After 5 months of follow-up the patient is asymptomatic, without radiological disease or increased neoplastic markers.

Results: The specimen was 1737g and the ovary was replaced by a 21x17x10cm partly solid tumour, with capsular rupture. The specimen was extensively sampled with 2 fragments / cm. On histological examination the tumour was composed by tissue of all germinal layers, with areas of skin and cutaneous appendages, adipose tissue, cartilage, respiratory and gastrointestinal epithelium. No immature neuroepithelium or neurorosettes were identified. The fallopian tube and peritoneal nodules showed multiple foci of mature glial tissue, establishing the diagnosis of solid mature ovarian teratoma with GP. Peritoneal fluid was negative for neoplastic cells.
Conclusion: This case highlights the importance of a complete differential diagnosis in a patient presenting with disseminated peritoneal disease and increased serum levels of neoplastic biomarkers. Benign entities should be considered, such as GP in the context of an ovarian teratoma. Two main explanations are proposed for the origin of GP, being glial metaplasia and cellular spread from the teratoma itself. This case supports capsular rupture as the main event for GP, however further investigation is needed to clarify both mechanisms.

E-PS-09-027

The role of mast cells in the morphogenesis of cervical cancer

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Background & objectives: Cervical cancer has been and remains one of the main trends in oncology, especially among people of non-reproductive age. The role of mast cells in tumour oncogenesis is still unclear, including in cervical cancer.
Methods: The biopsy material obtained from 21 women between the ages of 25 to 74 years, exclusively with cervical cancer, without other pathologies of the reproductive organs. The mast cells stained with tryptase and chymase antibodies. Mast cells were analysed in the tumour and along the periphery of the tumour process. The degree of mast cell degranulation has been established.
Results: During the research we were trying to work out the correlation between mast cells and some important morphological indicators. We have studied the distribution of mast cells and the depth of tumour invasion, the mitotic activity of the tumour, severity of peritumoral inflammation. No correlations were found. It turned out that with an increase in the degree of differentiation (from high to low-differentiated), there was a tendency to decrease the number of mast cells. But this result was not statistically reliable either. However, the largest number of degranulated cells is located in the tumour itself, and not on its edge.
Conclusion: The relationship between the distribution of mast cells and the depth of invasion, mitotic activity and severity of inflammation was not revealed. Degranulation of MC occurs actively in the tumour, and not in the invasive edge. It is possible to continue the study of the role of mast cells in the morphogenesis of cervical cancer, but only taking into account the functional activity of mast cells.

E-PS-09-028

Vaginal sarcoma with COL1A1- PDGFB fusion: a rare and newly described fibrosarcoma like neoplasm

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Background & objectives: Recent advances in molecular biology have allowed to define a new uterine sarcoma, with COL1A1-PDGFB fusion and only 4 cases described in the literature. We describe the fifth case in order to provide more knowledge about this entity.
Methods: We are reporting the only case of uterine fibrosarcoma like neoplasm with COL1A1-PDGFB fusion diagnosed in our hospital and describe clinical, radiological, histopathological, immunophenotypic and molecular features. This is a 44-year-old female with no medical history of interest except for a dermoid cyst of left ovary operated 15 years ago.
Results: The exophytic tumour of the cervix observed in imaging tests was biopsied and showed a malignant neoplastic proliferation, treated with anterior pelvic exenteration and intraoperative radiotherapy. Macroscopically, it was a big (6,5x5,5x3 cm) lobulated whitish lesion with fibrous consistency. Histologic examination revealed a spindle cell neoplasm with mild nuclear atypia, low proliferative activity and no necrosis. Immunohistochemical stains were positive for CD34, CD10 and p16 and negative for epithelial, muscular and melanic markers, ER, PR, cyclinD1, DOG1, EMA, BCOR, SS18-SSX, STAT-6 and pan-TRK. Gene fusion study (Archer FusionPlex Sarcoma Panel) identified COL1A1-PDGFB fusion, the final diagnosis being sarcoma with COL1A1-PDGFB rearrangement, AJCC Stage pT2pNxpMx.
Conclusion: There is a wide variety of uterine mesenchymal tumours whose understanding improved thanks to recent advances in molecular biology, that allowed to define a new group of uterine fibrosarcoma like neoplasms. It includes a new entity with COL1A1- PDGFB fusion, with only 4 cases reported in the literature and not yet described in the WHO classification of female genital tumours. At the time of this work, our patient is doing well, waiting for a radiological examination and neovaginal dehiscence surgery.

E-PS-09-029

Indoleamine 2,3-dioxygenase expression in ovarian carcinoma

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Background & objectives: Indoleamine 2,3-dioxygenase (IDO) is an enzyme acting as immune modulator through suppression of T-cell immunity. IDO is overexpressed in various cancers. This study aims to investigate the distribution of IDO expression in ovarian carcinoma and its correlation with clinic-pathological characteristics.
Methods: Twenty-one cases of ovarian tumours were enrolled for IDO immunohistochemistry. We studied both tumour tissues and adjacent normal tissues. Correlations between IDO expression and clinico-pathological parameters were also examined.
Results: The mean age of patients was 54 years. IDO was expressed in all tumour tissues and not in normal tissues (Mann-Whitney test: $p<0.0001$). High IDO expression (Mean of positive cells=71%) concerned tumour size >50mm (Mean=116mm). Low IDO expression (Mean of positive cells=25%) concerned tumour size not exceeding 50mm (Mean=70mm). No difference in IDO expression was linked to disease characteristics, nor to metastasis ($p>0.05$).
Conclusion: Altogether, our preliminary results showed that IDO could be proposed as a candidate biomarker useful for the advancement of ovarian carcinoma profiling.

E-PS-09-030

Metastatic epithelioid trophoblastic tumour: a case report

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Background & objectives: Epithelioid trophoblastic tumour (ETT) is a rare form of gestational trophoblastic tumour and 25% present with FIGO stage IV disease. We report a case of a patient with stage IV ETT expressing programmed cell death protein 1 (PD-L1).
Methods: A 40-year-old woman presented with abnormal uterine bleeding and recent weight loss. An MRI revealed a 4.3cm endometrial tumour. On biopsy, a diagnosis of undifferentiated carcinoma was suggested. Hysterectomy with bilateral adnexectomy and omentectomy was performed. Pre-surgical β-HCG levels were not assessed and post-surgery β-HCG was 4.1mUI/mL. Currently, 3 months after surgery, the patient is under adjuvant chemotherapy.
Results: Gross examination revealed a white tumour invading the outer half of the myometrium and multiple small white nodules in the omentum. Histologically, the tumour showed a multinodular proliferation of monotonous medium-sized eosinophilic cells, arranged in strands and nests, associated with extensive geographic necrosis and deposits of hyaline-like material. The cells displayed eosinophilic/clear cytoplasm with round nuclei and small nucleoli. Neoplastic cells expressed keratins (AE1/AE3 and cam5.2), p63, GATA3, inhibin (focal), HPL (focal) and PD-L1 (>50%). The cells did not express SMA, desmin, β-HCG, PAX2 or PAX8. The proliferative index Ki-67 was 20%. A diagnosis of an epithelioid trophoblastic tumour with epiploic metastasis was rendered.
Conclusion: Epithelioid trophoblastic tumours most often present in FIGO stage I/II and treatment is therefore surgical. In the rare event of advanced disease, conventional chemotherapy has a low success rate. Since ETT often shows strong PD-L1 expression, as seen in our case, a few case reports have showed a good clinical response to immune checkpoint inhibitors (such as pembrolizumab). Immunotherapy may prove useful in the treatment of metastatic drug-resistant ETT.

E-PS-09-031

Histological particularities of pulmonary phyllodes tumour metastasis: a case report

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Background & objectives: Phyllodes tumours (PT) are rare neoplasms accounting for less than 1% of all breast cancers. Malignant phyllodes tumours are likely to metastasize mainly to lungs. We, hereby, present an uncommon histological pattern of lung metastasis of a Phyllodes tumour.
Methods: We present a case of lung metastasis in a patient known to have a breast phyllode tumour.
Results: A 40-year-old woman with history of left mastectomy for phyllodes tumour three years earlier presented with a rapidly growing mass of the right lung. Chest-Tomography Scan showed a tumour of the middle lobe along with pleural infiltration. A lobectomy was performed. Histological examination showed a mesenchymal proliferation entrapping ductal structures that showed to be bronchic lumens expressing TTF1 and not a ductal tumoral component. The tumour cells were arranged in intersecting bundles. They had atypical spindle-shaped nuclei. Mitosis and mitonecrosis figures were noted. The tumour was highly vascularized. The diagnosis of pulmonary and pleural metastasis of phyllodes tumour was established.
Conclusion: PT are biphasic tumours composed of both stromal and an epithelial component. PT has an inherent recurrence and metastatic potential especially to the lung. Histologically, mesenchymal component may be the only pattern observed in metastasis site. That could be challenging for the diagnosis especially if no history of breast cancer is known.

E-PS-09-032

Uterin spindle cell mesenchymal neoplazm, NTRK fusion-positive uterine sarcoma

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Background & objectives: Uterine sarcomas are a rare type of tumour with a wide range of morphological and genetic characteristics. Recent improvements in the genetic characterisation of these tumours have created a new clinicopathological category that includes NTRK-rearranged uterine sarcomas.
Methods: In the hysterectomy material of a 52-year-old female patient with menorrhagia, a 5 cm diameter solid tumoral lesion was identified. When the histomorphological observations were combined with the immunohistochemical profile, the group of CD34,S100,Pan-Trk positive uterine spindle cell neoplasms was classified as NTRK fusion uterine sarcoma. The next generation of sequencing investigation found fusion between the NTRK1gene exon10 and the TPM3gene exon7 and junction regions.
Results: These neoplasms have a variably cellular and fibrosarcoma-like appearance and are distinguished by generally homogeneous spindle cells with a scant cytoplasm. Atypia is usually mild to moderate. Mitotic activity is varied. Differential diagnosis includes high-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, inflammatory myofibroblastic tumour, COL1A1-PDGFB fusion sarcoma, solitary fibrous tumour, adenosarcoma and malignant melanoma. In leiomyosarcoma-like uterine sarcomas that are desmin and h-caldesmon negative and lack ER and PR expression, if S100 and CD34 is positive, we recommend pan-Trk immunostaining and if it is positive then molecular studies to screen for NTRK fusion for differential diagnosis and treatment options.
Conclusion: The importance of NTRK mutations in the development of numerous solid tumours is increasingly recognized. Accurate identification of these rare tumours is critical for the treatment option of TRK inhibitors like Larotrectinib that is a pan-TRK inhibitor. This case demonstrates the importance of considering newly defined NTRK fusion sarcomas in the histopathological evaluation of uterine sarcomas in terms of diagnosis and treatment.

E-PS-09-033

Benign cystic mesothelioma: a rare case report

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Background & objectives: Benign cystic mesothelioma is a mesodermal tumour that covers the surface of organs such as the peritoneum, pleura, and pericardium. It is a proliferative neoplasm composed of mesothelium epithelial and mesenchymal cells.
Methods: A 31-year-old female patient presented to the gynaecology outpatient clinic with inguinal pain. Ultrasonographic imaging revealed a 200*117 mm cystic tumour on the anterior abdominal wall. Total abdominal colectomy, low anterior resection, subtotal

pancreatectomy, splenectomy, cholecystectomy, partial bladder excision, visceral parietal peritonectomy, and ileorectal anastomosis procedure were performed on the patient.
Results: Pathological investigations revealed cysts lined with epithelium covering the serosa of the abdominal organs. Many samples showed no evidence of invasion or atypia. Papillary structures were observed in very few areas. Calretinin, WT-1, EMA positivity, and moderate to weak expression of BAP-1 were observed in immunohistochemical studies. Desmin and P16 had weak expression in some areas. Also, there were endometriosis foci seen in the fibroadipose tissue between the cervix and the rectum. Cystic lymphangioma of the retroperitoneum, endometriosis, mullerian cysts, cystic adenomatoid tumours, and cystic mesonephric duct remnants are all benign lesions in the differential diagnosis for benign cystic mesothelioma. Malignant mesothelioma, serous tumours including peritoneum, and ovarian clear cell carcinomas are examples of malignant lesions that mimic benign cystic mesothelioma.
Conclusion: Our case was assessed in light of these potential diagnoses, and immunohistochemistry tests validated our diagnosis. In the case of benign cystic mesothelioma, treatment choices range from conservative to full resection followed by hyperthermic intraperitoneal chemotherapy (HIPEC). We wanted to discuss a case that we thought was similar to previous examples in the literature because of the endometriosis background, broad involvement, and repeated recurrence.

E-PS-09-034
E-cadherin and ber-ep4 expressions in tubal ectopic and intrauterine pregnancies
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Background & objectives: Epithelial-mesenchymal transition (EMT) may have a significant role in tubal pregnancies. We aimed to evaluate and compare the expressions of e-cadherin as a hallmark of EMT and another adhesion molecule, Ber-Ep4, in tubal pregnancies and intrauterine pregnancies.
Methods: The study included 17 cases who underwent salpingectomy for tubal ectopic pregnancy and 17 cases who underwent curettage for intrauterine pregnancy between 2019-2021. All blocks were stained immunohistochemically with E-cadherin and Ber-Ep4. Villous and extravillous trophoblastic cells, surface epithelium and stromal cells in tubal and intrauterine pregnancies were evaluated according to their immunohistochemical staining intensities.
Results: There was a significant decrease in extravillous syncytiotrophoblast staining in tubal ectopic pregnancies ($p<0.001$). No significant difference was observed in staining with E-cadherin of villous and extravillous cytotrophoblast, villous syncytiotrophoblast, stroma and surface epithelium between tubal and intrauterine pregnancies. Ber-ep4 expression intensity was found to be lower in villous cytotrophoblasts in intrauterine pregnancies than tubal pregnancies ($p=0.01$).
Conclusion: Epithelial mesenchymal transition (EMT) is a physiological process in which cells lose their adhesion and undergo mesenchymal character such as migration and invasion. Decreased E-cadherin expression has been reported to be the hallmark of this cellular process. Ber-ep4 is known to be anti Ep-Cam which is also an adhesion molecule Although elucidating the underlying cellular mechanisms remains limited, e-cadherin may play a role in the development of ectopic pregnancy via extravillous syncytiotrophoblasts and Ber-Ep4 via villous cytotrophoblasts.

E-PS-09-035
Mixed adenoneuroendocrine carcinoma (MANEC) of the uterine cervix: unravelling its histogenesis
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Background & objectives: Neuroendocrine carcinomas of the uterine cervix are very rare and often occur in association with other neoplasms. Herein we describe a mixed adenoneuroendocrine carcinoma (MANEC) of the uterine cervix, a very rare entity with few cases reported in the literature.
Methods: A 46-year-old woman presented with atypical glandular cells on cytology, followed by low-grade intraepithelial lesion on cervical biopsy, associated with Human Papillomavirus (HPV) 18. Conization was performed, with histological observation of the whole specimen and immunohistochemical study.
Results: Histological examination showed a neoplasia with two distinct components: an adenocarcinoma of usual type (predominant) with glandular and cribriform architecture and Silva growth pattern-B; and neuroendocrine carcinoma with a solid nested growth pattern with monotonous cuboid small-cells, oval nuclei, occasional eosinophilic granules, and 12 mitotic figures/2mm2. In the tumour periphery, the endocervical glands showed adenocarcinoma in situ (AIS) and wedged between the AIS cells and situated along its basement membrane, there were many endocrine cells forming linear and micronodular clusters. Strong and diffuse block staining for p16 was found in both components. Chromogranin-A and synaptophysin were positive in neuroendocrine component.
Conclusion: Cervical MANECs are very rare neoplasms associated with high-risk HPV-infection. No conclusive studies addressed their histogenesis. They may arise from simultaneous proliferation of multiple cell-lineages or from a common stem-cell capable of differentiating along different cell-lineages. Molecular studies from lung and gastrointestinal tumours demonstrated that the two components are clonally related and thus derive from a common progenitor cell. Our finding of co-localized AIS and neuroendocrine precursor lesions also supports the common progenitor cell histogenesis in cervical MANECs.

E-PS-09-036
Primary carcinoid of uterus. Case report and review of the literature
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Background & objectives: Neuroendocrine tumours of the cervix are rare. Uterine carcinoids are distinct neuroendocrine tumours, representing a comparatively small percentage, 2% of them. These well-differentiated neoplasms are far less prevalent than small- and large-cell carcinomas, characterized by a more favourable biological course.
Methods: Endometrial curettage biopsy was performed first with the result of Endometrial Hyperplasia with Atypia. Total abdominal hysterectomy was performed and the result was an incidental Endometrial Carcinoid in the mucosa.
Results: Neuroendocrine tumours of the cervix are rare and often under- or misdiagnosed. Uterine carcinoids are distinct neuroendocrine tumours, representing a comparatively small percentage, 2% of them. These well-differentiated neoplasms are far less prevalent than small- and large-cell carcinomas, characterized by a more favourable biological course. This study presents a case of typical carcinoid tumour of the uterine corpus in a 56-year-old

woman. The tumour was a primary carcinoid tumour arising from the endometrium which showed as a polipoid mass, with the typical organoid patterns with a positive reaction for neuroendocrine markers. No evidence for the carcinoid syndrome was noted. She remains free of disease.
Conclusion: Scant reports in the literature prohibit any reliable prediction of uterine carcinoid prognosis. Thus, prompt identification of the disease and subsequent therapeutic intervention could alter the final outcome.

E-PS-09-037
HER2 expression and mismatch repair status in endometrial clear cell carcinoma
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Background & objectives: High-grade endometrial carcinomas (HGEC) are difficult to classify. With the current use of HER2-based therapy in serous carcinoma, a diagnosis of CCC has the potential to exclude patients from receiving therapy. Therefore, we examined HER2 expression in our CCC patients.
Methods: Immunohistochemically, HER2, ER, PR, HNF1β, Napsin A, MLH1, MSH2, MSH6 and PMS2 were applied to 8 endometrial CCC cases diagnosed between 2016-2022. HER2 staining pattern, ASCO/CAP protocol used for breast was used.
Results: HER2 was positive in 3 of our 8 CCC patients (37.5%). While all of our HER2+ cases were Napsin A and HNF1β positive, MMR proteins were intact and ER and PR were negative. Two patients had wild type p53 and 1 patient had aberrant p53 staining.
Conclusion: The fact that 37.5% of our CCC cases were HER2+ is a finding with strong implications for the therapeutic approach. As a result of our study, in patients with CCC, if MMR is intact and ER-PR is negative, regardless of the p53 staining pattern, HER2 testing may be an objective screening method for patients who are likely to benefit from HER-targeted therapy. Consequently, patients with a diagnosis of CCC can be candidates for future clinical trials of HER2-targeted therapy.

E-PS-09-039
Evaluation of PD-L1 expression in vulvar cancer
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Background & objectives: The PD-L1 pathway role is still debated in gynaecological malignincies. We analysed PD-L1 expression in vulvar cancer by immunohistochemistry and its correlation with histoprognostic factors.
Methods: A retrospective study was conducted in the Pathology Department of Saleh Azaiez Institute, involving 55 patients followed for vulvar cancer over a period of 13 years, from January 2008 to December 2021. Clinicopathologic data were collected from medical records and pathology reports. Immunohistochemical analysis was performed using an automaton (LeicaBiosystems™).
Results: PD-L1 expression in vulvar squamous cell carcinoma was observed in 44% of cases. This expression was noted in 11% of cases at the level of lymphocytes. Lymph node dissection was negative among all these cases with a maximum tumour size of 40 mm. PD-L1 was expressed in tumour cells in 33% of cases. Among them, positive inguinal dissection was observed in 22% of cases, with a maximum tumour size of 90 mm.
Conclusion: PD-L1 expression was detectable in a subset of vulvar squamous cell carcinoma. Cases with PD-L1 expression on tumour cells showed less favourable histoprognostic factors, which suggests its implication in tumour progression. The PD-1/PD-L1 pathway represents a promising prognostic factor and therapeutic target that may optimize the therapeutic management of vulvar cancer.

E-PS-09-040
Vulvar fibroadenoma: a case report
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Background & objectives: The vulvar fibroadenoma is a rare oligosymptomatic benign nodular tumour. The most accepted theory about its origin is the failure of milk line regression in embryonic development.
Methods: This is a case report of a vulvar fibroadenoma in a 40-year-old female patient with a vulvar ulcerated lesion that has not healed for 6 months.
Results: The patient reported a left vulvar lesion that had not healed for 6 months. Biopsy was performed, obtaining a fragment of skin at subcutaneous level. Macroscopy revealed a single hypochromic, elevated, asymmetric lesion with a regular border, with dimensions 0.7 x 0.7 cm in area and 0.5 cm thick. Microscopy showed glands in a lobular pattern similar to mammary tissue, with cystic changes and apocrine metaplasia. Compressed ducts were seen in the dense fibrotic stroma, similar to breast fibroadenoma. Without evidence of mitosis figures and other signs of malignancy.
Conclusion: The occurrence of vulvar fibroadenoma is extremely rare in the literature, there are about 60 cases described in the world. With this, there is a need to disseminate information about this pathology so that cases like this can be clarified. The case reported has aspects in agreement with those reported in the world literature, such as the patient's age group and the characteristic of the lesion, which is elevated and has irregular edges.

E-PS-09-041
Ovarian mixed malignant Brenner-mucinous tumour: report of a unique case
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Background & objectives: Malignant Brenner tumour is a rare ovarian carcinoma. The presence of an associated malignant mucinous component is exceptionally reported. This study aims to describe the pathological and immunohistochemical features of a unique case of ovarian mixed malignant Brenner-mucinous tumour.
Methods: Clinical data and history were extracted from the patient medical records. Immunohistochemical (IHC) analysis and molecular characterization by Next-Generation sequencing were performed.
Results: A 65-year-old woman underwent surgery for a 5 cm left ovarian lesion. Gross examination revealed a partly cystic, multiloculated mass filled with abundant gelatinous mucinous substance.

Microscopically, the lesion was morphologically heterogeneous, consisting of a poorly differentiated transitional component (IHC: GATA3+, p63+) interspersed with areas of mucinous carcinoma of intestinal type (IHC: CK7-, CK20+/-, CDX2+, SATB2-, GATA3-). In addition, areas of borderline and benign Brenner tumour were present. The neoplasm was confined to the ovary. Molecular analysis by NGS panel identified PIK3CA and TP53 mutations in both components. Patient is disease-free at 24 months after diagnosis and adjuvant chemotherapy.
Conclusion: Although benign Brenner tumours with a mucinous component are relatively common, the combination of a primary ovarian mucinous carcinoma with a malignant Brenner tumour is unique and has been exceptionally reported in literature. Integration of an adequate immunohistochemical profile and molecular analysis is crucial for a correct diagnosis.

E-PS-09-042
An exceptional case of primary ovarian angiosarcoma
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Background & objectives: Primary angiosarcomas of the ovary are exceptionally reported neoplasms, some of which associated with mature teratomas. The aim of the study is to present the clinicopathological and immunohistochemical features of a case of ovarian angiosarcoma.
Methods: Clinical data and history were extracted from the patient's medical records. An extensive immunohistochemical profile was performed together with molecular analysis by Next-Generation sequencing panels and in situ hybridization.
Results: A 40-year-old patient, with a previous resection of ovarian mature teratoma, underwent bilateral hystero-annessiectomy, omentenctomy, and peritoneal biopsy for a right ovarian mass suggestive for malignancy. Microscopic examination showed a high-grade neoplasm of predominantly undifferentiated appearance with extensive areas of haemorrhage and necrosis. Tumour cells were epithelioid and spindle with marked pleomorphism and prominent nucleoli. Mitotic rate was of 3 mitoses/HPF. Peripherally, the lesion showed abnormal vascular-forming endothelial cells associated with papillary-like projections. The immunohistochemical profile showed negativity for epithelial, melanocytic, sex-cord and muscular markers. Diffuse and strong expression of CD31, ERG and partial expression of CD34 and CD117 were present. No significant genetic and molecular alterations were observed.
Conclusion: Ovarian angiosarcoma is a challenging diagnosis that requires an accurate microscopic evaluation. Only few cases have been reported in literature. Histological features include the presence of undifferentiated and proliferating tumour cells with epithelioid and spindle appearance, associated with aberrant vessels and a marked CD31 positivity. It is also crucial to rule out all the other histotypes characterized by morphological overlapping (i.e. melanomas, carcinomas, sex-cord tumours and sarcomas).

E-PS-09-043
Clinicopathological features of two ultra-rare cases of malignant Perivascular Epithelioid Cell Tumours (PEComas) involving uterus
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Background & objectives: Malignant perivascular epithelioid tumours (PEComa) involving the uterine corpus are extremely uncommon tumours. Herein, we present clinicopathological features of two such rare cases.
Methods: Case1 A 62-year-old-lady presented with vaginal bleeding. Ultrasonogram revealed a heterogeneous uterine mass. She underwent endometrial biopsy and total abdominal hysterectomy with bilateral salpingo-oophorectomy(TAH-BSO), which revealed 3.2 cm-sized proliferative tumour in the fundus.
Cae2 A 45-year-old-lady presented with recurrent abdominal pain. She underwent cytoreductive surgery twice with adjuvant chemotherapy for multiple tumours and TAH-BSO for uterine tumour, 2 years back.
Results: Microscopic examination in both cases revealed hypercellular tumours composed of markedly atypical, polygonal-shaped/epithelioid cells arranged in nesting pattern with intervening blood vessels, containing eosinophilic cytoplasm, mitotic figures ($\geq$6/10 hpf) and tumour necrosis. Tumour infiltration was more than half the myometrial thickness in the first case with pelvic nodal metastasis. The second tumour revealed rhabdoid-like and vacuolated cells along with scattered osteoclastic giant cells. Immunohistochemically, both tumours were positive for HMB45 and desmin while negative for S100P and epithelial markers. The second tumour was also positive for SMA and TFE3. Both patients developed tumour recurrences. In view of multiple tumour deposits, the second patient was induced on m-TOR inhibitor everolimus.
Conclusion: Malignant PEComas involving the uterus are extremely rare tumours. An index of suspicion, based on certain histomorphological features, supported by immunohistochemical expression of myomelanocytic markers is necessary for a correct diagnosis. Certain PEComas display TFE3 positivity. A correct diagnosis has significant implications, including an aggressive clinical course and the possibility of targeted therapy, especially in recurrent or metastatic tumour settings, as observed in our second case.

E-PS-09-044
Hydatiform mole: clinico-pathological characteristics in the central Tunisian region
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Background & objectives: Hydatidiform mole is defined as a partial or complete hydropic degeneration of the chorionic villi with variable degree of trophoblastic cells proloferation. It is a heterogeneous group of rare and aggressive disease which evolution may be marked by malignant transformation.
Methods: we aim to investigate the clinical and pathological characteristics of hydatidiform mole. This is a retrospective study of 59 cases of hydatidiform mole. The cases were collected in the department of pathology of the Farhat Hached Hospital, Sousse, Tunisia over a period of 5 years [2016-2020].
Results: The mean age of our patients was 35 years. Metrorrhagia in a context of amenorrhoea was the most frequent revealing symptom (80%). BHCG levels were high in 100% of cases. Ultrasound examination was suggestive of molar pregnancy in 71% of cases. Endouterine aspiration was performed in 96% of the patients. Urgent hysterectomy was performed in two cases due to the abundance of metrorrhagia. Histological examination found complete mole in 36 cases (61%) and partial mole in 23 cases (39%). The evolution was marked by transformation into invasive mole in 3 cases (4%), confirmed on postoperative hysterectomy specimen.

Conclusion: Hydatidiform mole is real public health problem in developing countries. Ultrasound and elevated BHCG levels are reliable diagnostic tests. Microscopic examination allows the classification of hydatidiform mole into complete mole and partial mole. This distinction is sometimes difficult, hence the interest of a complementary immunohistochemical study using anti-p57 antibodies. Early diagnosis of a degeneration into invasive mole or choriocarcinoma is based on close monitoring.

E-PS-09-045

Mixed Müllerian tumours of the ovary: a Tunisian case series

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Background & objectives: Malignant mixed Mullerian tumours (MMMT) of the ovary, also called carcinosarcoma, are defined by the presence of a double epithelial and mesenchymal component. These aggressive neoplasms originate from the Mullerian derivatives of the female genital tract. The prognosis is very poor.
Methods: Ten cases of MMMT were collected in the department of pathology of the Farhat Hached hospital, Sousse, over a period of 10 years. The various data were collected from the medical files and the pathology reports. Immunohistochemistry was performed on 4 µm FFPE tissue sections. The antibodies used were cytokeratin, vimentin, desmin, h-caldesmone, myogenin and protein S100.
Results: Mean age was 53 years. The main symptom was pelvic pain. Tumour was bilateral in two cases with a FIGO stage of IIa in one patient, IIIc in three patients and IV in six patients. Total hysterectomy with bilateral adnexectomy was performed in eight patients followed by chemotherapy in seven patients. Microscopic and immunohistochemical study revealed the presence of a heterologous component in six patients, this component was rhabdomyosarcomatous in four cases and chondrosarcomatous in two cases.
Conclusion: MMMT of the ovary is rare representing 2% of malignant ovarian tumours. pathological examination is the key examination for the diagnosis and staging of these tumours. MMMT are histologically defined by the presence of dual-component tumour, with a high-grade carcinomatous epithelial component and a sarcomatous mesenchymal component that may be homologous or heterologous. The heterologous component may be rhabdomyosarcomatous, chondrosarcomatous or, more rarely, osteosarcomatous. The prognosis is poor with a median survival of less than 24 months.

E-PS-09-046

Vitamin E reduces the suppression of oestrogen receptors in the rat endometrium caused by exposure to heavy metals

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Background & objectives: The spread of heavy metals is directly related to the growing risk of uterine pathologies. Moreover, disorders of uterine hormonal sensitivity depend on pollutants combinations, concentration, pathways and exposure duration.
Methods: Female rats were divided into control (group I) and experimental groups. Experimental rats were orally treated by HMs (Zn, Cu, Fe, Mn, Pb, Cr) with (group III) and without vitamin E (group II) administration for 90 days. The immunohistochemical investigation was performed utilizing primary antibodies to ER (rabbit anti-ER Monoclonal Antibody – E115 clone).
Results: A strong (+++) positive nuclear ER immunoexpression was found in the majority of the epithelial (luminal and glandular) and stromal cells of the endometrium of control animals. In contrast, the level of ER-positive endometrial cells was significantly decreased (+) in HM-treated rats (group II). Herewith, vitamin E administration leads to a suppression decrease of ER expression (++) in the rat endometrium (group III), compared to the II experimental group. Moreover, the intensity of ER signal was also reduced in both experimental groups.
Conclusion: The prolonged influence of heavy metals leads to a significant decrease in ER expression and its intensity in rats' endometrium. Vitamin E supplementation is accompanied by less pronounced changes in the generation of oestrogen receptors in the uterine mucosa in heavy metals-exposed rats.

E-PS-09-047

Clinicopathological features of clear cell carcinomas of the uterus: a single institutional experience, India

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Background & objectives: Clear cell carcinoma (CCC) of the uterine corpus is an uncommon yet aggressive malignancy, with few studies evaluating its clinicopathological features, including none from our country. This retrospective study aims at analysing various clinicopathologic features of uterine CCCs.
Methods: Twenty two CCCs of the uterus were reviewed. Three cases were excluded. Remaining 19 cases were analysed for various clinicopathological features, including outcomes. Immunohistochemical expression of Napsin A was graded as 1+(<10% tumour cells), 2+(10-60%) and 3+(>60% staining pattern. Age-range was 40-75 years(median=63). Thirteen patients had endometrial tumours, 5 had cervical and one patient had tumour in endometrium and cervix.
Results: Average tumour-size(n=15) was 4.5 cm. Stage-wise(n=7), patients had 1A(n=2), 1B(n=1), III(n=3) and IV(n=1) tumours. Most common histopathologic pattern was tubulocystic+papillary(n=14,73.6%), followed by solid/hypernephroid(n=2,10.5%). Thirteen were pure CCCs, while six were mixed-types, including serous(n=4), endometrioid(n=1) and serous+endometrioid(n=1) components. Myometrial infiltration ≥50% was in 5/11(45.4%) cases and lymphovascular invasion in 4/16(25%) cases. Immunohistochemically, tumour cells were positive for Napsin A(19/19, mostly 2+/3+), ER(6/17, 35.3%, variable), PR(4/11, 36.4%), p53(n=15, wild-type=7, mutation-type=8), CK7(4/4) and PAX8(4/4), while negative for WT1(0/6). Therapeutically, 16/19 patients underwent hysterectomy, including total abdominal hysterectomy with bilateral salpingo-oophorectomy(n=9, 56.2%); 8 received adjuvant chemotherapy(CT)+radiotherapy(RT); 2, adjuvant RT, and one received adjuvant CT. On follow-up(n=9, median=6 months), 7 were free-of-disease and 2 were alive-with-disease(recurrence=1, metastasis=1).
Conclusion: CCC of the uterine corpus is a rare tumour, mostly involved the endometrium. An index of suspicion based on certain morphological features, supplemented with Napsin A immunostain, in our settings, is useful for its exact diagnosis. Most cases were treated with surgical resection, followed by adjuvant therapies in some. Rarely, mixed patterns, including component of serous and endometrioid types co-exist, the former, associated with p53-mutation type expression.

E-PS-09-048

Mucinous borderline ovarian tumours: challenging diagnostic

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Background & objectives: Ovarian mucinous borderline tumours (MBT) are characterized by an epithelial proliferation similar to those of well differentiated adenocarcinomas but are distinguished by the absence of stromal invasion. The aim of the work was to specify the pathological and clinical features.
Methods: Retrospective study including 49 cases of primary ovarian MBT, diagnosed at the Patholgy Department of Salah Azaiez Institute from 1992 to 2019. We included in our study all patients who presented with a primary MBT on a surgical specimen. The collection of clinical data was made from the medical records.
Results: Median age was 48 years old. Histologically, the cases were divided into 34 cases of pure MBT, 13 cases with intraepithelial carcinoma and 2 cases associating an intraepithelial carcinoma with microinvasion. The majority of our cases were classified FIGO I and only one case FIGO III. Sixteen patients received conservative treatment and 30 received radical treatment. The treatment wasn't specified in three patients. The prognosis was good in the majority of cases. Only one patient had a contralateral recurrence after a follow-up period of three years.
Conclusion: The diagnosis of MBT is difficult. Indeed, the distinction of MBT from carcinomas remains the greatest challenge for pathologists. Once this diagnosis is made with certainty, the tumour can be considered to have a good prognosis, especially stage I tumours which are the most common. Prospective and multicentre studies would be necessary for a better understanding of these tumours and their evolution.

E-PS-09-049

The role of eIF signalling in benign proliferative disorders of the endometrium

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Background & objectives: Adenomyosis, endometriosis and typical endometrial hyperplasia are common benign proliferative disorders of the endometrium that afflict many women with life-impacting consequences. The aim of this analysis was to explore the impact of different translational markers on non-malignant endometrial diseases.
Methods: We assessed evidence on the expression of eukaryotic translation initiation factors (eIFs) in adenomyosis, endometriosis and typical endometrial hyperplasia compared to their expression in normal endometrium. We analysed the impact of deranged eIF expression on endometrial function and pathogenesis of non-malignant neoplastic endometrial disorders. This database analysis was performed through PubMed and Google Scholar.
Results: Adenomyosis is characterized by dysregulation of eIF2 and eIF4 signalling. The factors eIF4a2, eIF3K and eIF4b are expressed differently between adenomyotic and normal endometrium. Furthermore, decreased expression of eIF3e in adenomyosis and ovarian endometriosis tissue has been implied to promote EMT in these conditions via TGF-β1 or Snail activation. In addition, eIF2α signalling can serve as a treatment target for endometriosis. Specifically, the progestin medication dienogest as well as the flavonoids naringenin and chrysin exhibit a suppressive role in endometriotic cell lines by activating eIF2α and thus enhancing endoplasmic reticulum stress. Moreover, eIF2α signalling seems to be involved in the pathogenesis of typical endometrial hyperplasia in PCOS.
Conclusion: eIF signalling is dysregulated in adenomyosis, endometriosis and typical endometrial hyperplasia. The derangement of eIF2, eIF3 and eIF4 expression seems to contribute to the development of these benign endometrial conditions and those eIFs may serve as druggable targets for these life-impacting diseases.

E-PS-09-050

Collision tumour: a rare case report

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Background & objectives: Collision tumours are composed of two histologically distinct neoplasm in the same organ without intermixture of cell types. We present here the case of a 79 years female with bilateral high grade serous carcinoma with mature cystic teratoma.
Methods: Microscopic examination revealed hematoxylin sections of the right and left ovaries, with cystic structure containing skin joints keratin hair follicles, tumoral islands with bizarre nuclei in large necrosis areas Bilateral fallopian tubes also showed high grade serous carcinoma. In the immunohistochemical study, tumour cells were stained positive with CK 7P53 and negative with CK20 CDX2. Ki 67 proliferation index is 90%.
Results: Collision tumour containing bilateral serous carcinoma and mature cystic teratoma component is very rare entity.
Conclusion: Collision tumour containing bilateral serous carcinoma and mature cystic teratoma component is very rare entity.

E-PS-09-051

High-grade endometrial carcinomas: diagnostic challenges

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Background & objectives: The distinction of certain histologic subtypes of high grade carcinomas is not uncommonly problematic, and as such, immunohistochemical study is often needed. We performed an overview of the histologic and immunohistochemical features of the different subtypes of high-grade endometrial carcinomas.
Methods: Retrospective study of 26 high-grade endometrial carcinomas collected in the pathology laboratory of Salah Azaiez Institute in Tunis over a period of 20 years. We selected the cases of high-grade endometrial carcinomas that couldn't be classified based only on the histopathology and required complementary immunohistochemistry. We performed clinicopathology data collection which involved age, tumour size, histologic subtype and immunohistochemical data.
Results: The average age was 63 years old. Endometrioid carcinoma grade 3 represent 23%, serous carcinoma 27%, clear cell carcinoma 8%, carcinosarcoma 19% and 23% of cases were classified as high grade carcinoma. The most frequent immunohistochemical profile for endometrioid carcinoma grade 3 is strong positivity for ER/PR, negativity to patchy positivity for p16, and wild-type p53 staining pattern. Serous carcinomas were mutation-type p53 staining, ER and PR variable postivity and strong p16 positivity. Clear cell carcinomas were negative for ER, RP, p16 and p53. Carcinosarcoma profile was focal CD10 staining and negativity of cytokeratin, vimentine and caldesmone. Immunohistochemistry was inconclusive in five cases classified as high grade carcinoma.

Conclusion: In summary, the use of ancillary testing, including immunohistochemistry, is helpful in the identification, differential diagnosis, and classification of high grade endometrial cancers.

E-PS-09-052

Microenvironment of endometrial cancer: are there new prognostic and theranostic biomarkers?

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Background & objectives: Endometrial carcinoma is an ever-growing gynaecologic malignancy worldwide. PD1/PDL1 immune checkpoints are among the important players of immunosuppression in the tumour microenvironment. We determined the level of PD1 and PDL1 expression in the tumour environment and their impact on prognosis.
Methods: This was a retrospective, descriptive study of a series of 46 cases of endometrioid carcinoma at the Salah Azaiez Institute collected between 2007 and 2017.
Results: Our series included 70% of postmenopausal patients. Stage I (45.6%) and grade 1 (41.3%) were the most dominant. Immunohistochemical analysis showed a higher expression of PDL1in tumour-infiltrating lymphocytes (26%) than in tumour cells (17%). As for PD1, this protein was expressed in 63% of cases. Statistical correlation revealed a correlation between PDL1 expression and menopausal status (P=0.001 and P=0.014). Indeed, PDL1 expression in epithelial cells was positively associated with less than 50% myometrial invasion (P=0.037). However, no association was found between PD1 expression and histoponostic features. We found that endometrial carcinoma has a heterogeneous immunogenic profile, which emphasizes the controversial role of PD1/PDL1 immune checkpoints in tumour progression.
Conclusion: PD1/PDL1 expression in endometrioid adenocarcinoma is remarkable, without relevant association with prognostic elements. Future research on large cohorts may be useful to detect clearly the role of biomarkers in tumour progression.

E-PS-09-053

Pregnancy luteoma: a rare lesion as an incidental finding. Case report

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Background & objectives: Pregnancy luteomas (PL) are rare, non-neoplastic proliferation of luteinized cells during pregnancy, forming single or multiple nodules in ovaries. Are thought to be caused by the hormonal effects of pregnancy. Most are asymptomatic and incidentally discovered during imaging or surgery.
Methods: 33-year-old woman in her second full term pregnancy, with gestational-diabetes, was admitted in obstetrics ward for occlusive placenta previa. The patient underwent caesarean section. A female baby was born without complications. Intraoperatively, surgeons found right sided ovarian mass measuring 3,7cm, semi-soft, brownish. Suspecting that it was an ovarian neoplasm, unilateral oophorectomy was performed. The specimen was subjected to histopathological examination.
Results: Macroscopic-examination showed an enlarged ovary measuring 3.7x2.5x2cm. Cut surface of the ovary was circumscribed, soft, fleshy, and gray-brown. Microscopically, the lesion showed well defined margin, with solid growth pattern of polygonal luteinized cells with abundant amount of finely granular eosinophilic cytoplasm, and frequently showed follicle-like spaces filled with eosinophilic-fluid. Nuclei were small, round, vesicular with prominent nucleoli, that did not contain stainable lipid. Occasional mitotic figures, without areas of necrosis. Reinke crystals were not found. Immunohistochemical-stains showed strong-positivity Calretinin, Inhibin-A, Melan-A; were negative for CKAE1/AE3, CKCam5.2, S100; and Reticulin enveloped clusters of cells. The final diagnosis of PL was made. Two years later the patient is asymptomatic and without recurrence.
Conclusion: PL is a rare tumour-like lesion mostly appearing in late-pregnancy, probably secondary to high-levels of human-chorionic-gonadotropin, that will usually regress spontaneously. We present a case of PL detected incidentally during a caesarean-section. It is important to bear this condition in mind, as it is rare and thus misdiagnosis and inappropriate treatment may occur. The main-differential-diagnoses include Steroid-cell-tumour, Luteinized adult granulosa cell tumour or thecoma, Juvenile granulosa cell tumour, Metastatic-carcinoma. The gross, immunohistochemical-staining, and reticular-fiber-staining results may help diagnose this disease.

E-PS-09-054

Chemotherapy and breast cancer gene (BRCA) mutation associate with quantified tumour infiltrating lymphocytes in high-grades serous ovarian carcinoma

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Background & objectives: There is a controversy about the role of tumour infiltrating lymphocytes (TILs) and BRCA gene mutation as prognostic biomarkers in high-grade serous ovarian carcinoma (HGSOC). By this reason, we have evaluated the clinical significance of quantified TILs in HGSOC.
Methods: A series of 48 HGSOC III or IV staged (FIGO) cases were studied. H&E representative sections were evaluated in a blinded manner semiquantitatively and digitally using learning image analysis algorithms. Intraepithelial and stromal TILS in representative areas were selected. BRCA gene mutation was determined by next generation sequencing using Illumina platform. Statistical evaluation using SPSS software was applied.
Results: Morphologically, in tumours with neoadjuvant treatment a striking intraepithelial TILs infiltration was observed. BRCA gene mutated and neoadjuvant treated carcinomas cases were 35% and 50%, respectively. Stromal TILs in both neoadjuvant treated and BRCA gene mutated tumours were higher than non-neoadjuvant and BRCA gene mutated ones (p=0.038). Neoadjuvant chemotherapy treated carcinomas showed a higher number of stromal TILs than in non-neoadjuvant ones, although differences were not statistically significant. No difference of TILs density in mutated in respect with wild-type BRCA gene carcinomas was observed. The median of patient survival was 70 months, with no difference between mutated and wild-type BRCA gene mutated neoplasms.
Conclusion: Neodjuvant chemotherapy plus BRCA gene mutation produce a significant increase in stromal TILs density in HGSOC, but it has not relationship with survival. BRCA gene mutation has not been associated with a higher survival. We postulate a possible TILs recruiting effect of neoadjuvant chemotherapy on BRCA gene mutated tumours.

E-PS-09-055

Langerhans cell histiocytosis: a case report and review of the literature

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Background & objectives: Langerhans cell histiocytosis is a rare group of diseases that comprises a wide spectrum of diseases initially known as histiocytosis and there are few cases described in the literature on topography of the vulva.
Methods: Report case of 65 years old woman in the climacteric period, with a clinical history of long lasting vulvar burning and itching, combined with the presence of erytema and cracks, with a diagnostic suspicion of sclerosus lichen was submitted to a vulvar biopsy.
Results: The histopathologic showed an atypical cell proliferation at the submucosa, abnormal immature Langerhans cell proliferation rounded by eosinophils, macrophages and Birbeck granules. Immunohistochemical reveals positivity to CD1, CD68, Ki-67 and S-100 protein markers and negativity to AE1/AE3, CD138, CD20, CD3, CD30, Ki-1, CD45, HMB45, Melan-A, MPO, MUM 1 and SOX-10 markers.
Conclusion: LCH should be considered in the diagnosis of vulvar lesions and when it occurs in only at this site it has the potential for aggressive clinical behaviour, either as a local recurrence or as a disseminated disease.

E-PS-09-056

Small cell carcinoma of ovary, hypercalcemic type: the synergism of immunostains and molecular studies

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Background & objectives: Small cell carcinoma of ovary, hypercalcemic type (SCCOHT) is a rare tumour with typical immunoprofile and mutations in SMARCA4. Here we describe a SCCOHT case with unusual immunostain results. The combination of molecular studies and immunostains enabled the diagnosis.
Methods: The medical records, imaging tests, pathological findings and molecular studies of the patient have been studied and are presented.
Results: A 12 years old female premenarche adolescent presented with abdominal pain. Pelvic US revealed enlarged ovary of 9 cm in diameter and oophorectomy was performed. Histological evaluation showed undifferentiated small round cell malignant tumour with positive staining for SALL4 (focally), MNF116 (focally), synaptophysin, CD99 (diffusely), Fli-1 (diffusely), BRG1 (focally), SATB2, TLE1 and BCL1 with Ki67 of 80%. The stains for CD30, LCA, inhibin, SOX10, PLAP, OCT4, D2-40, CD117, AFP, myogenin, CD3, CD20, AE1/AE3, EMA, CK7, CK20, FOXL2, calretinin, myogenin, desmin, chromogranin, CD56, WT1 and NKX2.2 were all negative. Various FISH studies were negative for rearrangements but FoundationOne Heme test identified a mutation in SMARCA4 (splice site 2438+1G>A).
Conclusion: A diagnosis of SCCOHT was made in spite of negative staining for WT1 and retained but attenuated staining for BRG1. It is the combination of elaborated immunostaining, FISH studies and extensive genetic analysis that brought to this rare diagnosis. As genetic studies become more prevalent, it is expected to note growing variability in gene expression for any described gene alteration, that should not exclude the related diagnosis. The synergism of the various available techniques is crucial for accurate diagnosis.

E-PS-09-057

Transitional cell neoplasm in both ovaries with serous tubal intraepithelial carcinoma-like lesion, ovarian origin or metastases?

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Background & objectives: The ovary is the most common location of metastases in the gynaecological tract. Serous tubal intraepithelial carcinoma (STIC) is considered a high grade serous carcinoma precursor but metastases to the epithelium of the fallopian tube can mimic STIC.
Methods: We present a 64-year-old woman with history of nephroureterectomy and recurrent high-grade urothelial carcinoma of the bladder. A CT scan revealed a left ovarian mass suspicious of malignant primary ovarian neoplasm, so she underwent surgical staging including hysterectomy with bilateral salpingooophorectomy and omentectomy.
Results: The left ovary (17cm) and right ovary (4cm) showed a neoplasm with a solid-transitional cell pattern. The left fallopian tube showed in situ epithelial proliferation with nuclear stratification, marked nuclear pleomorphism, mitotic figures and positive p53 staining resembling a STIC. Although the morphological appearance in the ovaries and fallopian tube was concordant with a high grade serous carcinoma, the differential diagnosis included metastatic urothelial carcinoma due to its previous history. Immunohistochemistry showed strong and diffuse nuclear staining for p53 but negativity for WT1. In addition, the tumour showed diffuse cytoplasmic positivity for CK7 and CK20, p63 and GATA3, concordant with a metastatic urothelial carcinoma.
Conclusion: Urothelial carcinoma metastases to the ovary and fallopian tube are extremely rare, with only few cases described in the literature. Diagnosis is not easy due to its resemblance to primary ovarian carcinomas with a transitional cell pattern. In present case, the presence of STIC-like lesions added difficulty to the recognition of the metastatic nature of the lesions. Therefore, the final diagnosis should be made based on the clinical history and the immunohistochemical profile.

E-PS-10 | E-Posters Haematopathology

E-PS-10-001

Follicular lymphoma masquerading as Crohn's disease. A case report with literature review

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Background & objectives: While Follicular lymphoma (FL) is largely a nodal disease, it can be primarily extranodal, and mimic other neoplastic or non-neoplastic conditions clinically and radiologically. We report a patient with FL presented with a terminal ileal ulcer clinically mimicking a Crohn's disease.
Methods: A 56 year-old man with no past medical history had positive faecal occult blood test upon screening in year 2017. A circumscribed terminal ileal ulcer was identified on colonoscopy. Biopsy revealed an ulcer base and inflamed granulation tissue with no granuloma, infective organism or dysplasia.

Results: Patient subsequently lost in follow up and came back 4 years later with another positive faecal occult blood test. The same terminal ileal ulcer with similar histological findings on biopsy were obtained. A clinical impression of Crohn's disease was rendered after excluding infectious aetiologies. Computerised tomography (CT) scan showed enhanced, circumferential mural thickening in the terminal ileum with surrounding fat stranding, suspicious for neoplastic conditions. Right hemicolectomy was eventually performed 3 months later and disclosed a FL, WHO grade 2 and 3A, involving the terminal ileum, appendix, caecum and mesenteric lymph nodes, with an overlying ulcer and granulation tissue. No evidence of Crohn's disease is identified.
Conclusion: The review of slides from previous biopsy proved no discrete evidence of lymphoma. The case re-emphasizes the importance of representative sampling for histological examination and interdisciplinary discussion.

E-PS-10-004
Aggressive CD5 + MALT lymphoma in a patient from an ultrasound-guided minimally invasive autopsy: a case report
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Background & objectives: Expression of CD5 has been described typically in CLL/SLL and mantle cell lymphoma, but also in a subset of MALT lymphomas. According to the literature, CD5+ MALT tends to originate in nongastric locations with an aggressive behaviour and disseminated disease.
Methods: We report a case of an 85-year-old woman previously diagnosed with ocular aggressive MALT lymphoma, with both parotids involvement and multiples lymphadenopathies. An Ultrasound Guided Minimally Invasive Autopsy (US-MIA) was accomplished. US Fine Needle Aspiration and Core Needle Biopsy of right orbital and parotid lesions were performed, and adequate material were sent to Flow Cytometry, Cytogenetic and Molecular Oncology laboratories.
Results: The gross autopsy examination showed tumoral lesions in both breasts, trachea, larynx, thyroid gland, oesophagus, right orbital and both parotids that were confirmed later in the microscopic study. All these lesions were morphologically identical, formed by small- to medium-sized cells with round to slightly irregular nuclear contours, dispersed chromatin, and a moderate amount of cytoplasm. The lymphoma cells expressed CD5, CD20, PAX5, BCL2 and were negative for CD10, CD23, Cyclin D1, SOX11, BCL6, MUM1, MNDA and LEF1. Moreover, molecular oncology reported a mutation in MYD88 gen, however our patient never debuted with high levels of IgM.
Conclusion: This case report is interesting for so many reasons: we describe a CD5+ MALT lymphoma with a disseminated disease at diagnosis, with mutation in MYD88 and an extraordinary aggressive behaviour with a nule response to chemotherapy, causing a prompt fatal outcome to the patient. Besides that, the autopsy study was performed with an unconventional method: ultrasound-guided minimally invasive autopsy with subsequent Rapid On-Site Evaluation -ROSE- of tissue to ensure an adequate specimen on site for additional studies and postmortem diagnosis.

E-PS-10-005
Large B-cell lymphoma with IRF4 rearrangement involving lacrimal gland: a case report
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Background & objectives: Large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4) is reported in the paediatric population, predominantly in tonsil and neck lymph nodes. We report a case of LBCL-IRF4 in an adult female at an unusual location, the lacrimal gland.
Methods: A 34-year-old female presented with persistent epiphora on the left eye for two years despite antibiotics and conservative management. Computed tomography and dacryocystography showed a cystic soft tissue lesion in the proximal and distal lacrimal duct opening with duct obstruction with sac dilatation. Excisional biopsy was performed. Grossly, the tissue was whitish, soft and friable.
Results: Microscopic examination revealed diffuse proliferation of large atypical cells with coarse chromatin, irregular membranes, and occasional small basophilic nucleoli with frequent tingible-body macrophages and mitosis. Immunohistochemistry and EBV in situ hybridization revealed that the tumour cells were positive for CD20, Bcl-6, CD10 and Mum1 but negative for Bcl-2, cyclin D1, c-Myc and EBV-encoded RNA, with no visualization of follicular dendritic cells by CD21 or CD23. Fluorescence in situ hybridization revealed IRF4 rearrangement by using an IRF4/DUSP22 break-apart probe but not the c-Myc or Bcl-2 gene. No other involvement was observed in bone marrow biopsy, peripheral blood smear or positron emission tomography. The final diagnosis of LBCL-IRF4 was made.
Conclusion: LBCL-IRF4 is a rare entity recognized in the revised 4th edition of the WHO Classification of Tumour. It manifests as diffuse, follicular or mixed architecture, making morphological differential diagnosis challenging. As epidemiologic and pathogenetic information are limited, coexpression of CD10, BCL6 and MUM1 should raise suspicion of LBCL-IFR4. Even with unusual extranodal sites and age, IRF4/DUSP22 FISH may lead to the accurate diagnosis of LBCL-IRF4.
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E-PS-10-006
HHV8-positive diffuse large B-cell lymphoma (DLBCL), NOS - a case report and review of the literature
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Background & objectives: HHV8-positive DLBCL NOS, usually arising in association with Multicentric Castleman Disease (MCD) and originating from a naive IGM lambda-positive B cell, is a rare neoplasm with characteristic plasmablastic morphology. A case of HHV8-positive DLBCL, NOS associated with MCD is presented.
Methods: A 74-year-old male patient with history of MCD was admitted with worsening constitutional symptoms (fever, fatigue, loss weight), enlarging of cervical lymph nodes and massive splenomegaly. Laboratory findings included severe anaemia, neutropenia, thrombocytopenia, hypergammaglobulinaemia and elevated C-reactive protein. A right cervical lymph node, measuring 1cm at maximum diameter, was excised.
Results: Histopathological examination revealed effacement of lymph node by a lymphoid neoplasm consisting of large, plasmablastic cells coalescing to large aggregates. Tumour cells had

amphophilic cytoplasm, vesicular nuclei and prominent nucleoli. The mitotic activity was high. Few follicles with atrophic hyalinized germinal centres, "onion skin"mantle zones and prominent endothelial venules, a morphology typical of CD, remained. The differential diagnosis included HHV8-positive DLBCL, NOS and HHV8-positive germinotropic lymphoproliferative disorder(GLPD). On immunohistochemical examination the plasmablastic cells had a LCA+, CD20+, CD138+, MUM1+,HHV-8+ phenotype with lambda light chain restriction and cIGM strong expression. ISH for EBV-encoded small RNA (EBER) was negative. The morphological and immunohistochemical results established the diagnosis of HHV8-positive DLBCL, NOS.
Conclusion: HHV8-associated lymphoproliferative disorders include MCD, HHV8-positive DLBCL, NOS (EBV-negative usually), and HHV8+ germinotropic lymphoproliferative disorder (GLPD) (EBV-positive usually). GLPD patients are asymptomatic and have a favourable response to chemotherapy or radiation, whereas HHV8+ DLBCL is associated with poor prognosis. HHV8+ DLBCL patients in association with MCD usually experience a severe immunodeficiency. The disease, under these circumstances, has an aggressive course. Our patient, a week after the diagnosis, succumbed to his disease.

E-PS-10-007
Hidden mantle cell lymphoma
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Background & objectives: Adenocarcinoma is the most common prostatic malignancy where clinical management, Gleason score (GS) and cancer staging (WHO/ISUP) play critical role in. Mantle cell lymphoma originates from malignant transformed B-lymphocytes of lymph follicle outer edge, with pathognomonic overexpression of CD5/Cyclin D1.
Methods: Tissue specimens were H&E stained and analysed, as well as immunohistochemical biomarker panel for lymph nodes. Performing serial cuts, gross examination showed homogenous appearance of many nodes that were white to greyish, with soft consistency and in different diameters. The prostate was enlarged, measured 6x5x2.5 cm and mostly homogenous in appearance, some spongy consistency and no visible defects during grossing.
Results: A 68-year-old male was referred to our tertiary care institution for elective radical prostatectomy due to previously diagnosed adenocarcinoma performing prostatic core needle biopsy. Having performed a thorough histological examination, diagnosis of prostatic adenocarcinoma with Gleason score 3+4=7, ISUP GG2, was set. Microscopic analysis of lymph nodes were with no metastatic deposits, but unexpected, lymph node architecture was disturbed due to diffuse small lymphoid cell proliferation, with irregular nuclei, wide mantle zone and hyalinized blood vessels. After using immunohistochemical staining, it was shown expression for CD20/CD5/CyclinD1/Bcl-2 and negativity for CD3/CD10/Bcl-6 with proliferative index up to 20%, so additional diagnosis was set, and it was non-Hodgkin mantle B-cell lymphoma.
Conclusion: A prostatic adenocarcinoma can extremely rarely be in a coexistence with undiagnosed lymphoproliferative disease, such as non Hodgkin mantle cell lymphoma in our case. This lymphoma is usually synchronously present with plasma cell dyscrasia or granulomatous diseases such as sarcoidosis. It can also occur with metastasis from a different anatomical site, but in the same lymph node. This case indicates that extensive and detailed lymph node examination is necessary in order to prevent underdiagnosed lymphoproliferations.

E-PS-10-008
A rare case of an Epstein-Bar virus positive mucocutaneous ulcer in the rectum of an HIV positive patient. A case presentation and review of literature
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Background & objectives: Epstein-Bar Virus positive mucocutaneous ulcers (EBVMCU) affect mucosal and cutaneous surfaces, rarely involving the rectum. We present a case of a rectal ulcer in a 40-year-old HIV positive male who complained of severe rectal pain radiating to his thighs.
Methods: Examination under anaesthesia identified a rectal ulcer that was biopsied. The tissue biopsy was stained with Hematoxylin and Eosin. Following initial evaluation, additional stains including Pan-Keratin, SOX-10, MART-1, CD3, CD4, CD8, CD10, CD15, CD20, CD30, CD79a, Ki-67, MUM-1, PAX-5, EBV (EBER), OCT-2, BOB-1, HSV I, HSV II, CMV and GMS were performed. Literature review was done using PubMed.
Results: The histomorphology of the lesion demonstrated a mucosal ulcer and nodular aggregates of inflammatory cells composed of small lymphocytes, eosinophils, granulocytes, plasma cells and histiocytes with scattered large atypical lymphoid cells morphologically mimicking Hodgkin/Reed-Sternberg-like cells. These cells were positive for EBV (EBER), CD30, MUM-1 and BCL-6. PAX 5, BOB1 and OCT-2 showed weak positivity. The cells were negative for CD15, CD20 and CD79a. Based on the histomorphology and immunohistochemical staining pattern, a differential diagnosis of EBVMCU versus mixed-cellularity classic Hodgkin lymphoma was entertained. The clinical history of HIV-positivity, the absence of lymphadenopathy and a reduced CD4/CD8 ratio led to the final diagnosis of EBVMCU.
Conclusion: EBVMCU, a relatively new entity, is associated with advanced age, iatrogenic immunosuppression, HIV/AIDs and post-transplant therapy. While EBVMCUs mimic malignancy, their indolent course typically results in spontaneous regression. The median age is >70-years. Per PubMed search, EBVMCUs primarily involve the oropharynx (69.3%) and cutaneous surfaces. Out of 186 cases reviewed only 3 showed rectal involvement (1.6%). It is important to keep EBVMCU in mind in isolated classic Hodgkin lymphoma-like disease, even in younger patients, especially if they are immunocompromised.

E-PS-10-009
ALK-positive anaplastic large cell lymphomas (ALCL): our experience. Inter-observer variation in the interpretation of ALK immunohistochemistry staining
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Background & objectives: ALK-positive anaplastic large cell lymphoma (ALCL) is a rare T-cell lymphoma. We aim to characterize its clinical and histological features, and to analyse inter-observer variation in evaluation of ALK expression patterns, which correlates with different fusion partner genes.
Methods: This is a retrospective, descriptive report of ten cases diagnosed in the last ten years in the Hospital Doce de Octubre. Patients' characteristics, such as age and gender, and clinical and histopathological data were subtracted from patients' medical records and analysed. Furthermore, ALK immunohistochemistry staining patterns were re-evaluated by three pathologists and inter-observer variation was established using the kappa coefficient.

Results: 70% (n=7) of ALK+ ALCL are men, and only 20% (n=2) are children (<18y). 80% (n=8) were diagnosed at an advanced stage (Ann-Arbor staging III-IV), involving nodal and extranodal sites in 60% (n=6), and limited to nodal compartments in 3 cases (30%). 40% (n=4) had bone marrow involvement, and 30% (n=3) presented hemophagocytic syndrome. Upon follow-up, survival rate is 70% (n=7). 100% of cases are CD30+. Morphological patterns and immunohistochemistry markers were reviewed. Moreover, molecular tests (FISH) for ALK were conducted in two cases. Inter-observer agreement regarding ALK staining pattern was low with a kappa coefficient of 0,197 (CI 95% -0,135-0,520, p value: 0,127).
Conclusion: For the majority of the variables analysed, our findings agree with current knowledge. ALK immunohistochemistry is useful for diagnosis, but there is high inter-observer variability in the assessment of ALK staining patterns; thus, molecular testing may be advisable in order to characterize the genetic alterations. These findings should be consolidated on future studies with a larger sample size and a higher number of observers.

E-PS-10-010
Splenic Epstein-Barr virus (EBV) associated inflammatory pseudotumour (IPT)
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Background & objectives: IPT is a rare lesion that is composed of variable proportion of spindle cells, which can express myofibroblastic or follicular dendritic cell (FDC) markers, interpersed with polymorphous inflammatory cellularity. Splenic IPT associated with EBV infection can be a diagnostic challenge.
Methods: We report the case of a 63-year-old male, with abdominal pain and clinical suspicion of chronic cholecystitis. His initial work up revealed two well-demarcated hypodense solid lesion in his spleen, with abnormally uptake on CT scan, raising suspicion for malignancy. The patient underwent a diagnostic splenectomy.
Results: The histopathological evaluation revealed 4 nodular lesions, with a bland spindle cell population (SMA/LMP-1/EBER+; ALK/CD21/CD23-) associated with a mixed cellular infiltrate composed of lymphocytes, plasma cells, histiocytes and scattered eosinophils. We also identified multiple non necrotizing granulomas, with multi-nucleated giant cells and foreign body reaction. The histological findings were compatible with a diagnosis of splenic inflammatory pseudotumor associated with EBV infection.EBV associated IPTs are slow growing masses that are usually seen in liver, spleen and, less frecuently, in lymph nodes.
Conclusion: Splenic IPT-like FDC tumours and EBV+IPTs without expression of FDC markers are 2related entities that have in common that the spindle cell is the one infected by EBV.Both are considered low-grade malignant lesions, possibly of mesenchymal origin capable of differentiating along different pathways (some will show myofibroblastic phenotype with positive for SMA, while others will acquire FDC characteristics and CD21+). In contrast to splenic conventional EBV-negative IPT (which is considered a benign entity) total splenectomy is the main treatment for this pathology.

E-PS-10-011
A case of multicentric Castleman's disease mimicking non-Hodgkin lymphoma: when splenectomy is diagnostic and therapeutic
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Background & objectives: Castleman's disease encompasses a group of disorders with well-defined histological features. Non-specific symptoms can mimic a wide variety of conditions. We describe a multicentric Castleman's disease diagnosed on splenectomy with a complete response after 6 years of follow up.
Methods: A 65-years old man experienced B-symptoms. Laboratory examination revealed anaemia, monoclonal gammopathy, splenomegaly and small deep lymphadenopathies. The patient underwent splenectomy with diagnostic purposes. After the pathological examination, a diagnosis of HHV8-related multicentric Castleman's disease was made, R-COP (Pituximab, Cyclophosphamide sulphate, Vincristine and Prednisolone) chemotherapy was administered, and complete remission was obtained. The patient is disease-free after 6 years.
Results: Splenic localization of Castleman's disease is rare. To date, three unicentric Castleman's disease involving the spleen (Lee, 2015; Taura, 2000; Kujat, 1990) and three cases involving accessory spleen (Sakaguchi, 2005; Sbrana, 2017; Al Rasheed, 2018) have been described. Splenectomies performed for splenomegaly associated with B-symptoms are anedoctical (Levo, 1987; Carr, 2002; Han, 2008; Mantas, 2016) and only four cases of Castleman's disease were foun in these studies. The association of splenectomy and high-dose chemotherapy, which was never described before, attenuates symptoms and prevent relapses; our patient did not develop either HHV8-related neoplasm or relapsing of Castleman's disease after R-COP treatment and blood analysis resulted normalized after splenectomy.
Conclusion: We describe a case of Castleman's disease successfully treated with splenectomy and R-COP. Although splenomegaly alone is not a typical manifestation, in symptomatic patients with splenomegaly, splenectomy represents a diagnostic and therapeutic procedure alternative to lymphadenectomy.

E-PS-10-012
Auer rod-like inclusions in B lymphoblastic leukaemia: a diagnostic quandary for the morphologist
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Background & objectives: Auer rods are diagnostic of myeloid differentiation with a compatible blast morphology. Albeit rare, auer rod-like inclusions(ARLI) can be seen in other hematopoietic neoplasms. Here we report a rare case of ARLI in B lymphoblastic leukaemia with review of literature.
Methods: A comprehensive workup of the current case was undertaken along with literature search using the keywords 'auer rod-like inclusions' and 'lymphoblastic leukaemia'. Only few case reports have been published till date. All cases showed a B-lymphoblast immunophenotype. The clinicomorphological and immunophenotypic data were analysed and compared with our case.
Results: 70-year-old male presented with pancytopenia. Peripheral blood showed pancytopenia with absent blasts. Bone marrow aspirate revealed numerous blasts with azurophilic needle shaped inclusions and few obscuring the nucleus. The nuclear morphology showed coarse granular chromatin with occasional nucleoli connoting a lymphoblastic origin. The inclusions were negative for Sudan Black B and periodic acid-schiff. Flow cytometry showed 82% gated blasts expressing CD79a, CD19, CD20, CD10, TdT, CD34, HLA-DR and negative for MPO, CD15, CD13, CD117, CD33,

CD14, CD7 and CD3. Immunohistochemistry confirmed CD20, CD10, CD19, TdT, CD34, PAX5 positivity and MPO, CD117, CD5, CD3 negativity. Findings were consistent with B-lymphoblastic leukaemia. (Comparison table with prior case reports in final submission)
Conclusion: B-lymphoblasts with ARLI can be misleading and can lead to an erroneous diagnosis of myeloid leukaemia which might alter the management algorithm in a resource limited or an emergency on call setting where morphology is heavily relied upon. Although rare, the finding of ARLI does not preclude the diagnosis of lymphoblastic leukaemia and underscores the importance of comprehensive immunophenotypic workup aiding in an accurate diagnosis and reflex molecular testing resulting in optimal patient management.

E-PS-10-013
Multiple small bowel perforations: an aggressive haematological cause
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Background & objectives: Small bowel perforation as clinical presentation is seen in inflammatory bowel disease, tuberculosis, ischemia, obstruction and malignancy. Here we discuss a case of extranodal NK/T cell lymphoma presenting as multiple small bowel perforations.
Methods: Clinicopathological analysis of a case presenting with multiple small bowel perforations.
Results: A 68-year-old male who presented to emergency department with abdominal pain. CT scan revealed multiple small bowel perforations. A segmental jejunectomy and ileectomy was performed. Histology confirmed perforations with presence of atypical large lymphoid cells involving the entire bowel wall. These atypical cells were positive for CD3, CD56, CD2 (weak), Bcl2 (weak), Granzyme B and EBV (EBER-ISH). Molecular analysis was negative for specific mutations. A diagnosis of extra nodal high-grade NK/T cell lymphoma was offered. Subsequent PET scan done revealed a nasal mass. Unfortunately, the patient died in a few days following the surgery and biopsy of the nasal mass could not be performed.
Conclusion: Small bowel perforations can occur in variable common clinical conditions. This case highlights the importance of thorough morphological and immunohistochemical analysis required in recognising unusual causes such as NK/T cell lymphoma of small bowel causing perforations. Awareness of such entities amongst general physicians and surgeons would be beneficial in clinical practice as these patients present with advanced disease and have poor outcome.

E-PS-10-014
Acute myeloid leukaemia presenting with an acute fibrinous and organizing pneumonia
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Background & objectives: Acute fibrinous and organizing pneumonia (AFOP) is an unusual histologic pattern of lung injury. In acute myeloid leukaemia, pulmonary injury is mostly due to infection or other malignancies. We report a case of acute monoblastic leukaemia (AML) presenting as AFOP.
Methods: Patient history was collected from the clinical files and histologic samples were reviewed. PubMed search for similar cases in the English literature was performed.
Results: A 56-year-old-man presented with marked asthenia. Blood tests showed anaemia, leukopenia, and elevated PCR. An angio-CT-scan revealed peripheral consolidations on the left lung. The patient was hospitalized in the context of a community-acquired pneumonia and bicytopenia of unknown aetiology. Bone marrow workup revealed an AML. During hospitalization, despite multiple antibiotic cycles, he had persistent fever which delayed the beginning of chemotherapy. Blood and bronchoalveolar lavage cultures were negative. A follow-up CT-scan showed bilateral pulmonary infiltrates. A lung biopsy was performed and a diagnosis of AFOP was rendered, after which corticotherapy was instituted with imagiological improvement. Treatment for the AML was also initiated and the patient currently awaits bone marrow transplant.
Conclusion: Pulmonary manifestations of acute myeloid leukaemia are usually misinterpreted as infectious disease, undergoing multiple antibiotics without clinical improvement. This report increases awareness of this unusual manifestation, enabling correct diagnosis and treatment whilst avoiding unnecessary delays in chemotherapy.

E-PS-10-015
Composite mantle cell and diffuse large B-cell lymphoma
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Background & objectives: Composite lymphoma is the presence of two or more different subtypes of lymphoma in the same organ. We describe a rare case of a composite mantle cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL), along with literature review.
Methods: The clinical history was obtained from the clinical file. FISH complemented histological diagnosis for CCND1. IGH and IGK gene rearrangement analysis was based on PCR and Genescanning using the BIOMED-2 protocols. A PubMed search for similar cases was performed.
Results: A 77-year-old-man presented with a cervical mass. CT-scan revealed a large lymph node (LN), and also submandibular, mediastinal and lombo-aortic. An excised cervical LN showed two distinct B-cell populations: large-cells with necrosis, BCL6+, MUM1+, BCL2+, and MYC+; and small-cells, CD5+, CCND1+, SOX11+. Both were CD3-, CD10-, CD23-, EBER-. A CCND1 break by FISH was present only in the small-cell population. After macrodissection, IGH and IGK PCR-based analysis was in agreement with the presence of two clonal populations. A diagnosis of a composite MCL and DLBCL was made. PET-CT scan revealed FDG-avid lymphadenopathies above and below the diaphragm. Only MCL was found on the bone marrow. The patient is under R-CHOP.
Conclusion: Composite lymphomas are interesting models for lymphomagenesis understanding, and to our knowledge, this is the fifth described case of a composite MCL/DLBCL. All cases in the literature are male patients, one corresponding to a primary testicular lymphoma. Excisional biopsy is imperative for diagnosis since a FNAC may miss one of the components. The presence of two morphological, immunohistochemical and genetically different cell populations, suggests two independent lymphomas as opposed to the unlikely transformation of MCL.

E-PS-10-016

Testicular plasmacytoma. A case report and correlation with imaging findings

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Background & objectives: Plasmacytoma refers as a malignant plasma cell tumour growing within bones or extraosseous (extramedullary). Testicular plasmacytomas are rare malignant neoplasms with relatively poor prognosis. At the time of diagnosis, our patient did not have multiple myeloma
Methods: A 87 year-old -patient presented to our hospital with a painless testicular mass, accompanied by a sense of heaviness. CT scan reveals a solid mass 6,5X5X4 cm in dimensions. An orchiectomy was the surgery of choice. On dissection of the surgical specimen, a brownish mass was recognized.
Results: Microscopic examination showed a lesion composed entirely of mature and immature plasma cells, ranging from small and mature to large in size and atypical cells with prominent nucleoli. Sheets of plasma cells with abundant pink cytoplasm were also present invading the seminiferous tubules. Sparse, single, pale staining nuclear inclusions, with the morphologic features of "Dutcher bodies" were also present. Immunohistochemically, the neoplasm had the following profile: CD138 (+), CD19 (-), CD20 (-), CD117 (-), PLAP(-), CD56 (-), KLMW rarely (+). Confirmation of a clonal plasma cell lesion was accomplished immunohistochemically for Ig light chains.
Conclusion: Plasmacytomas have been described in bones and in other tissues, most commonly in the upper respiratory tract with spread to cervical lymph nodes, but they may occur also in the gastrointestinal tract, breast, testis and in many other anatomical locations. Very few have been reported in the testis. Isolated testicular plasmacytoma accounts for only 0,03-0,1 %. The vast majority of patients with testicular plasmacytoma either have disseminated disease at the time of diagnosis, or develop disseminated disease later in life

E-PS-10-017

ALK-positive large B-cell lymphoma: a very rare and aggressive neoplasm

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Background & objectives: ALK-positive B-cell lymphoma is a rare CD-20 negative aggressive non-Hodgkin lymphoma with less than 200 cases published in the literature. We describe a new refractory case with a view to improving its knowledge and so, its diagnostic and therapeutic management.
Methods: We report the only case diagnosed in our hospital and describe clinical, radiological, histopathological, immunophenotypic and molecular features. This is a 12 year-old boy with a left axillary lump and intermittent scapular pain without any other medical history. Imaging tests was performed and a lytic scapular lesion with axillary and splenic adenopathic conglomerates were evidenced.
Results: Axillary fine-needle aspiration and core-needle biopsy were realized and revealed a completely infiltrated lymph node tissue by a diffuse neoplasm, composed of monomorphic large cells with plasmablastic features with round pale nuclei containing a large central nucleolus and abundant amphophylic cytoplasm. Immunohistochemical stains were positive for CD45, CD79, CD138, MUM-1, IgA-Kappa, c-MYC, EMA, BCMA and ALK with restricted granular cytoplasmic staining pattern and presented a very high proliferation index. Lymphoid markers, EBER and HHV8 resulted negative. FISH studies confirmed ALK translocation t(2;17) and clonality tests showed immunoglobulin heavy chain rearrangement. Two years after diagnosis, in stage III disease, is receiving the sixth-line of treatment awaiting for CAR-T cell therapy (BCMA).
Conclusion: Large B-cell lymphoma is one of the most common lymphoma. Recent advances in molecular biology allowed to describe new subtypes, including ALK-positive large B-cell lymphoma, a rare entity that represent a diagnostic challenge. It is important to correctly diagnose it as long as its aggressivity turns it into a therapeutic problem with a poor median prognosis (<2 years). Our patient's refractory process shows that despite the variety of therapies described, additional research is necessary to better understand this pathology.

E-PS-10-018

Beyond reactive lymphadenitis: what else can they tell us?

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Background & objectives: Lymph node follicular hyperplasia and plasmacytosis have been considered as non-specific alterations with little attention in the literature. However, these findings may lead the pathologist to include an autoimmune process in the diagnosis of a lymph node biopsy.
Methods: We present the morphological and immunohistochemical features in a series of four cases of autoimmune-related lymphadenopathies, three systemic lymphadenopathies (with no autoimmune disease related) and two multicentric Castleman disease cases diagnosed between 2018 and 2022; emphasizing the location and quantification of plasma cells within the lymph node. Epidemiological data and clinical findings are also included in the study.
Results: All four patients diagnosed with an autoimmune process showed florid follicular hyperplasia and varying degrees of polytypic inter (grade 2-3) and intrafollicular (grade 1) plasmacytosis. No light chain restriction was detected in such cases. Within the systemic non-autoimmune –related lymphadenopathies, two cases proved intrafollicular (grade 1-2) plasmacytosis with kappa light chain restriction and mild interfollicular plasmacytosis (grade 1). Multicentric Castleman disease showed intense interfollicular plasmacytosis (grade 3) with no intrafollicular presence of plasma cells.
Conclusion: Follicular hyperplasia and polytypic inter and intrafollicular plasmacytosis are common findings within autoimmune affected patients. The pathologist must be capable to recognize these features and include the possibility of an underlying autoimmune process in the differential diagnosis in patients with multiple lymphadenopathy.

E-PS-10-019

Kikuchi-Fujimoto disease following COVID-19 infection: case report

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Background & objectives: Kikuchi-Fujimoto disease is a rare, self-limited disease, characterised by a regional (usually cervical) lymphadenopathy associated with mild systemic symptoms. The diagnosis relies on histopathological examination which reveals necrotising, histiocytic lymphadenitis with a characteristic absence of neutrophils. The aetiology remains unknown.
Methods: We report the case of a 27-year old male who presented to his general practitioner with mild fever, fatigue, coughing and cervical lymphadenopathy. The diagnosis of COVID-19 infection was established based on PCR testing. Following treatment, the complete resolution of symptoms was noted, except for a persistent cervical lymphadenopathy. Excisional biopsy and histopathological examination of the lymph node was performed
Results: The microscopic examination revealed the presence of several irregular areas of necrosis comprised of nuclear debris and apoptotic cells surrounded by an abundant population of histiocytes. Rare plasma cells were identified in the background of the lymph node, along with normal lymphocytes and some immunoblasts. A complete absence of neutrophils was also documented. Atypical cells were not identified. Serology and special stains ruled out infectious causes. Immunohistochemical stainings revealed a CD68 positive population of histiocytes and an abundance of CD8 and CD4 positive T cells. Fewer CD20 positive B cells were noted in the background. Thus, a diagnosis of Kikuchi-Fujimoto disease (KFD) was established.
Conclusion: Kikuchi-Fujimoto disease is a challenging diagnosis, especially considering that at certain stages of the disease, it can mimic other entities, such as systemic lupus erythematosus or lymphoma. Thus, awareness of this disease is crucial in preventing misdiagnosis and improper treatment. Although its aetiology remains unknown, it is theorised that it may represent a T-cell and histiocyte mediated response to some infectious agents and there are cases reported in the literature of KFD in conjunction with COVID-19 infection or vaccination.

E-PS-10-020

Anaplastic large cell mymphoma ALK-negative - MSC(E116K) mutation and novel in-frame fusion-gene EIF4E3-FOXP1

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Background & objectives: In a subgroup of ALK-negative (ALK-) anaplastic large cell lymphoma (ALCL) a repetitive mutation in the musculin gene [MSC(E116K)] has been recently described. Recurrent fusion-gene including *EIF4E3-FOXP1* has been identified only in single studies under multiple myeloma and breast cancer.
Methods: A 62-year-old female with ALK- ALCL, AnnArbor IIIB, IPI-2/5 was qualified for histopathological consultation. Immunohistochemical assessment and the extended molecular testing with a comprehensive 125-gene panel assay dedicated to lymphomas were performed The status of the MSC gene was explored with the Sanger method.
Results: The showed classic histopathological ALK- ALCL morphology and immunophenotype (CD30+, ALK-, CD43+/CD4+/CD3+, Granzyme B+/Perforin+, MUM1+, PAX5-/CD20-, CD15-). Molecularly it was a triple-negative ALK- ALCL with *MSC(E116K)* mutation and a novel in-frame fusion of *EIF4E3* exon 7 to *FOXP1* exon 3. Other point changes detected in transcripts included: *CDKN2A*: c.*29G>C, *CREB3L2*: c.299_301del, p.(Thr100del), *NOTCH1*: c.5168-1_5168insA, p.(Ser1723LysfsTer2), *BATF3*: c.134dup, p. (Asn45LysfsTer17). Our patient had received induction treatment (6 cycles of CHOP) and achieved complete remission (CR). The consolidation treatment included high-dose chemotherapy with Be-EAM supported by auto SCT. After two years of follow-up, the patient presents with CR, with no symptoms suggesting disease progression.
Conclusion: ALK- ALCL shows a variable and potentially "molecularly-related" prognosis. We present for the first time the coexistence of MSC(E116K) and *EIF4E3-FOXP1* fusion-gene. The importance of these genetic changes is still limited. MSC(E116K) mutation seems to be related to *DUSP22* rearrangements and a better prognosis. The *EIF4E3-FOXP1* fusion-gene was not previously described in ALCL; therefore it's crucial to study ALCL in-depth on larger groups of patients concerning clinical prognosis.

E-PS-10-021

Littoral cell angioma of the spleen: unexpected finding in splenectomy specimen. Case report and review of the literature

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Background & objectives: Littoral cell angioma (LCA) is a rare and benign primary vascular neoplasm of the spleen, with characteristic histopathologic features, reported by Falk et al in 1991. It is thought to arise from the cells lining the red pulp sinuses (littoral-cells).
Methods: A 67-year-old man with palpable and hard splenomegaly, of 10cm below the costal rim; with leukocytosis, anaemia and plateletopenia. CT-scan showed enlarged spleen (20cm), heterogeneous, with hypodense nodules inside, some solid and others cystic necrotic; no hyper-enhancement on PET-scan. The differential diagnosis included metastatic disease, lymphoma/leukaemia. Bone marrow biopsy was performed, showing reactive hyperplasia, without neoplastic infiltration. Splenectomy was performed.
Results: The spleen weighed 1802gr and measured 24×18.4×6cm. Externally polylobulated-appearance. Serial-sections showed multiple spongy, reddish-venous nodules of variable size, up to 1.5cm, blood-filled, throughout entire spleen. Histologically, the lesions were not-encapsulated, consisted of vascular-channels with red-blood-cells inside. The vascular-lumina showed irregular lining endothelium with both histiocytic and endothelial features, without atypia or mitosis; cells of histiocytic-habitus often sloughed into the lumen and some showed erythrophagocytosis. Papillary-projections into vascular spaces and extramedullary-haematopoiesis were observed. The unaffected white-pulp showed mild reactive follicular-hyperplasia. By immunohistochemistry the tall-lining-cells (with histiocytic-features) were positive for CD68, Factor-VIII, CD163; and the flat-lining-cells (with endothelial-features) were positive for CD31, Factor-VIII. CD8, WT1 were negative. The final diagnosis was LCA.
Conclusion: LCA is a rare primary splenic vascular tumour, likely secondary to hemodynamic disturbance in spleen. So far, about 329 cases have been described in the literature. When diagnosed, it is necessary to search for synchronous or metachronous visceral neoplasia. LCA can also mimic metastatic lesion of the spleen. This case report underlines the rarity of this neoplasm, with morphological and immunophenotypic features like those described in the literature; that needs to be included in the differential diagnosis of multiple hypodense-splenic-nodules.

E-PS-10-022

Kikuchi-Fujimoto disease following vaccination against COVID-19: case report and review of the literature

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Background & objectives: Kikuchi-Fujimoto disease (KFD) is a rare benign self-limiting disease which predominantly affects young women and Asian populations. KFD is characterized by cervical lymphadenopathy and mild fever. We report a case of KFD following the SARS-CoV2 vaccination.
Methods: A 30-year-old woman with no medical history of interest, presented left axillary lymphadenopathy with reactive appearance on ultrasound, 12 days after the first dose of SARS-CoV2 vaccination in the left arm. More than 6 weeks after the second dose, these adenopathies were increased in number and size on ultrasonography, so a core needle biopsy was requested.
Results: Histological study revealed a lymph node parenchyma with paracortical hyperplasia and multiple circumscribed foci of necrosis with abundant karyorrhexis and eosinophilic debris. Numerous histiocytes (some C-shaped) and plasmacytoid dendritic cells were seen in association with apoptotic cells. No neutrophils or hematoxylin bodies were observed. The predominant cellularity corresponded to CD3+ T lymphoid population and nests of CD123+ plasmacytoid dendritic cells, especially around necrotic foci. The immunohistochemical study with CD30, kappa and lambda showed no alterations. Isolated fibrin thrombi in blood vessels were present. Histologic findings were compatible with a Kikuchi-type necrotizing lymphadenitis.
Conclusion: Only three cases of KFD have been reported following vaccination against COVID-19. Although KFD pathogenesis is unknown, it is believed to be a consequence of an aberrant immune response of T cells and histiocytes to an immunogenic antigen (infectious agents or physicochemical factors). Because the patient had no discomfort before the vaccines were administered, COVID-19 vaccine was the more likely cause of KFD. Vaccination should be added to the list of potential triggers/factors associated with the development of KFD.

E-PS-10-023
Clinical implication of CD30 expression in De Novo Epstein Barr virus-positive diffuse large B-Cell Lymphoma NOS
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Background & objectives: EBV+ Diffuse DLBCL NOS, is an aggressive clinicopathological entity recognized in the last edition of the 2016 classification of the World Health Organization (WHO). Our aim is to determine the impact of prognostic of CD30 expression in EBV(+)-DLBCL.
Methods: CD30 expression was compared on 78 EBV(-)-DLBCLs including 67 with ABC and 11 GCB phenotype to 13 EBV(+)-DLBCLs ABC phenotype. The patients were treated by R-CHOP over a period of 44 months, from January 2015 to August 2019. The cut-off for CD30 positivity was 20% of neoplastic cells.
Results: In our series, there was a significant difference between the expression of CD30 EBV (+)-DLBCL and EBV(-)-DLBCL ($p<0.001$). CD30 was positive in 76.9% EBV(+)-DLBCL and 20.5% of EBV(-)-DLBCL. It was expressed in 70% of the non-GC ABC molecular subtype DLBCL. The Pearson test showed a significant correlation between EBER expression and CD30 expression ($r=0.367$, $p=<0.000$). CD30 was significantly associated with EBV status and survival in both CD30 and EBV positive. Patients showed a very low survival rate Log Rank (Mantel-Cox)=0.0008. The multivariate analysis by Cox regression in our study retained CD30 as an independent variant ($p=0.03$).
Conclusion: Expression of CD30 in EBV(+)-DLBCL is linked to a lower survival rate and poor treatment response suggesting a strong rationale for therapy targeted at the CD30 activation pathway for these patients positive for both CD30 and EBV.

E-PS-10-024
Plasmacytoma of the testis as initial presentation of multiple myeloma: case report
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Background & objectives: Extramedullary plasmacytoma represents 5% of plasma cell neoplasms. Plasmacytoma of the testis is extremely rare and may occur as isolated tumour or in concomitance with multiple myeloma. We report a case of testicular plasmacytoma in 77-year-old male patient.
Methods: The physical examination and ultrasonography revealed enlarged left testicle. Based on a clinical diagnosis, an inguinal orchidectomy was performed. On gross examination the testicle measured 7x4x4cm and was entirely occupied by a solid white fleshy tumour. Formalin fixed, paraffin embedded tissue samples were stained with HE and immunohistochemically with CD138, MUM 1, CD79, CD3, CD20, CD117, PLAP and Ki 67.
Results: Microscopic examination revealed a malignant neoplasm composed of atypical plasma cells with pale eosinophilic cytoplasm and polymorphic and polychromatic nuclei which diffusely obliterated underlying testicular parenchyma and infiltrating the epididymis and surrounding peritesticular fibrous tissue. Immunohistochemically the cells were positive for CD138, MUM1 and CD79 and negative for CD3, CD20, CD117 and PLAP with Ki67 80%. After period of two and half months the diagnose of multiple myeloma was established with bone marrow aspiration showed 60% plasma cells, flow cytometry with CD38 and CD138 plasma cells and serum protein immunoelectrophoresis IgA idiotype. Patient died after two-week therapy with corticosteroids, four months after initiate diagnose of plasmacytoma of testis.
Conclusion: Testicular plasmacytoma is extremely rare presentation of extramedullary plasmacytoma. Taking into account the additional data obtained about the patient we concluded that in our case it was the first manifestation of systemic disease referred as multiple myeloma.

E-PS-10-025
Atypical case of angioimmunoblastic T-cell lymphoma (AITL), cutaneous monoclonal plasma cell neoplasm and POEMS-like syndrome: a tricky confounding case
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Background & objectives: Patients with AITL typically present with the onset of a systemic illness, but they rarely manifest typical findings of POEMS syndrome and skin nodules related to secondary plasma cell neoplasm. This case illustrates atypical manifestations and, therefore, its diagnostic challenge.
Methods: A 73-year-old man was admitted to the hospital because of weakness, paresthesias and violaceous cutaneous plaques. Complementary tests revealed organomegaly, hypogonadism, enlarged lymph nodes and polyclonal gammopathy, although the

immunofixation urine test was positive. Bone marrow biopsy was inconclusive due to extensive sclerosis. The first lymph node biopsy showed hyperplastic changes with increased polyclonal plasma cells and PD-1 positive cells.
Results: As the diagnosis of clonal lymphoproliferative disorder was not confirmed in the first biopsy, the clinical hypothesis of Castleman disease was raised and appropriate treatment was initiated. However, there was no improvement and cutaneous lesions and thrombocytopenia worsened. A skin biopsy was performed, showing diffuse infiltration of the dermis and subcutaneous tissue by apparently mature plasma cells with kappa light chain restriction. In view of this, PCR-based clonality test was required in prior lymph node biopsy material, which resulted positive for a clonal T-cell proliferation. By reviewing the subtle morphological features in the histopathology, the diagnosis of Angioimmunoblastic T-cell lymphoma was finally made.
Conclusion: AITL generally causes a variety of immune dysfunctions, something that can mimic a number of other diseases and cause diagnostic delays. In addition, atypical and unusual manifestations reported in this case may contribute to inappropriate treatments. Further studies are necessary to clarify the interplay between this lymphoma and plasma cell proliferations in order to prevent misdiagnosis. A detailed clinical evaluation and auxiliary tests, such as PCR-based clonality, are essential for precise diagnosis and must be available in medical practice.

E-PS-11 | E-Posters Head & Neck Pathology

E-PS-11-001
Nasal glomangiomyoma

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Background & objectives: Glomangiomyoma is a histological variant of glomus tumour. These are benign tumours, typically located in the subcutis or deep dermis of the subungual region of the fingers. We describe the clinico-pathological, immunohistochemical findings of a case of nasal glomangiomyoma.
Methods: A 63-year-old man presented with a 2-month history of intermittent epistaxis and partial nasal obstruction with a duration of two months. Posterior rhinoscopy revealed the presence of a nodule, less than 1 cm in diameter, in the left posterior nasal cavity, based in the middle turbinate and protruding in the middle meatus. The lesion was endoscopically excised, with macroscopically clear margins.
Results: The excised material was a round nodule with diameter 9 mm. Histopathology showed that the tumour was characteristically composed of solid sheets and cords of uniform cells with pale or eosinophilic cytoplasms and round or ovoid nuclei, compatible with glomus cells, interrupted by variable sized vessels. In a central area of the tumour, spindled cells with elongated nuclei and bipolar eosinophilic cytoplasm resembling smooth muscle differentiation were present. The immunoreaction of tumour cells, positive for smooth muscle actin and negative for CD34, that was positive in blood vessels, supported the diagnosis. It was suggestive of glomangiomyoma. Nuclear pleomorphism, mitoses and necroses were absent.
Conclusion: Glomangiomyoma shows variable proportions of glomus cells, vascular structures, and smooth muscle cells. The most common site is the hand, particularly the fingers. Nasal glomangiomyomas are extremely rare. This may suggest that the histological type may be more important in predicting the clinical presentation than the anatomical location of the tumour. Despite being a rare entity, it should be included in the differential diagnosis in patients with common rhinological symptoms.

E-PS-11-002
Primary intraosseous spindle cell carcinoma of the jaw bones: Is it a new histological entity?

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Background & objectives: Intragnathic carcinomas mainly consist of primary intraosseous squamous cell carcinoma, central mucoepidermoid carcinoma and ameloblastic carcinoma, whereas they are very rare. We reported two extremely rare cases of primary intraosseous spindle cell carcinoma (PIOSpCC), clinico-pathologically.
Methods: We selected intragnathic epithelial neoplasms from a pathology file of our institutions, selected intraosseous spindle cell carcinoma of jaw bones, and examined them, clinically, histologically and immunohistochemically.
Results: Two cases (0.4%) were selected: Case 1 was 43-year-old male with the swelling of the left mandible. Case 2 was 42-year-old male with the painful swelling of the right maxilla. Both showed the smoothly-surfaced masses, where the main tumours existed in the jaw bones with osteolytic destruction. Both showed the fascicular proliferation of atypical spindle cells. In case 1, the small nests of epithelioid cells were focally seen, whereas case 2 showed necrosis and multinucleated giant cells. Both were diffusely immuno-positive for pan-CK and vimentin. In case 2, spindle cells were focally desmin, but negative for myogenin. Ki-67 labelling index was 38% and 72%, respectively. Case 2 died of disease.
Conclusion: We diagnosed both cases as PIOSpCC. PIOSpCC harboured neither squamous cell carcinoma component nor ameloblastic component. The worse prognosis of PIOSpCC is related to necrosis and high Ki-67 labelling index. Case 2 showed focal positivity for desmin, but was negative for other myogenic markers. Therefore, it was not intraosseous rhabdomyosarcoma of the jaw bones. We propose that PIOSpCC is an extremely rare but a new entity of primary intraosseous carcinoma.

E-PS-11-003
Nasopharyngeal hairy polyp: a rare case report

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Background & objectives: Hairy polyps are rare developmental malformations mostly occurring in infants and neonates arising in nasopharynx or oropharynx. They have a higher female incidence (6F:1M) with a left side predilection. Airway obstruction can be lethal and should be managed carefully.
Methods: We report a case of a female neonate presenting a severe obstruction of the oropharynx with epistaxis and feeding difficulties. It was caused by a large mass that extends from the most posterior portion of the right nasal cavity to the aryepiglottic folds. The MRI documented an elongated heterogeneous lesion measuring 33x9x8mm, virtually occupying the entire lumen of the oropharynx.
Results: Simple surgical excision of the mass was performed. Gross examination showed a gray pear-shaped pedunculated mass bearing few hair shafts. Histologic evaluation revealed a polypoid lesion, composed of ectodermal and mesodermal elements, namely adnexal structures, adipose tissue and cartilage, covered

with keratinized stratified squamous epithelium, prompting the diagnosis of congenital hairy polyp.
Conclusion: Congenital hairy polyps should be considered in the differential diagnosis in cases of life-threatening airway obstruction in neonates. They are composed of tissues derived from mesoderm and ectoderm. Histological examination gives the definitive diagnosis, crucial in differentiating hairy polyp from other lesions, being essential for prognosis and follow-up. Malignant transformation has never been reported. Surgical resection is the treatment of choice. Knowledge of this type of development malformation make easier early intervention and avoids significant morbidity.

E-PS-11-004
Juvenile nasopharyngeal angiofibroma and familial adenomatous polyposis: an extraordinary case report
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Background & objectives: Juvenile Nasopharyngeal Angiofibroma (JNA) is a rare and benign vascular neoplasm affecting almost exclusively adolescent males. It may occur as a component of the Familial Adenomatous Polyposis (FAP), making it 20-25 times more prevalent compared to the general population.
Methods: We present a case of a 14-year-old male with a personal and familial history of FAP with colorectal polyps and cancer and desmoid tumours, presenting with a mass in his left nasal cavity, with recurrent epistaxis and nasal obstruction. MRI revealed a non-encapsulated lobulated heterogeneous mass lesion in the left side of the nasopharynx with 85x46x55mm, extending to adjacent structures.
Results: He underwent tumour embolization followed by endoscopic excision. Gross examination revealed a fragmented lobulated and pedunculated mass. Histologically, it was a biphasic lesion with a vascular component consisting of variable sized and shaped vessels, small rounded or slit-like to larger staghorn, with variable wall thickness, with single layer of endothelium and occasionally smooth muscle wall. The stromal component varies from highly cellular, collagenized areas to less cellular regions with a fibromyxoid background. CD34 and CD31 immunohistochemistry highlighted endothelial cells. Smooth muscle actin showed the muscular wall of the vessels and beta-catenin revealed nuclear staining in tumour stromal cells and membranous/cytoplasmic staining in endothelial cells.
Conclusion: FAP is an inherited autosomal dominant syndrome due to a defect in the APC gene characterized by multiple gastrointestinal adenomas and risk of adenocarcinomas and extracolonic manifestations. In patients with an association of PAF and JNA, mutations in APC gene were described in the stromal cells of the tumour, which highlights the idea that JNA may be the first manifestation of FAP. Therefore, it is important to consider FAP as an underlying condition in patients with a diagnosis of JNA.

E-PS-11-005
A rare case of respiratory epithelial adenomatoid hamartoma of the nasal cavity
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Background & objectives: Respiratory epithelial adenomatoid hamartoma (REAH) is a rare benign proliferation of mature sinonasal tissue presenting as a polypoid mass, first described by Wenig and Heffner in 1995, mostly involving the posterior nasal septum. Surgical excision is the treatment of choice.
Methods: A 38-year-old man with a history of unilateral nasal obstruction was diagnosed with a unilateral polypoid mass located in the left posterior nasal cavity in contact with the nasal septum. Simple surgical excision with functional endoscopic sinus surgery (FESS) was performed.
Results: We received a yellowish polypoid mass with gelatinous, glistening outer surface, measuring 4,5X2X1cm. Microscopic examination showed a florid proliferation of widely spaced, partly confluent, small to medium, round to oval, partly cystically dilated tubular glands, lined by ciliated respiratory epithelium, without nuclear atypia. Invagination of the surface epithelium gave rise to ciliated tubular glands. Some glands showed mucinous metaplasia, similar to colonic glands. Some seromucinous normal glands were interspersed with the tubular glands. Stromal hyalinization was present with envelopment of glands by a thick, eosinophilic basement membrane. The stroma was oedematous, with inflammatory cells and eosinophils, similar to an inflammatory polyp. The diagnosis was of a respiratory epithelial adenomatoid hamartoma.
Conclusion: REAH, is an uncommon entity with distinctive morphologic features including a glandular component originating from the overlying surface respiratory epithelium and polypoid growth as a result of respiratory epithelial adenomatoid proliferation. REAH, especially those with a metaplastic mucinous component should be differentiated from low grade sinonasal adenocarcinomas, which are locally aggressive tumours. REAH is CK20-/CDX-2-, in contrast with the low-grade sinonasal adenocarcinoma. Pathologists must be aware of this entity in order to avoid overdiagnosis and radical surgery.

E-PS-11-006
Pleomorphic adenoma of the parapharyngeal space. A common tumour in an uncommon location
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Background & objectives: The majority of minor salivary gland tumours are malignant. Pleomorphic adenoma is the commonest benign tumour, most often found in the oral cavity. A very rare case of a large pleomorphic adenoma arising in the parapharyngeal space is reported.
Methods: A 37-year-old man presented with difficulty in swallowing and obstructive sleep apnea of three months' duration. CT scan showed a 7cm mass extending from the left lateral oropharynx to the larynx. There was no neck lymph node enlargement. The tumour was examined with transoral FNA, which was diagnostic of a pleomorphic adenoma. The tumour was transorally enucleated.
Results: On gross examination the lesion was measuring 7X4X4,5cm, with a whitish, faintly lobulated and focally glistening cut surface. Histological examination showed a neoplasm with an admixture of epithelial and stromal components. Ducts lined by inner epithelial and outer myoepithelial cells surrounded by a chondromyxoid stroma, consistent with pleomorphic adenoma. Foci of quamous metaplasia were also present. Postoperative period was uneventful.
Conclusion: Pleomorphic adenomas may occur in the parapharyngeal space from displaced/aberrant salivary gland tissue within a lymph node, in contrast to tumours arising from minor salivary glands medial to the constrictor muscles of the pharynx or the deep lobe of the parotid gland. The treatment of choice is resection with adequate margins. For parapharyngeal tumours

wide resection may not be possible due to proximity to vital structures. High index of suspicion and an adequate clearance is the key to successful treatment.

E-PS-11-007

Primary small cell neuroendocrine carcinoma of the tonsil: a case report

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Background & objectives: Neuroendocrine tumours account for 0.5% of all malignancies and are mainly found in the gastrointestinal track and the lung. We present a very rare case of primary small cell neuroendocrine carcinoma (NEC) of the right tonsil.
Methods: A 82-year-old male patient was admitted with symptoms of throat pain and dysphagia. Clinical examination revealed a right tonsil mass along with a palpable right inguinal lymph node. A biopsy of the tonsillar mass, as well as a fine needle biopsy (FNB) of the lymph node was performed.
Results: Microscopical examination of the tonsillar mass showed small round to oval tumour cells arranged in nests or rosettes with granular nuclei and scant cytoplasm. Apoptosis, necrosis and numerous mitotic figures (>10mit/2mm2) were also found. Immunohistochemical staining was positive for CKAE1-AE3, CK8-18, CK20 (dot-like pattern), chromogranin and synaptophysin. Ki-67 mitotic index was high (>80%). Same histopathological results were identified on the lymph node FNB. The aforementioned features of the tumour established the diagnosis of a primary poor-differentiated small cell neuroendocrine carcinoma of the tonsil with inguinal lymph node metastasis.
Conclusion: Small cell NEC that primarily occurs in tonsil is extremely rare with an aggressive disease course and poor prognosis (18 months median overall survival time). During the past 40 years, there have been only 14 cases added in the English literature with a male predominance. Paraganglioma and malignant lymphoma should be considered in the differential diagnosis. Owing to its rarity, standard treatment protocol remains uncertain.

E-PS-11-008

A case of multiple cutaneous squamous cell carcinomas of the head and neck in a patient with primary lung adenocarcinoma

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Background & objectives: Here we present a case of multiple skin nodules in the head and neck area arising simultaneously in a 70-year-old man just diagnosed with primary lung adenocarcinoma. The clinical suspicion was skin metastases.
Methods: During chemotherapy and immunotherapy for the lung tumour the nodules shrunk in size. The clinical suspicion was skin metastases. Incision biopsy was performed on some of the nodules and they were histologically and immunohistochemically examined.
Results: Histology revealed poorly differentiated epithelial tumours and immunohistochemical studies confirmed them to be of squamous origin. A diagnosis of eruptive primary cutaneous squamous cell carcinomas was made.
Conclusion: Although rare, the possibility for multiple simultaneous primary malignancies should always be in the differential diagnosis with metastatic disease, and clinical response to therapy cannot be used as a reliable distinguishing criterion.

E-PS-11-009

NTRK-rearranged thyroid carcinomas with evidence of anaplastic transformation in lymph node metastases: clinicopathological and molecular features

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Background & objectives: The actionable NTRK-rearranged thyroid carcinoma carcinomas (PTC) are not infrequently clinically aggressive and are predominantly differentiated follicular-derived carcinomas. Rare NTRK-rearranged PTCs have shown disease progression and aggressive clinical behaviour, but their pathologic and molecular features remain understudied.
Methods: Of 40 BRAF negative PTCs available for review, we identified 3 NTRK-rearranged thyroid carcinomas. We examined the clinicopathological and molecular features of 3 NTRK-rearranged thyroid carcinoma cases.
Results: One NTRK-rearranged PTC, despite surgical, radioiodine/chemotherapy, had multiple lymph nodes/local recurrences over 17 years. The most recent recurrence demonstrates biphasic components of differentiated PTC and dedifferentiated (anaplastic transformation) anaplastic transformation with sarcoma-like morphology. Immunostains show that AE1/3 and PAX8 are positive in differentiated-PTC but negative in the dedifferentiated component. Both components are negative for TTF-1, desmin, and p53. Ki-67 is 40% in dedifferentiated carcinoma and less than 10% in the differentiated PTC. NGS showed ETV6-NTRK3 gene fusion, BCL3, and BCL9 in both components. The other two NTRK-rearranged cases show indolent clinical behaviour with neither high-grade features nor anaplastic transformation in their primary tumours or in lymph node disease
Conclusion: This report identified a recurrent PTC with ETV6-NTRK3 gene fusion mutation that was prone to undergo an anaplastic transformation with sarcoma-like morphology in the nodal recurrence, which may mimic other spindle cell sarcomas. This finding, also, has important implications for clinical outcomes and aggressive clinical behaviour

E-PS-11-010

Malignant melanoma metastasis in a parotid lymph node, without an identifiable primary site

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Background & objectives: The parotid gland hosts metastases, but most often from primary tumours of the head and neck region, which have the potential of spreading to the regional lymph nodes, such as cutaneous squamous cell carcinomas or cutaneous melanomas.
Methods: A 58-year-old male patient was admitted to the Oral and Maxillofacial Surgery Department with a tumour nodule that has been located in the right preauricular area for two years and which grew rapidly two months before presentation, for which a right partial parotidectomy was performed and the nodular mass was sent for histopathological examination.
Results: The macroscopic aspect showed a 35x35x10 mm encapsulated nodule, with tan and white colour areas on the cut section. Histopathological evaluation revealed lymphoid tissue pushed to the periphery and mostly replaced by a proliferation of atypical, pleomorphic cells, with melanin pigment content, arranged in clusters and placards, with areas of haemorrhage and necrosis. The neoplastic cells presented BRAF-V600E/EC gene mutation, expressed HMB45, MelanA, Sox10, and were negative for Cytokeratin-AE1/AE3. Based on these aspects, the final diagnosis was malignant

melanoma metastasis in a parotid lymph node. The patient's history unveiled that he used to have a cutaneous pigmented lesion in the right supraorbital area which suffered a complete regression over time.
Conclusion: A malignant melanoma metastasis should not be excluded, even in cases with an absent primary tumour site. A complete examination of the head and neck region and a detailed history of the patient can aid in discovering the primary tumour.
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E-PS-11-011
Viable adenosquamous carcinoma of the larynx after chemotherapy and radiotherapy - a case report
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Background & objectives: Adenosquamous carcinoma (ASC) of upper aerodigestive tract is a rare malignant tumour. Laryngeal ASC is extremely unusual malignant neoplasm, representing only 0.35%–0.5% of all laryngeal malignancies. Because of its rarity there is no overall consensus as to its best management.
Methods: A female 67-year-old presented to our hospital for a laryngeal lesion in the glottic region. The biopsy showed moderate to high-grade invasive squamous carcinoma. She received neoadjuvant therapy (chemotherapy, radiotherapy). In the biopsy after neoadjuvant therapy the diagnosis of viable invasive squamous carcinoma remained. A total laryngectomy was performed.
Results: On gross examination an ulcerated polypoid glottis tumour, 3cm. in diameter, with transglottis extension was recognized. In the same container we received two lymph nodes 0.2cm and 0.3cm. in great diameter. On histopathologic examination, a viable ulcerated high grade squamous cell carcinoma was revealed [CK5/6 (+), p40 (+), p16 (-)] admixed with adenocarcinoma, moderately differentiated [CK18/8 (+), EMA (+)].
The two lymph nodes were negative for metastasis. The pathological stage (in our specimen) was ypT3N0, with response after neoadjuvant therapy R2 (CAP 2021).
Conclusion: ACS is a malignant neoplasm with an aggressive course, characterized by local recurrences, with early cervical lymph node metastasis and distant dissemination, most commonly in lung. The prognosis is poor and the mean overall survival rate is approximately 2-3 years. The current treatment involves surgical excision and/or adjuvant chemoradiotherapy, depending on the stage.

E-PS-11-012
A GLI-full diagnosis – a case report of a GLI-1 re-arranged head and neck mesenchymal neoplasm
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Background & objectives: A 19-year-old male patient presented complaining of a 12-month history of a gradually increasing lump on his posterior dorsal tongue. The lesion was reported to have ruptured prior to excision. The lesion was excised and sent for histological assessment.
Methods: Histological examination showed a well circumscribed, multinodular, and submucosal tumour without a capsule. The tumour mass was formed by nests of monotonous cells separated by a fine vascular network. The cells had round to ovoid nuclei with clear to eosinophilic cytoplasm. Minimal atypia and mitoses were seen. Evidence of lymphovascular invasion was identified in the superficial vasculature.
Results: Immunohistochemistry showed diffuse Vimentin expression in lesional cells. Weak focal positivity was seen for CD56 and GLUT1, with SMA expression only at the periphery of the tumour islands. Staining for S100, SOX10, Desmin, CD31, CD34, AE1/AE3, HMB-45, CD99, ERG, CD68, EMA, Calcitonin and muscle specific actin was negative. Pan-RNA fusion panel testing confirmed the presence of an ACTB-GLI1 fusion protein leading to a definitive diagnosis of a GLI-1 re-arranged head and neck mesenchymal neoplasm.
Conclusion: GLI 1 re-arranged mesenchymal neoplasms are a relatively newly described entity with a propensity to arise in the tongue within the head and neck regions. The distinct morphological and variable immunohistochemical profile should raise the possibility of this entity as a differential diagnosis and prompt pathologists to undertake additional molecular testing to establish the presence of GLI1 re-arrangement. Emerging evidence suggests these lesions have the potential for malignant behaviour therefore knowledge of this entity is paramount for appropriate management.

E-PS-11-013
Neuroendocrine large cell carcinoma with myoepithelial differentiation of the parotid gland - a case report
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Background & objectives: Salivary gland carcinoma is a rare neoplasm accounting for 0.3% of all cancers. Large cell neuroendocrine carcinoma (LCNC) in the salivary glands is extremely rare, with poor prognosis similar to small cell carcinoma (SCC).
Methods: A male 58-years-old was referred to our hospital for swelling on the right site of the parotid area. Imaging revealed a circumscribed solid mass 5.5cm in size. A fine needle aspiration was performed and the cytological features shows a high-grade carcinoma. Total parotidectomy was performed.
Results: On macroscopic examination of the salivary gland, weighing 39g. and 7.5X4.5X2.5cm in dimensions, a yellowish myxoid tumour was found.
Microscopy showed a high grade neoplasm within myxoid stroma, with organoid infiltrative pattern, composed by large cells with marked nuclear atypia and hyperchromatic nuclei. Up to 10 mitotic figures / 10HPF, comedo necrosis and perineural infiltration were observed.
The immunohistochemistry was positive for CK8/18, CK5/6, CK14, CD117, GFAP, S-100, Synaptophysin, Chromogranin A. Ki-67 was positive in 40-50%. Negative immunoreactivity was observed for CK7, EMA, TTF-1. PETscan demonstrated no lesions elsewhere. Based on morphological and immunophenotypic features the diagnosis of a primary LCNC with myoepithelial differentiation of the parotid gland was confirmed.
Conclusion: The lung is the most common site of this tumour, but LCNC has been found in other organs. The treatment for salivary gland carcinoma is mainly surgery, including primary tumour resection with or without neck lymph node dissection and adjuvant therapy. LCNCs are very rare and there is no consensus on management guidelines. The main differential diagnosis of LCNC is with poorly differentiated carcinoma or squamous cell carcinoma. Immunohistochemistry is important in making the right diagnosis of LCNC.

E-PS-11-014

Odontogenic keratocysts in the setting of Nevoid Basal Cell Carcinoma Syndrome: a case report and literature review with an emphasis on CD56 immunohistochemistry analysis

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Background & objectives: 10-20% of odontogenic cysts are odontogenic keratocysts (OKC). Unicystic ameloblastomas are differential diagnoses of these lesions. Up to 5% of OKC are associated with Nevoid Basal Cell Carcinoma Syndrome (NBCCS), caused by a mutation in the PTCH1 gene.
Methods: We present a case report of a 13-year-old patient with five multicentric and metachronous OKC. Immunohistochemical analysis for CD56 in the primary specimen was performed. Additionally, we did a review of current literature indexed on PubMed, and WHO Classification of Tumours (2017).
Results: The patient was referred to our hospital four years ago for removal of a palpable mass on her lower jaw. On histology, in addition to typical OKC findings, we highlight areas of budding growth from the basal cells, daughter cysts, and remains of odontogenic epithelium. Since then, the patient has had the need to remove another 4 masses with the same characteristics. The presented case is consistent with NBCCS but the patient is yet to show any cutaneous manifestations of NBCCS, such as basal cell carcinoma. CD56 was positive, namely in the aforementioned budding growth areas. Recent studies have shown a positive correlation between expression of CD56 and syndromic OKC.
Conclusion: Recurrence rates in OKC related to NBCCS are higher than in isolated cases. It is advised that when OKC are found at a young age or multiple are seen in the same patient, NBCCS should be considered. CD56 is commonly associated with unicystic ameloblastoma, which helps in the differential diagnosis with OKC. However, as found in literature, in the context of morphological and clinical findings, it may be helpful in detecting syndrome-related occurrences of OKC, such as in NBCCS.

E-PS-11-015

A rare tumour of the parotid gland: lymphoepithelial carcinoma

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Background & objectives: Lymphoepithelial carcinoma (LEC), an uncommon malignancy, occurs usually in nasopharynx and rarely in salivary glands. It is strongly associated with Epstein-Barr virus (EBV) and emerges at limited patients of the local areas as Asia or Arctic Circle.
Methods: We reported a case of a Caucasian female with a LEC of the parotid gland (PG).A 48-year-old female presented with a right-sided, painful facial mass. PET/CT revealed a mass about 4.5 cm in diameter with intense FDG uptake on the right-PG and involvement of the level II unilateral cervical lymph nodes. The potential non-parotid focus was excluded.
Results: She underwent total parotidectomy and ipsilateral selective neck dissection.On macroscopic examination, the mass was irregular in border and cream coloured. Microscopically, the tumours were widely infiltrative, characterized by large polygonal to spindled cells arranged in a syncytial, lattice-like network in a background of lymphoplasmacytic cells. The neoplastic cells showed an open-vesicular nuclear chromatin to a more basaloid-morphology, the latter showing hyperchromatic nuclei and less cytoplasm. Immunohistochemistry staining revealed that the epithelial cells were reactive for panCK and p63, patchy reactive for CK 5/6, 75% strong positive for Ki67 and negative for p16. Overexpression of p53 in the epithelial cells was monitored. The case was EBV positive by ISH.
Conclusion: In conclusion, LEC commonly occurs at the nasopharynx and rarely occurs at other sites in the head and neck region. It has a strong tendency to metastasize to the regional lymph nodes with predominant involvement of the PG and the majority of those are radiosensitive. Combination therapy with surgery and radiation is desirable. Our patient has been disease-free for 3 years after combination therapy.

E-PS-11-016

Filamin-A expression in laryngeal squamous cell carcinoma and its clinical significance

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Background & objectives: Recent strategies to improve the overall prognosis of laryngeal squamous cell carcinomas (LSCCs) have focused on biomarkers' discovery. Recent genomic studies reported that filamin-A is associated with metastatic LSCCs. This study was undertaken to analyse this protein's expression in LSCCs.
Methods: This study analysed the expression of filamin-A, using immunohistochemistry, in a tissue microarray of 80 cases of laryngeal cancers. Clinicopathological parameters were analysed according to filamin-A expression in the tissue microarray. Furthermore, microarray tumours expressing this protein were further categorized according to the intensity of staining.
Results: A significant majority of this array's laryngeal squamous cell carcinomas exhibited positive expression of filamin-A protein. All the filamin-A positive tumours expressed the protein in their cytoplasm. Significant correlation were found between filamin-A expression and the tumours' grade, stage, lymph node status and metastases. A significant majority of the tumours exhibited the highest intensity of filamin-A immunohistochemical expression (IRS=12).
Conclusion: A significant majority of the LSCCs of this study's array expressed filamin-A in their cytoplasm. This expression correlated with poor prognostic parameters of LSCCs. These findings are in line with evidence seen in other head and neck cancers, suggesting an important role for filamin-A in LSCCs.

E-PS-11-017

An unusual case report of carcinoma ex pleomorphic adenoma with double morphology: salivary duct carcinoma and squamous cell carcinoma

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Background & objectives: Carcinoma ex pleomorphic adenoma (CXPA) represents carcinoma of any type arising from a primary pleomorphic adenoma (PA). CXPA is considered aggressive, affects mainly the parotid glands, and constitutes nearly 12% of all malignant tumours of the salivary glands.
Methods: We report the clinical, histological, immunohistochemical, and genetic features of one novel submandibular-located CXPA case of 68-year-old men. The patient presented

with a long-standing painless mass in the left lateral neck with rapid progression, pain, and skin ulceration — no other significant clinical burden. Computed tomography showed heterogeneously enhancing mass in the left submandibular fossa, originating from the submandibular gland.
Results: Grossly, a cream-colored, ulcerated, exophytic tumour of the skin, 3.4 x 2.8 cm in size and up to 2.6 cm in thickness, infiltrating the salivary gland parenchyma. Microscopically, the tumour consisted of three components: poorly differentiated squamous cell carcinoma (SCC), salivary duct carcinoma (SDC), and hyalinizing residual PA with no capsule. The SCC component infiltrated both the salivary gland and the skin without a visible pre-invasive component. SDC was visible in the salivary gland in SCC's immediate vicinity. Immunohistochemically, the SCC cells expressed p40 and SDC expressed AR, mammaglobin, and GATA3. Targeted Next-Generation sequencing detected TTC23-PLAG1 fusion in carcinoma component. The patient was referred for radiotherapeutic treatment.
Conclusion: The microscopic observation supports the diagnosis of the carcinoma developed in PA with a rare, double morphological differentiation (SCC and SDC). The detected PLAG1 fusion supports the diagnosis of double differentiation CXPA. Further research might explore whether the histologic type of the CXPA malignant component modifies the survival and efficacy of the implemented therapies.

E-PS-11-018
Sinonasal glomangiopericytoma; a case report and histopathological overview
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Background & objectives: Approximately 75% of the sinonasal tumours are benign and squamous cell carcinoma is the most common malignant tumour. Sinonasal glomangiopericytoma (SNGP), accounting for <0.5% of sinonasal neoplasms was first described in 1942 by Stout and Murray.
Methods: Here, we present a clinico-pathological analysis of a nasal mass composed of pericytic cellular morphology.
Results: A 78-year-old male presented with a mass in the left nasal cavity, which showed avid enhancement in MRI. Nasal polypectomy was performed. Histopathological examination revealed an ill-defined sub-epithelial tumour composed of sheets, lobules and nests of monotonous cells with round nuclei, indistinct nucleoli and scanty eosinophilic cytoplasm with minimal cytologic atypia in a background of collagenous stroma containing varying sized blood vessels showing dense perivascular hyalinization. There was no increased mitotic activity or necrosis. These lesional cells were positive for SMA, CD99, Factor XIIIa and Cyclin D1, supporting myoid differentiation typical of pericytes. The tumour showed diffuse dense nuclear expression of beta-catenin.
Conclusion: Though the occurrence is rare, SNGP exhibits highly distinctive histopathologic features, as seen in this case. As the clinical behaviour of SNGP has been poorly understood, more cases need to be reported for better establishment of treatment modalities. Heterogenous mutations in the beta-catenin gene and expression of cyclin D1 have been identified in SNGP.

E-PS-11-019
Submandibular adult type rhabdomyoma – a case report
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Background & objectives: Rhabdomyoma is a benign skeletal muscle neoplasm, mainly cardiac. Extracardiac locations are rare. Morphologically, it is categorized as foetal, genital or adult types, depending on the degree of differentiation. Some cases are associated with PTCH1 mutations and with Birt-Hogg-Dubé syndrome.
Methods: We present a case of a 68-year-old male with a painless, submandibular mass, slowly growing for one year. The ultrasound study showed a well-defined mass consistent with the diagnosis of lipoma. He underwent surgical excision and the hypothesis of lipoma was doubted by the surgeon, due to the gross features. There was no relevant medical history.
Results: Gross examination showed a well-circumscribed nodular lesion with 6,2x5,8x4,2cm, weighting 47g, with a yellowish, slightly lobulated outer surface, uniform elastic brown on cut surface.
Histologically, it had expansile growth and was non-encapsulated, faintly lobulated. The cells were polygonal with abundant, eosinophilic and granular cytoplasm and the nuclei were round to oval, sometimes with prominent nucleoli. Some cells had vacuolated cytoplasm, resembling spider webs. Mitoses and necrosis were absent. Complementary immunohistochemical studies revealed diffuse positivity to desmin, and negativity to S-100 protein, CD68, TFE3 and myogenin. It was rendered a final diagnosis of adult type rhabdomyoma.
Conclusion: Adult type rhabdomyoma is a benign neoplasm arising mainly in the head and neck region. Although rare, it is the commonest subtype of extracardiac locations and can be linked to a loss of function of the PTCH1 gene, which is, nevertheless, more frequent in the foetal type. There is a reported association to Birt-Hogg-Dubé syndrome.
The main differential diagnosis are alveolar soft part sarcoma and granular cell tumour, the first one being a malignant entity with fusion gene involving TFE3.

E-PS-11-020
Primary nasopharyngeal papillary adenocarcinoma: report of a rare entity and review of the literature
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Background & objectives: Primary nasopharyngeal papillary adenocarcinoma (PNPA) is a low-grade neoplasm with low propensity for recurrence and metastasis. Only few cases have been reported in the literature. We report here a new case of this rare entity to discuss its clinicopathological features.
Methods: The histological features of PNPA occurring in a 25-year-old man who presented with unilateral nasal obstruction are described with a review of the related literature.
Results: Nasal endoscopy showed a peduncle mass in the right nasal cavity. Cerebral scannography revealed an 18 mm tumour located in the upper wall of nasopharynx. Nasopharynx biopsy was performed. In microscopic examination, the tumour has a papillary architecture, with hyalinised fibrovascular cores lined by cuboidal to columnar cells with round vesicular nuclei presenting mild nuclear atypia. Some cells had nuclear groove. Nuclear pseudoinclusion and mitosis were absent. There was neither necrosis nor psammoma body. Immunohistochemistry revealed that the tumour cells were positive for thyroid tissue factor-1 (TTF-1), keratin 7, keratin 19, epithelial

membrane antigen, keratin 5/6, and negative for protein S100 and thyroglobulin. The diagnosis of PNPA was made.
Conclusion: PNPA is a rare subtype of conventional nasopharyngeal adenocarcinoma accounting for less than 0.48% of all malignant nasopharyngeal tumours. It is characterized by a papillary architecture and an unusual expression of TTF-1. Pathologists should be aware to distinguish it from thyroid papillary carcinoma due to morphological similarities. The negativity for thyroglobulin supports the diagnosis of PNPA.

E-PS-11-021
Human papillomavirus-related multiphenotypic sinonasal carcinoma: a report of three cases
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Background & objectives: Human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma (HMSC) is an emerged tumour restricted to sinonasal tract. We will describe an unique feature of HMSC, discuss its distinction from other tumours, and draw attention to the uncommon HPV subtypes in given cases.
Methods: We selected 3 HMSC cases diagnosed between 2015 and 2021 at our hospital. Immunohistochemical stains for p16, c-kit, p63, and SOX-10 were performed along with HPV DNA test using PANA RealTyper™ HPV Kit (PANAGENE Inc., South Korea).
Results: All cases were from men aged 60 to 86 years (mean, 75), and all tumours were larger than 3cm in size (mean, 4cm). Histologically, solid nests of basaloid cells and cribriform pattern were the main characteristics. Every case demonstrated atypia of surface squamous epithelial layer, morphologically similar to the squamous cell carcinoma in situ. All 3 cases showed strong, diffuse positivity for p16, and it is noteworthy that positive results were also obtained in the surface squamous epithelial layer, including the lesion showing the atypical change. As a result of the HPV DNA test, all three cases had different high-risk HPV subtypes (18, 56, and 82, respectively).
Conclusion: These results may suggest the possibility that the dominant HPV subtypes of HMSC in East Asia are different from those in the West. Still, an accurate interpretation is difficult due to the limited number of cases.

E-PS-11-022
High-grade transformation of acinic cell carcinoma with amplification of HER2 gene
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Background & objectives: Acinic cell carcinoma is a salivary gland carcinoma showing serous acinar differentiation. It is usually slow-growing with a 10-year survival of almost 90%. However, high-grade transformation has been rarely reported, and is associated with a significantly worse outcome.
Methods: We reported a newly diagnosed acinic cell carcinoma with high-grade transformation in the parotid gland of a 64-year-old female. The clinical history, morphologic features and immunohistochemical profiles were described. HER2/neu gene amplification was analysed by fluorescence in situ hybridization (FISH).
Results: Our case presented with a right parotid 3 cm-sized painful tumour with facial paresis for four months. She underwent total parotidectomy, and the histology revealed focal classic acinic cell carcinoma. High-grade transformation was identified, characterized by anaplastic cells with abundant cytoplasm and pleomorphic nuclei, arranged in irregular islands with comedonecrosis. Both the classic and high-grade components exhibited positive nuclear staining for NR4A3. The high-grade area showed stronger expression of cyclin D1 and p53, and had a higher Ki-67 index. These high-grade foci also demonstrated 2+ staining of HER-2/neu. FISH confirmed the HER-2 gene amplification in the high-grade component (HER2/CEP17: 2.13; HER2 copy number 5.5), but not in the conventional component.
Conclusion: Prevalence of HER2 positivity in salivary gland carcinoma varied significantly between histological subtypes. Here, we described the first case of acinic cell carcinoma with HER2 gene amplification confirmed by FISH. The amplification detected in the high-grade foci but not in the conventional area further suggested the possible role of HER2 in the pathogenesis of high-grade transformation in acinic cell carcinoma. Recognizing this molecular event is crucial because HER2 is an important potential target for therapies.

E-PS-11-023
Desmoplastic small round cell tumour of parotid gland: a rare case report
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Background & objectives: Desmoplastic Small Round Cell Tumour (DSRCT) is an uncommon malignant mesenchymal tumour that affects mostly children and young adults with a striking male predilection and it commonly involves the soft tissue of abdomen and pelvis.
Methods: Around 6% DSRCT"s have been reported in various extra-abdominal sites. Primary involvement of Parotid gland by DSRCT is extremely uncommon with only seven cases reported in literature. Here we present another case of DSRCT involving the parotid gland of a male patient. The detailed clinical, radiological and pathological findings of this case have been analysed and presented.
Results: A 54 year old male presented with a swelling in right parotid region for 6 months duration. On examination, the swelling was 6x5 cm in size, hard and was lifting the ear lobe. CT neck revealed a right parotid mass. FNAC was inconclusive and thus right total parotidectomy was done. Grossly, the tumour was grey white with areas of necrosis. Microscopic examination showed salivary gland parenchyma with an adjacent malignant neoplasm composed of uniform small round cells with scant eosinophilic cytoplasm and regular round nuclei arranged in nests separated by broad bands of desmoplastic fibrous stroma. IHC revealed S100, CKAE1/AE3, desmin and synaptophysin positivity. Final diagnosis of DSRCT was made.
Conclusion: DSRCT is considered as a tumour of uncertain histogenesis. Extra-abdominal DSRCT involving the parotid gland should be differentiated from other primary salivary gland tumours and several small round blue cell tumours. The tumour shows polyphenotypic differentiation expressing epithelial, mesenchymal and neuroendocrine markers in IHC studies. Molecular studies show characteristic translocation, t(11,22) with EWSR-WT1 gene fusion. Extra-abdominal DSRCT involving Parotid gland poses diagnostic challenge. Careful microscopic examination aided by IHC and molecular studies will help in diagnosing this uncommon mesenchymal tumour.

E-PS-11-024

Mandibular osteosarcoma: a retrospective study with review of the literature

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Background & objectives: Osteosarcomas are the most common bone sarcomas. They are preferentially located in the long bones of the limbs. Mandibular localization is rare, only a few cases have been reported in the literature.
Methods: we present a study of 6 cases diagnosed in the department of pathology at the CHU Habib Bourguiba in Sfax over a period of 10 years (2012-2021)
Results: The mean age was 40 years (extreme: 24-54). Four of the patients were men (sex-ratio:2). A history of irradiation was noted in two cases. All tumours were located in the body of the mandible. The average tumour size was 6.5cm (extreme: 3.5-10 cm), the histological type was chondroblastic osteosarcoma in 5 cases and osteoblastic in one case. Four out of six patients had received neoadjuvant chemotherapy. The histological evaluation of the therapeutic effect showed a stable calcified appearance of the tumour in one case and tumour necrosis rates of 20%, 30% and 40% for the others. Surgical margins were positive in 5 cases.
Conclusion: Mandibular osteosarcoma is a rare tumour; the most common histological type is chondroblastic, then osteoblastic and fibroblastic osteosarcoma with frequencies of 48%, 29% and 23% respectively. Its prognosis depends mainly on the quality of surgical excision. A surgical margin of at least 1 cm was recommended to avoid recurrence. Neoadjuvant chemotherapy prevents rapid disease progression and reduces tumour size.

E-PS-11-025

Benign smooth muscle proliferations of the tongue. Retrospective cohort study of a case series in a 31-year single institution

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Background & objectives: Leiomyomas are benign spindle cell tumours. Less than 1% are seen in the head and neck area. The definitive diagnosis is established upon histology. The differential diagnosis includes benign and malignant soft tissue tumours that may arise in the tongue.
Methods: We performed a retrospective search for cases signed-out as leiomyoma or hamartoma in the pathology database between the time interval of January 1990 and December 2021. A total of 5 cases were identified for which slides and blocks were available. The medical records were reviewed. All lesions located on the tongue but with different diagnosis were excluded from this analysis.
Results: 4 patients were women. Median age was 65 years (2 months–89 years). Three patients had complaints of a slow-growing and painless mass. One patient referred occasional bleeding. At birth, the infant had no anatomical alterations of craniofacial structures or midline defects. On physical examination, the lesion was located: dorsal lingual surface (N=2), tip of tongue (N=2) and right lateral border (N=1). Surgical resection of all lesions was performed. Histologically we had three different variants of benign smooth muscle proliferations: angioleiomyoma (N=3), non-vascular leiomyoma (N=1) and leiomyomatous hamartoma (N=1). During follow-up, there was no evidence of local recurrence or the appearance of leiomyomas in other body locations.
Conclusion: Leiomyomas are benign lesions in which surgical resection is curative in most cases. Therefore, despite being infrequent lesions in the oral cavity, compared to other anatomical locations, it is necessary to think about them when the pathologist is faced with a soft tissue lesion in this location, relying whenever necessary on complementary immunohistochemical studies.

E-PS-11-026

Diagnostic challenge: rare secretory carcinoma subtype identified in a parotid carcinoma ex pleomorphic adenoma

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Background & objectives: Salivary gland secretory carcinomas represent a relatively new entity, whereas carcinomas ex pleomorphic adenoma account for a modest percentage of salivary glands tumours. Therefore, the adjoining of the two appears to be a rather shy occurrence in practice.
Methods: Our Department of Pathology received a total parotidectomy specimen, samples from which were fixed with 10% buffered formalin and processed by conventional histopathological methods, using paraffin embedding, sectioning and Haematoxylin–Eosin (HE) staining, as well as PAS and mucicarmine staining. Afterwards, the sections were deparaffinized and prepared for immunohistochemical staining, using the following markers: CK7, p63, S100, GATA3 and Ki67.
Results: We report the case of a 51-year-old male with a 15-year history of an asymptomatic mass in the parotid region. Gross examination revealed a spheric, white, firm tumour. Microscopic examination identified a heterogenous, encapsulated mass presenting ductoglandular and solid structures, embedded in fibro-hyalin stroma. Tumoural cells exhibited cito-nuclear atypia, eosinophilic cytoplasm, mucous cells and intraluminal secretions that stained positive for PAS and mucicarmine. Tumoural cells stained positive for CK7, S100, GATA3, negative for p63, with Ki67 positive in 10% of them. Pleomorphic adenoma looking nodules were identified adjacent to the malignant proliferation. Thus, the diagnosis of carcinoma ex-pleomorphic adenoma, secretory carcinoma subtype with focal high-grade areas has been established.
Conclusion: Secretory carcinoma of the salivary glands or mammary analogue secretory carcinoma is a relatively new and rare entity that needs additional special and immunohistochemical stains to differentiate it from the multitude of histological subtypes. The occurrence of this subtype in a rather infrequent carcinoma ex-pleomorphic adenoma further advocates for the need to carefully assess all histological and immunohistochemical characteristics, given the poor prognosis of the high-grade variant and treatment options.

E-PS-11-027

Unique initial manifestation of salivary gland adenoid cystic carcinoma as a solitary liver metastasis

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Background & objectives: Liver metastases from salivary gland tumours are rare and presenting as the initial manifestation of disease is extremely rare with only four cases reported to date.
Methods: A 68-year-old man discovered elevated GGT and alkaline phosphatase during routine laboratory tests. He was further

investigated with computed tomography (CT) scan of the abdomen, which revealed a large liver mass measuring 16 cm in maximum diameter, occupying most of the right hepatic lobe. The mass had imaging characteristics of cholangiocarcinoma and a CT-guided needle biopsy was performed.
Results: Histopathological examination showed fragments of an epithelial neoplasm with adenoid cystic and focally cribriform growth pattern embedded in hyalinized stroma, and necrotic tissue. Neoplastic cells were small, with scant cytoplasm and oval to angulated, minimally pleomorphic and hyperchromatic nuclei, with palisading and basaloid areas peripherally, consistent with myoepithelial origin. Mitoses were not identified. Almost all neoplastic cells were positive for keratin 7(K7), K19, EMA and CD117 and the myoepithelial component was positive for p63. Morphological and immunohistochemical findings were consistent with metastatic adenoid cystic carcinoma (ACC). Clinical examination had revealed a 3 cm palpable neck mass, which after fine-needle biopsy was proved to be an ACC of the submandibular gland.
Conclusion: ACCs run a slow but progressive course and have a high likelihood of distant metastasis. The most common sites of metastases are lung and bone, followed by brain and liver. Liver metastases are often synchronous or metachronous with multiorgan metastatic disease and only a handful of studies of isolated liver metastasis have been reported in the literature. Due to the absence of consensus concerning the appropriate treatment, a multidisciplinary approach is necessary to manage this rare and aggressive neoplasm.

E-PS-11-028
Spindle cell lipoma in an unusual location, a case report
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Background & objectives: Lipomas are the most common mesenchymal tumours, although only 0.6% of them occur in the larynx. We report the case of a 62-year-old man who presented with dysphonia and dyspnea because of a supraglottic mass.
Methods: A CT was performed which revealed a fatty density lesion dependent on the left ventricle. The patient underwent laryngeal microsurgery. Afterwards, light microscopy, immunohistochemistry (IHQ) and molecular pathology studies were made. A literature revision also was performed.
Results: A 2.2 x 1.5 cm exophytic lesion was received. Gross pathology of the specimen showed yellow to orange cut surface. Microscopic examination revealed a well-circumscribed and non-encapsulated mass underlying normal appearing squamous mucosa. The tumour consisted of mature adipocytes, bland spindle cells and occasional pleomorphic multinucleated giant cells arranged in a "floret-like" pattern. The stroma alternated myxoid and collagen rich areas. With IHQ studies, stromal cells showed CD34 expression. The adipocyte component was negative for CDK4 and MDM-2. Ki-67 and PHH3 were <1%. Molecular pathology revealed deletion of one copy of the RB1 gene and absence of amplification of the MDM-2 gene. Thus, spindle cell/pleomorphic lipoma (SC/PL) diagnostic was made.
Conclusion: Laryngeal spindle cell lipomas are rare, with only six cases reported to date. Due to their benign nature, and in order to avoid overtreatment, it is important to distinguish them from a more aggressive entity such as well-differentiated liposarcoma/atypical spindle cell lipomatous tumour (WDLS). SC/PLs and WDLS have multiple histopathological similarities, that's why the key to distinguish them is based on cytogenetic analysis. WDLS does not show changes in the RB1 gene, while it exhibits MDM-2 gene amplification.

E-PS-11-029
Nasal chondromesencymal hamartoma; a rare case report
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Background & objectives: The nasal chondromesenchymal hamartoma (NCMH) is a rare benign tumour of sinonasal tract with predilection to paediatric age groups. We present a case of NCMH with characteristic histomorphological features, differential diagnosis and review the literature.
Methods: An 8- year-old-girl presented with occasional left sided epistaxis for a year and absence of breathing through the left nostril. She had a history of adrenal neuroblastoma with partial adrenal insufficiency and oral corticosteroid therapy. Differential diagnosis was antrochoanal polyp, angiofibroma inverted papilloma with endoscopic examination.
Results: Computed tomography scan revealed a 48x40 mm sized mass; in nasal passage, attached to the septum without bone destruction. Endoscopic excision of the mass showed polypoid white mass with vaguely nodular appearance. Microscopically mass was covered with respiratory epithelium. Stroma was mainly consisted of disorganized benign spindle cells distributed among fine collagen fibres with focal cartilaginous tissue. There were sparse areas with myxoid changes and occasional small vessels, nerve fibres and dilated cystic spaces. No signs of cellular atypia, necrosis and mitoses have been identified. The spindle cells was negative for muscle cell markers (Desmin, SMA and Myogenin). The Ki-67 proliferation index was less than 1%. Final diagnosis was NCMH.
Conclusion: NCMH is a rare tumour of upper respiratory tract and may mimic other benign and malignant lesions clinically. The correct diagnosis is essential for proper management. Histopathological features of NCMH are of great assistance for establishing the diagnosis.

E-PS-11-030
Bilateral subgemmal neurogenous plaque of the tongue: a case report
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Background & objectives: Subgemmal neurogenous plaque(SNP) is a biphasic neural structure associated with the taste buds and presents as an asymptomatic, normally coloured, papule located in the posterior lateral border of the tongue. We present a rare case of bilateral SNP on tongue.
Methods: A 38-year-female patient presented with asymptomatic wounds on bilateral posterior lateral sides of tongue. Hashimoto's thyroiditis is present in medical profile and she doesn't smoke. Bilateral biopsy was performed to rule out neoplasia.
Results: The surface of both biopsy materials were ulcerated, cut surface were beige coloured, and had soft consistency. Histopathologic examination revealed same features for both biopsies¸ neural plexus composed of irregular, small bundles and scattered separate neural cells underlying the oral squamous epithelium, which showed normal taste buds. Neural cells were spindle-shaped, with oval normochromic nucleus and wavy eosinophilic cytoplasm with no nuclear atypia or mitosis. Deeper parts composed of small nerve fascicles showing scant ganglion cells. There was accompanying reactive lymphoid tissue with

prominent germinal centres. Immunohistochemically, neural cells were strongly positive for S100. SNP was considered in the presence of histopathological findings.
Conclusion: SNPs can be confused with neural neoplasms for their morphologic similarities. Oral pathologists must be aware of the clinical and histopathological features of SNP to avoid misdiagnosis.

E-PS-11-031
Mammary analog secretory carcinoma of parotid gland, report of two cases
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Background & objectives: Mammary analog secretary carcinoma(MASC) of salivary gland is a tumour of low histologic grade. Histopathologic features, immunohistochemical profile resembles secretory carcinoma of breast and share highly specific genetic translocation, ETV6-NTRK3. Differential diagnosis of MACS is adenocarcinoma-NOS and acinic cell carcinoma.
Methods: We report two cases, both in parotid glands and one with reccurence after 15 months. Patients were 62-year-old male and 50-year-old female, both presented with mass at right parotid localization. They both had parotidectomy, one had right neck dissection.
Results: On macroscopic examination, tumours had lobulated contours, solid, firm and white coloured. Histopathological examination revealed well circumscribed tumour with microcystic pattern. The glandular spaces filled with an eosinophilic homogenous secretory material. Tumour cells had vesicular, bland looking nuclei with prominent nucleoli with abundant pale pink cytoplasm. Immunohistochemically, cells showed diffuse and strong staining for CK7, CK8/18, S100, mammaglobin, S100, GCDFP15, and vimentin. Reccurent tumour had same morphology and immunohistochemical stainings with first diagnosis.
Conclusion: MASC is a morphologically and molecularly well-defined salivary gland neoplasm. Differentiation of MASC from its mimickers is important due to their differences in behaviour.

E-PS-11-032
Malignant peripheral nerve sheath tumour arising from melanotic schwannoma: a case report and literature review
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Background & objectives: Malignant peripheral nerve sheath tumour (MPNST) arising from schwannoma is extremely rare. Our objectives are to present a new case of MPNST arising from schwannoma, to discuss the different differential diagnoses and to review the relative literature.
Methods: A 56-year-old man presented to the department of maxillofacial surgery with a painful temporo-zygomatic mass. The patient had a history of melanotic schwannoma incompletely resected six years ago. Magnetic resonance imaging performed demonstrated a mass arising from temporal muscle measuring 50-mm. Surgical excision of the tumour was performed.
Results: Histopathologic analysis of the tumour showed sheets of large polygonal tumour cells with abundant basophilic cytoplasm, round nuclei and distinct nucleoli. These cells showed moderate pleomorphism and increased mitoses (10 mitotic figures per 10 HPFs). Focally, there were fascicles of residual schwannian cells. The tumour presented focally necrosis area. Immunohistochemistry for PS100 was performed showing a diffuse and strongly expression in both epithelioid and schwannian cells. Immunostaining for cytokeratin and HMB45 were negative. The diagnosis of atypical schwannoma was ruled out due to the presence of atypical mitoses and necrosis. Melanoma was also excluded due to the negativity for HMB45. We concluded to an epithelioid MPNST arising from schwannoma.
Conclusion: MPNST arising from schwannoma can show typically epithelioid or spindle-cell histology. Epithelioid subtype is rare. Its most common locations are the trunk and extremities. Our case is distinguished because of its unusual location. Differential diagnosis includes melanoma and cellular schwannoma. Histomorphologic similarity with these tumours and the lack of specific immunohistochemical antibodies make establishing the right diagnosis challenging. MPNST should be considered in patients with a clinical diagnosis of schwannoma. Prompt recognition of this tumour allows for early curative treatment.

E-PS-11-033
Cavernous venous malformation of the orbit: a series of 16 cases and review of the literature
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Background & objectives: Cavernous venous malformation (CVM) is the most common benign orbital lesion of adults. This "cavernous haemangioma" is now considered a venous malformation. We describe the clinicopathological features of 16 cases and review the literature on its aetiology and controversial terminology.
Methods: We searched for all orbital vascular lesions (biopsy or extirpation) diagnosed in our Department between January 2007 and December 2021. Standard slides stained with haematoxylin and eosin were examined in all cases. Clinical data were obtained from electronic medical records. Medical literature research was done using PubMed. Results were presented in descriptive form.
Results: In the last 15 years, 70 periocular vascular lesions were diagnosed in our centre, 16 of which were CVM. The mean age was 49 years and 68% were female. The most common presenting complaints were a palpable mass (43%) and vision loss (25%). Two cases were incidentally detected on imaging. Over 44% of lesions were located in the intraconal space. One patient had bilateral lesions. Histologically, all lesions were nodular, encapsulated and contained large vascular channels lined by mature endothelial cells. The stromal component was fibrotic and paucicellular, with minimal inflammation. There were no evident arterial elements. Chronic thrombosis was found only in one case. Surgical treatment was curative.
Conclusion: Despite the confusing historical nomenclature, the so-called cavernous haemangiomas are not tumours as they do not possess a proliferative endothelium. Their slow growth is attributed to ectasia and hypertrophy. Therefore, CVM should be best regarded as slow flow venous malformations. Recently, some genetic alterations have been described, such as chromosomal losses at 13q and EWSR1/FUS-NFATC2 rearrangement, but further investigation is needed to clarify the aetiology of this lesion.

E-PS-11-035

Thyrolipoma, a case report with literature review

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Background & objectives: Thyrolipoma (TL) also called adenolipoma of the thyroid gland is distinctively rare. Less than 50 cases have been reported in the English literature so far. We describe a representative case of TL along with a brief literature review.
Methods: A 57-year-old woman, with no relevant medical history, presented with a painless neck lump which have been slowly increasing in size for 2 years. Physical examination and ultrasound imaging showed a well defined, 4 cm, predominantly cystic, TIRADS 3 nodule in the left lobe of the thyroid gland. A left hemithyroidectomy was performed.
Results: Surgical specimen weighted 28 g. The left lobe of the thyroid measured 4,5 x 4 x 4 cm. Cut section showed a 3.7 cm, medio-lobar, well-circumscribed, mainly cystic nodule, with haemorrhage and a few brittle yellow foci. Two smaller, well defined, solid nodules measuring 4 and 7 mm were also identified. On microscopic examination, all 3 nodules were surrounded by fibrous capsules and consisted of mature adipocytes admixed with bland-looking thyroid follicles. The adipose lobules accounted for at least 40% of the total nodules sections. The remainder of the thyroid tissue was unremarkable.
Conclusion: Most reported cases of TL occurred in women, varied in size from 0.3 to 25 cm and presented as a solitary lesion or in association with multinodular thyroid hyperplasia, papillary carcinoma or thyroiditis. TL should be distinguished from thyrolipomatosis characterized by fat diffusely distributed throughout the thyroid gland. The two conditions can rarely coexist. Some thyrolipomas present as extrathyroidal nodules and should not be mistaken with enlarged parathyroid glands which normally contain adipose tissue and may display a follicular pattern.

E-PS-11-036

Mesenchymal chondrosarcoma of maxillary bones: two case reports

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Background & objectives: Mesenchymal chondrosarcoma (MCS) is a very rare and aggressive malignant bone tumour occuring in femur, pelvis, ribs and facial bones, with 25% of cases in the jaws.
Methods: We report two cases of maxillary MCS in a 65 and a 26 years-old women respectively, who presented a large submucousal tumour of the hard palate. In the first case, TDM and MRI were in favour of a chondrosarcoma.
Results: On biopsies, the first case presented a proliferation made of large atypical cells lying in a chondroid matrix, surrounded by small foci of small round blue cells showing « crush artefacts ». The second case presented atypical and mitotic small blue cell nests densely packed around vessels and separated by chondromyxoid trabeculae. The chondroid component showed a nuclear positivity for PS100+ and were SATB2-, MDM2-, CD99- and NKX2.2-; and conversally, the« mesenchymatous » component, a membranous positivity for CD99+, a nuclear positivity for NKX2.2+ and were PS100-. The presence of a HEY1-NCOA2 gene fusion confirmed the diagnosis of MCS. Surgery was performed, followed by radiotherapy in the first case.
Conclusion: MCS is a biphasic tumour, with an undifferentiated small blue cell component and a well-differentiated cartilaginous component, and a highly specific HEY1-NCOA2 gene fusion. When facing a chondroid tumours of the jaws, both chondrosarcoma and chondroblastic osteosarcoma hypotheses must be raised, but small blue cell foci that could suggest a MCS must be searched for. Conversally, it is important in malignant blue cell tumours, to look for foci of cartilaginous differentiation. A molecular confirmation is necessary in this tricky diagnosis.

E-PS-11-037

Solitary neurofibroma of maxillary sinus expanding to nasal cavity and orbit

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Background & objectives: Neurofibromas are benign peripheral nerve sheath tumours with infiltrative potential. We present a case of a large and unusually located sporadic neurofibroma that occupied a great extent of craniofacial regions.
Methods: Otolaryngologists of our institution, following clinical examination and imaging, located and were able to biopsy a large tumour protruding from the left maxillary sinus of a 59-year old female patient. This mass seemed to be extending inside the left nasal cavity and possibly reaching the adjacent orbit with radiological signs of osseous erosion.
Results: Histopathology report described a neoplastic lesion consisting of sparse, uniform cells with wavy nuclei inside a collagenous stroma. Only rare mitoses and no necrosis or atypia were observed. Mitotic index using Ki-67 was calculated about 1%. During ancillary examinations, the neoplastic population stained for S100, CD34 (focally) and EMA (focally), whereas was negative for CD117, Ck8/18 and MelanA. The diagnosis of neurofibroma was concluded.
Conclusion: In conclusion, the case described aims to increase awareness among clinicians and diagnosticians of this very rare site of this already quite uncommon entity, with only a few cases described in the existing literature.

E-PS-11-038

A forgotten entity in parotid gland lesions differential diagnosis – a case report

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Background & objectives: Haemangiomas are benign vascular abnormalities characterized by an increased proliferation and turnover of endothelial cells, accounting for 0.4-0.6% of all parotid gland tumours. They are common in infancy but extremely rare in adults, often misdiagnosed before surgical resection.
Methods: A 85-year-old woman presented in 2018 with a parotid nodule with 3x2,5cm. Between 2018 and 2021 she underwent 4 fine-needle aspirations (FNA), all constituted by blood and few epithelial cells, all considered non-diagnostic. Computed Tomography scan and Magnetic Resonance Imaging were inconclusive, favouring a benign tumour, and suggesting the possibility of a vascular lesion.
Results: In January 2022 a tumourectomy was performed. Intraoperatively, a vascular lesion involving the deep lobe of parotid gland was identified. Grossly, the specimen measured 5,5x5x2 cm and weighted 216,5 g. The cut surface revealed a multinodular expansive brown lesion, with white areas. It measured 3,3x3,2x1,4 cm and was partially coincidental with the excision margin. Microscopically, a

predominantly capillary vascular proliferation without atypia was identified, with a multinodular arrangement, partially involving the adjacent parenchyma comprised of serous salivary glands showing signs of atrophy. There were occasional thrombi and signs of old and recent bleeding. The immunohistochemical study supported the diagnosis of haemangioma (CD34+, CD31+, Podoplanin-, AE1/AE3-, Smooth muscle actin-, HHV-8-).
Conclusion: We highlight the importance of considering haemangiomas in the differential diagnosis of parotid tumours of adults. These are not usually considered due to their low prevalence in this population and are normally approached through FNA. This most often results in non-diagnostic aspirates, and ideally should be avoided to prevent iatrogenic hematomas. Diagnosis depends on integration of clinical and radiological data. When suspected, the patients should undergo early conservative surgery and a final diagnosis made on the surgical specimen.

E-PS-11-039
Rhinocerebral mucormycosis: a report of 11 cases
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Background & objectives: Mucormycoses are rare aggressive fungal infections that are rapidly extensive and usually fatal. Rhinocerebral mucormycosis is the most common form. We aim to study the clinical and anatomopathological aspects of this rare and life-threatening entity.
Methods: We retrospectively studied all cases of rhinocerebral mucormycosis diagnosed at Habib Thameur's hospital over a period of 13 years (from 2008 to 2020). Only cases confirmed by pathological examination were included in our study.
Results: Our sample consisted of 11 cases. They were eight men (72.7%) and three women (27.3%) with a sex ratio of 2.66. The age of the patients varied between 12 and 78 years with an average of 45 years ±18.62. In this study, eight patients were immunocompromised. One patient was on long-term corticosteroid therapy for systemic lupus erythematosus, the 12-year-old patient had bone marrow aplasia, three patients were diabetics, one patient had acute myeloid leukaemia, one patient had IgM type immunodeficiency and one patient had lymph node tuberculosis. Two of our patients had orbital cellulitis, only one patient had proptosis and all the other patients had acute sinusitis.
Conclusion: Rhinocerebral mucormycosis is a rare and underdiagnosed pathology. Its diagnosis is often challenging. It is a medico-surgical emergency. The diagnosis of certainty is based on pathological examination. Its management is based on surgery and antifungal treatment.It has poor prognosis with high morbidity and mortality rates. An early diagnosis is crucial and allows the rapid onset of appropriate treatment. A better knowledge of this pathology and its evocation, especially in immunocompromised patients, would improve the prognosis and survival rates.

E-PS-11-040
Adenomatoid hyperplasia of minor salivary glands - a case report
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Background & objectives: Adenomatoid hyperplasia of minor salivary glands is a rare lesion occuring predominantly in the palate with some rare cases described in the buccal mucosa. It is of unknown aetiology and imitates a salivary gland tumour.
Methods: A 60-year old man presented to the hospital for dysphagia and a 5 cm palatal mass was discovered. A biopsy was performed which came back as squamous cell carcinoma in situ. The mass was resected and was sent to the pathology department. Grossly the mass was covered by regular, smooth mucosa and resembled salivary gland parenchyma on the cut surface.
Results: Microscopically, scar tissue corresponding to the biopsy was identifiable. The epithelium presented pseudoepitheliomatous hyperplasia without dysplasia. The submucosa corresponded to mucous type acini with lobular architecture, separated by fine connective tissue bands. Rare ducts were identifiable as well as extracellular mucus. No dysplastic or malignant features were present. Inflammation was minimal; predominantly lymphocytes and plasmocytes were appreciated. The surgical resection margins were in contact with the acini.
Conclusion: Adenomatoid hyperplasia of the minor salivary glands is a rare benign lesion which can be cured by complete surgical resection. The clinical appearance can be in favour of a salivary gland tumour, therefore a biopsy is required in order to properly classify the lesion.

E-PS-11-041
Oral carcinoma cuniculatum: a diagnostic challenge
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Background & objectives: Carcinoma cuniculatum (CC) is a variant of squamous cell carcinoma characterized by crypt-like structures of squamous epithelium with minimal atypia. Given its rarity and lack of atypia, it has been a diagnostic challenge. We present a mandibular case of CC.
Methods: Forty eight-year-old male patient presented with left mandibular pain lasting for 1,5 years. Multiple incisional biopsies showed almost no sign of malignancy, except minimal cytologic atypia and burrow-like growth pattern. However, the last incisional biopsy was diagnosed as squamous cell carcinoma, considering radiologically detected extensive bone destruction. The patient underwent left hemimandibulectomy and ipsilateral cervical lymph node dissection.
Results: Macroscopic evaluation of the resection specimen revealed no distinct mass lesion, although some areas of the mandible were easy to cut. Histopathologic examination revealed a lesion which consisted of keratin-filled crypt-like structures lined by well differentiated squamous epithelium which showed multiple foci of microabscesses and almost no cytologic atypia. Crypt-like structures were extending deep into the underlying bone in a destructive fashion, suggesting a malignant process. No metastatic lymph node was observed. Immunohistochemistry results for p16 and HPV were negative. All these findings taken into consideration, the case was concluded to be compatible with CC, which is a very rare variant of squamous cell carcinoma.
Conclusion: This local aggressive histologic variant of squamous cell carcinoma remained under-diagnosed because of its extremely well differentiated nature and rare incidence. Some percentages of the cases are being reported as verrucous carcinoma (VC), since both entities show minimal cytologic atypia. However, unlike CC, VC shows invasion in a pushing manner. Very rare cases with lymph node and distant metastases have been reported. Our case report aims to raise awareness of such entity among pathologists and prevent misdiagnosis of this disease.

E-PS-11-042
Primary mucosal melanoma of the nasal cavity, report of 5 cases
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Background & objectives: Mucosal melanoma of the nasal cavity(MMNC) is extremely rare. Nevertheless, it is the most common mucosal melanoma of the head and neck region, with an increasing incidence in many western countries. We describe 5 additional cases with a literature review.
Methods: A retrospective study of 5 cases of MMNC, diagnosed and treated in our institution between 2000 and 2020. Clinical and pathological data were reviewed.
Results: Our series comprised 2 male and 3 female patients. The mean age at diagnosis was 63.2 years (range: 51-86). The most common symptoms at presentation were recurrent epistaxis (4/5 cases) and unilateral nasal obstruction (1/5 cases). All patients were treated surgically. Tumours measured 1.5 to 5 cm. Histologically, 2 tumours consisted exclusively of spindle cells. 3 others were mixed composed of both spindle and epithelioid cells. Surgical margins were negative in only 2 cases. Tumour cells stained with HMB45 and Melan-A antibodies respectively in 5 and 4 cases. One patient developed bone metastasis and two others experienced local recurrence during a median follow-up of 26 months.
Conclusion: MMNC is highly aggressive. Therefore, T1 and T2 stages were omitted in the 8th edition of the AJCC staging of these tumours. Prognosis is poor, with a 5-year survival rate less than 40% in most published series. The diagnosis is often delayed due to the "hidden" tumour site and the non-specific clinical presentation. No optimal treatment therapy has yet been defined. A better understanding of the biology of this tumour will enable the identification of targetable oncogenic driver.

E-PS-11-044
Persistent epistaxis – a neoplastic differential
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Background & objectives: Biphenotypic sinonasal sarcoma (BSNS) is a rare low-grade sarcoma with neural and myogenic differentiation. It was first described by Lewis et al. in 2012, and since then only about 100 cases have been described.
Methods: We submit a case of a 59-year-old man that presents to the emergency department with persistent epistaxis from the left nasal cavity in the previous two days. Nasal endoscopy showed a voluminous neoformation on the left middle turbinate. Magnetic resonance imaging revealed a 40x25x74 mm well-delimited mass with gadolinium enhancement in the same topography. Endoscopic sinus surgery was then performed.
Results: Several elastic fragments with dimensions between 10 and 45 mm were received. Microscopic examination revealed sections of respiratory mucosa intersected by a well-differentiated mesenchymal proliferation with a rich vascular stroma, composed by monomorphic spindle cells with clear nuclei. No mitosis, necrosis, perineural nor lymphovascular invasions were observed. Due to sample fragmentation, surgical margins were not assessed. The tumour cells exhibited focal staining for S100, SMA and β-catenin (both nuclear and cytoplasmic expression). CD34, Calponin, CK CAM5.2, CK AE1/AE3 and Desmin were negative. The lesion was diagnosed as BSNS.
Conclusion: BSNS oncogenesis is related to the PAX3 gene which is a transcription factor involved in the development of both muscle and neural tissues of nasal structures. Hence the characteristic staining pattern described. The symptoms are non-specific. It predominantly affects women, and 30-50% of cases recur. No cases of metastases have been reported and only one case of death due to disease is described. The differential diagnosis ranges from benign (e.g. glomangiopericytoma) to aggressive neoplasms with metastatic potential (e.g. synovial sarcoma).

E-PS-11-045
A review of adenoid cystic carcinoma patients in Ireland
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Background & objectives: Adenoid Cystic Carcinoma (ACC) of head and neck is a relentlessly progressive tumour. EU incidence is 13 cases per million annually. RVEEH files were analysed over a 20-year period (2002/2021) to establish the clinico-pathologic and molecular findings in Ireland.
Methods: Patients with a diagnosis of ACC were retrieved from pathology files. All clinical information was reviewed, and material submitted for NGS-based WES including genes known to be associated with ACC i.e.. MYB, MYBL, NOTCH, SPEN. A targeted Oncomine NGS mutation panel was also performed on 2 cases.
Results: From 15 identified cases, 4 were female and 11 male. The mean age was 45 (range: 20 to 72) at time of initial diagnosis. Primary tumour location; external auditory canal, nasal and oral cavity, lacrimal, parotid, and submandibular glands. All known histologic patterns were observed. Ten patients were treated by surgery and adjuvant radiotherapy (RT). Five patients were inoperable and were treated by RT. Two patients had a local recurrence and four patients developed systemic metastasis (follow-up period 42 to 153 months); sites included cervical and distant (pulmonary, renal, splenic). The average time to recurrence was 44 months. Six patients died on average 4 years post-diagnosis. Genetic analysis is underway.
Conclusion: From our findings, the incidence and prevalence of ACCs in Ireland appears to be in line with European average. There is a similar age range. In this study molecular findings will be correlated with clinical pathological characteristics in order to identify potential actionable genetic mutations.

E-PS-12 | E-Posters History of Pathology

E-PS-12-001
The relic of the Blessed Maria Lorenza Longo founder of the "Hospital of the Incurables" in Naples. A paleopathological and paleoradiological study
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Background & objectives: Maria Lorenza, born in Spain, followed the husband Joan Llonc (Longo in italian), the chancellor of King Fernando, in Naples. She founded the Hospital of the Incurables. This study aims to verify the historical accounts about Maria Longo.
Methods: Maria Longo died in 1539 and was beatified in October 2021. She suffered from a disabling disease attributed either to poisoning, syphilis or rheumatoid arthritis. Before the beatification, a scientific inspection of her relic was approved by the Curia. In particular, a 16-slice CT scanning with multiplanar reconstructions (MPR) and volumetric (3D) rendering was performed.
Results: The relic is represented by a completely skeletonized calvarium and was examined through both visual and digital radiology inspection on different projections. The biological profile

confirmed the female sex of the relic, whereas the estimated age at death was earlier than that proposed by historians. Neither vitamin nor nutrient deficiencies were found. The syphilis hypothesized by textual sources was excluded. A small rounded osteoma was detected by CT scan on the endocranial surface of the frontal bone. Interestingly, postmortem alterations of the relic were clearly visible at the top of the calvarium, demonstrating the worship of the relic since the death of the Blessed Maria Longo.
Conclusion: The paleopathological and paleoradiological study of the relic of the Blessed Maria Longo revealed a woman whose death occurred at a younger age than that reported by textual sources. Maria Longo neither suffered of syphilis nor experienced dietary deficiencies. Her relic showed signs of worshiping dating from the early years after the death.

E-PS-12-002
The Neapolitan Hospital for Incurables and the life and work of Domenico Cotugno
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Background & objectives: The purpose of this contribute is to describe the activities of Hospital for Incurables in Naples and to mention Domenico Cotugno's life. He was an Italian scientist famous in all Europe for his research activities and views of modern medicine.
Methods: According to our literature search, Maria Longo, the wife of Juan Lonc (Longo), Minister of the King Ferdinand the Catholic of Catalonia, founded in 1522 the Hospital of Incurables (people who nobody wanted to cure), and during the following years and centuries monastic orders were engaged in this Hospital, which was also considered the "Saint's Hospital" (among them Luigi Gonzaga).
Results: People affected by severe invalidating diseases were accepted in the Hospital: paralysis, epilepsy, icterus, syphilis, burns were among the diseases cured in the Hospital. The centre was so famous in Europe that many Gran Tour Tourists visited the Hospital, which was also a university site, during their trip to Naples. Domenico Cotugno, born in Ruvo pugliese in 1736 and graduated in Medicine at the Salerno medical school, became an assistant at the Hospital for incurables and, in 1761, professor of Surgery. He was professor of Anatomy and Director for 30 years of the Hospital, favouring a centre devoted to modify, with modern rules, the perspectives of the diseases.
Conclusion: Domenico Cotugno was convinced that medicine has a strong social commitment: to cure and to save as many persons as possible, simple persons as well as nobles. Cotugno's scientific activities on acqueducts of the human inner ear, on "De sedibus variolarum syntagma" were famous in Italy and Europe through the 18th century. For his promotion of vaccines, in Naples in 1807 Cotugno was named president of a committee promoting the vaccine against Smallpox. He was an outstanding example of physician-humanist.

E-PS-12-003
From war to earthquake. 100 years of Institute of Pathology University of Zagreb School of Medicine
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Background & objectives: WW 1 with all its horror led also to destruction of 3 out of 4 empires. In this, 1917. after 100 years of struggle with the Austrian Monarchy, founding of Faculty of Medicine was finally granted to Zagreb University.
Methods: The search for faculty was not easy in these war and post-war times. So it was for Pathology chair. After several attempts (including Vaclav Neuman from Brno) Sergei Saltykow, also a prominent pathologist with great experience was elected. It was in 1922 the Institute of Pathology became operational both in teaching and diagnostics.
Results: Its history was marked by struggle in order to finish the building, organize the teaching activity including a modern microscopy room for the students, spacious autopsy room and a top macroscopy museum. The Institute soon became a turning point not only for teaching but also for histopathology diagnostics, covering large areas of the newly formed kingdom of Yugoslavia. Saltykow's expertise together with great enthusiasm resulted also in a series of Pathology textbooks which remained the golden standard for decades to come. His followers expanded and modernized the institute launching new laboratories (EM, histochemistry, immunohistochemistry, molecular pathology) and new teaching techniques. The tradition of textbooks also remained.
Conclusion: In a moment where the vision of introducing new quality in diagnostic, teaching and research work appeared to become reality, the earthquake of March 22. 2020, seriously disrupted our plans. The teaching part of the institution can't be used at all and we resumed our work under broken walls, which meanwhile have been provisionally repaired. But we hope that the reconstruction will bring us the opportunity to realize our dreams, and maybe make them even better.

E-PS-12-004
Influence of the French geodesic mission in the first microscopic findings in Ecuador
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Background & objectives: The arrival of scientists from the French Geodesic Mission in Ecuador meant a time of academic boom that represented the first microbiological vision. European scientists gave us their most modern microscope built by John Cuff.
Methods: We performed a review of textbooks and database Scielo addressing the origins of pathology in Ecuador, starting with the first microscope.
Results: In Quito (1736), the French scientists delegates were welcomed by the Jesuits. After building a good relationship with Ecuadorian scientists, they gave them their modern microscope. Juan Bautista Aguirre, Ecuadorian priest and scientist, described the first findings in the "Tratado de Física"(1759), in which he described that diseases and plagues are caused by malignant worms and transmission. Years later, Marco Von Plenciz; a Slovenian doctor, published "Opera medico-physica"(1762), stating that microorganisms are the cause of diseases. Due to the European intellectual construction and the Jesuits at the University of San Gregorio, first Ecuadorian physician, Eugenio Espejo began his multiple microbiological thoughts in Ecuador (1785).
Conclusion: The geodesic mission that granted the first microscope in Ecuador, contributed to the knowledge of epidemics that caused high morbidity and mortality. This new development led to academic reconstruction in Ecuadorian society.

E-PS-12-005
N.I. Pirogov and the doctrine of vessels and vascular pathology
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Background & objectives: N.I. Pirogov is undoubtedly recognized as a world leader in the study of the surgical anatomy of blood vessels and vascular pathology. He described a huge number of vascular pathologies, having a very serious impact on medicine.
Methods: We analysed literary sources from the very N. Pirogov times to the present and to understand Pirogov's contribution to the development of angiology and vascular pathology as sciences.
Results: In the dissertation "Is the ligation of the abdominal aorta in an aneurysm of the inguinal region an easy and safe intervention", defended in 1832 in the city of Dorpat, N. Pirogov raised the question of to what extent and due to which arteries collateral circulation develops after ligation of the abdominal aorta. In addition, it is worth noting that, N. Pirogov had a huge number of other works in the context of angiology, filling in the gaps in the study of vascular pathology initiated by Hunter, Stromeyer, Larrey and even Lambert.
Conclusion: Thanks to the ideas of N.I. Pirogov about the possibility of collateral circulation, today it is possible to operate on the abdominal aorta and large arteries, clamping them for a certain time without the danger of immediate thrombosis and the development of acute ischemia. N. Pirogov is rightfully considered one of the greatest anatomists who very seriously influenced the development of normal and pathological anatomy.

E-PS-13 | E-Posters Infectious Diseases Pathology

E-PS-13-001
Features of the cell composition of the inflammatory infiltrate in different phases of diffuse alveolar lung damage with COVID-19

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Background & objectives: Mortality from ARDS with COVID-19 is 26.0 - 61.5%, and due to other causes - 35.3-37.2%. To find of the correlation between CD15-positive cells, CD3-positive cells and CD68-positive cells in the inflammatory infiltrate in lung with COVID-19.
Methods: The lung tissue of 25 patients who died from ARDS with COVID-19 without a secondary bacterial or mycotic infection, another thanatologically significant pathology of the lungs, was studied during autopsies. To study the cellular composition of the inflammatory infiltrate and the dynamics of its changes was used a double immunohistochemical analysis of the expression of antibodies to CD15, CD3, CD68.
Results: The inflammatory infiltrate in the exudative phase of DAD was represented by 56.8% of PMNs (CD15-positive cells; hereinafter, ratio percentage of positive cells to the total number of inflammatory infiltrate cells), 6.9% - lymphocytes (CD3-positive cells) and 19.5% macrophages (CD68-positive cells). In the early stage of the proliferative phase: 14.1% PMNs (CD15-positive cells), 38.7% lymphocytes (CD3-positive cells) and 13.5% macrophages (CD68-positive cells). In the late stage of the proliferative phase: 11.3% PMNs (CD15-positive cells), 14.5% lymphocytes (CD3-positive cells) and 39.3% macrophages (CD68-positive cells).
Conclusion: In the exudative phase CD15-positive cells predominate, which is probably the trigger for the development of DAD and determines the volume of lung signs and the severity of ARDS in COVID-19. In the early stage of the proliferative phase CD3-positive cells predominate, which corresponds to the beginning of proliferation and repair processes. In the late stage of the proliferative phase of DAD the predominance of CD68-positive cells was revealed, which correlates with the processes of organization in lung tissues.

E-PS-13-002
Immunohistochemical profile of control cell cycle, proliferation and differentiation proteins of atypical alveolar epithelium with diffuse alveolar damage caused by COVID-19 in comparison with lung lepidic adenocarcinoma

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Background & objectives: We aim to compare expression profiles of control cell cycle, proliferation, differentiation proteins and nuclei sizes in atypical epithelium (AE) of lung tissue with diffuse alveolar damage (DAD) and lung lepidic adenocarcinoma (LA).
Methods: Twenty-four autopsy cases of patients who died from acute respiratory damage syndrome induced by COVID-19, approving by PCR, (group 1) and four cases of lung lepidic adenocarcinoma (group 2). We made slides with the following antibodies: p53, Ki67, p16, p63 for each of the cases. Then the rate of stained cells of AE was calculated on each slide.
Results: We found statistically significant differences in p16 subgroup and p63 subgroup. We found a negative correlation between Ki67-index and number of days from onset of symptoms in group 1. No significant differences were revealed in subgroup p53 and Ki67.
Conclusion: The present study has shown heterogeneity in differences of expression levels of control cell cycle, proliferation and differentiation proteins between groups, and correlation between Ki67-index and number of days from onset reflecting decreasing proliferative activity. It shows similarities and differences of the lung AE in neoplastic and regenerative condition.

E-PS-13-003
COVID-19 associated mucormycosis: a case series

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Background & objectives: Since the start of the COVID-19 pandemic, mucormycosis cases have been on the rise. The most common form of the disease, rhino-orbital-cerebral mucormycosis (ROCM), has high morbidity and mortality. We present 4 cases of ROCM diagnosed in our hospital.
Methods: The 4 patients presented to the hospital between September 2020 and February 2022. After clinical assessment, MRI and CT imaging studies were performed. Tissue samples were sent to the Pathology Department, where mucormycosis was confirmed via histopathology.
Results: All 4 patients were male. The mean age was 65.5 years. On admission, two patients were COVID-19 positive while the other two had long COVID. Three patients had type 2 diabetes. Two cases presented with ground glass opacities on lung CT. One case had a Glasgow Coma Scale of 5 on admission, and imaging demonstrated changes suggestive of encephalitis, as well as intraventricular haemorrhage. Histopathology in all four cases revealed wide, ribbon-like hyphae that branched at right angles. The patients were treated by repeated surgical debridement coupled with antifungal medication. One patient died of pulmonary embolism while another died due to septic shock.

Conclusion: COVID-19 associated mucormycosis is most likely underdiagnosed. As our experience confirms, rapid initiation of both aggressive surgical debridement and antifungal therapy is vital in providing patients with better outcomes. In order to facilitate early treatment, a timely diagnosis is of utmost importance. A high index of suspicion is required in the face of patients with a history of COVID-19 presenting with sinusitis, proptosis or other craniofacial signs and symptoms.

E-PS-13-004

Clinico-morphological peculiarities in cases of COVID- 19 infection combined with diabetes mellitus

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Background & objectives: Diabetes mellitus(DM) as an underlying disease in cases of COVID-19 is associated with severe cause of infection and increased mortality. The aim of present study was to investigate organs' damages induced by COVID-19 infection in patients with diabetes mellitus co-morbidity.
Methods: Post-mortem examinations were performed in 34 lethal cases of COVID-19 infection with DM co-morbidity. Patients' medical records were evaluated. The group included 16 males and 18 females, 49 - 90 y.o. Hospitalization's duration was 1-39 days. Macroscopic examinations of the internal organs performed. Tissue samples were taken for histology. Microscopy of H&E stained slides done at x10, x20, x40.
Results: Autopsy has shown multi-organ damages in all cases. Diabetes – induced angiopathies were registered in 9, polyneuropathies - in 8, retinopathies - in 6 and nephropathies- in 10 cases. Diffuse lungs alveolar damage revealed in all patients. Histologically were found microangiopathies, perivascular, intrabronchiolar and intraalveolar haemorrhages interspersed with areas of alveoli filled by oedematous fluid. Vessels with erythrocyte sludge, fibrin and thrombi were recognized. Desquamation of the alveolar and bronchiolar epithelium cells were often replaced by hyaline membranes. Interalveolar septi were thickened due to vessels congestion, oedema, inflammatory infiltrations and haemorrhages. Myocardium, liver, kidneys were characterized by hypoxic and metabolic damage of various sizes accompanied with local microangiopathies and petechial haemorrhages.
Conclusion: The study has shown that diabetes mellitus as a comorbidity was the important risk factors for COVID-19 patients. Multiple organ dysfunctions due to diffuse structural injuries in lungs and other organs caused by the severe COVID-19 and affected by underlying diabetes mellitus was a prerequisite for the lethal outcome of the disease. Further studies of the pulmonary, blood vessels and parenchymal organs dysfunction' mechanisms may help designing effective clinical management of infected patients with diabetes comorbidity.

E-PS-13-005

Morphological characteristics of kidneys damage induced by SARS-COV-2

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Background & objectives: Infection with SARS-CoV-2 can not only cause respiratory system pathology but also result in multiple organs insufficiency. The aim of present study was to reveal structural peculiarities of kidneys damage in fatal cases of the COVID-19.
Methods: A full pathological post-mortem examinations were performed in 60 fatal cases of the SARS-COV-2. All clinical data were studied. Gross pathology of the lungs, kidneys, other internal organs and brain were examined. Tissue samples were taken for histology. Microscopy of H&E stained slides performed at x10, x20, x40. Kidneys pathology features were recorded and analysed.
Results: This study has shown the kidneys structural injuries presented with areas of dystrophy and necrosis in the epithelium of the convoluted tubules, various glomerulopathies in patients with COVID-19 infection. Morphological manifestations of mesangial glomerulonephritis occurred in many cases. Quite often in glomeruli fibrinoid necrosis of capillary loops was noted. Sclerotic changes in glomeruli, including focal and diffuse, were often detected in kidneys' tissue. There were also found ischemic infarctions as a result of SARS-COV-2 induced vascular thrombosis. Tubulo-interstitial pathology with stromal oedema and inflammatory infiltrates revealed in many cases. Features of pulmonary pathology, including atypical interstitial bilateral pneumonia, diffuse alveolar damage and hyaline membranes formation supported the COVID-19 diagnosis.
Conclusion: SARS-COV-2 infection has become a global health crisis, responsible for the significant growth of patient's morbidity and mortality worldwide. Post-mortem examination is an essential tool in understanding multi-organ pathology in this novel infection. The results have shown renal tropism along with severe respiratory distress syndrome. Kidneys tissues damages, inflammatory reactions, blood circulation disturbances significantly contributed to organ's insufficiency and fatal outcomes. Further investigations of kidneys affection as one of important SARS-COV-2' targets are considered essential.

E-PS-13-006

Lethal case of schizophrenia with generalized chlamydia infection

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Background & objectives: Schizophrenia remains very important disease with unclear aetiology. Among other theories infectious has many arguments, but direct detection of chlamydia antigen in brain has been never reported.
Methods: Lethal case of woman N.E., 37 ys. Nearby routine pathological examination has been done PAS reaction and immunohistochemistry including sera against Chlamydia trachomatis and Toxoplasma gondii.
Results: Patient suffered from paranoid form of schizophrenia for several years. Deterioration was due to coronavirus infection, confirmed at the autopsy. Additionally, was detected pseudomembranous colitis. Special attention was paid to changes of macrophages, nervous and epithelial cells in lungs, brain, kidneys, liver, spleen with multiple small vesicles. In all organs were detected extra- and intracellular PAS-positive inclusions. IHC investigation has been done. Chlamydia antigen was clearly detected in all internal organs. Special attention was paid to the brain, where positive reaction was noted in the cytoplasm of nervous cells and in white matter as well. IHC with serum against toxoplasma gave no distinct positive reaction.
Conclusion: Thus, our case strongly supports the infectious concept of schizophrenia although further studies including additional cases and methods are necessary.

E-PS-13-007

Clinico-pathological analysis in lethal cases due different genotypes of coronavirus

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Background & objectives: Among other aspects of new coronavirus infection important role of different genotypes causing disease with certain epidemiological and clinical peculiarities is known. There are no literary data related to morphological characteristics of lesions due to different virus genotypes
Methods: We made clinic-pathological analysis in 39 lethal cases in age 18-95 ys in which virus genotype was determined during life time by sequence of viral RNA: delta line PANGO B.1.6617.2, AY.12 -25 pts- 1 group , alpha line PANGO AT.1 - 5 pts – 2 group, rare forms lines PANGO B.1.1.317, B.1.1.396, B.1.1.291, B.1.1.121) 9 pts – 3 group.
Results: All patients suffered from pneumonia, majority (37-95,5%) had concomitant diseases/ Average time of hospitalization 19± 1,6 ds, average staying in intensive care unit 7,7 ±During the analysis between 2 and 3 group was shown difference between age of the patients (2 versus 3 group), duration of staying in the intensive care unit (1 versus 3 and 2 versus 3 groups) and grade of lymphopenia (2 versus 3 group). No differences were detected in average length of hospitalization, level of IL-6, D-dimer, CRP, ferritin. Histopathological picture in all investigated was grossly the same.
Conclusion: Thus, no significant differences between the changes due to different serotypes of new coronavirus could be detected, probably it can be explained by the fact that the mutations doesn't include parts of genome relevant to virulence factors, although further studies are obligate.

E-PS-13-008

Strongyloides stercoralis - a rare sighting in a gastroduodenal biopsy

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Background & objectives: A 53-year-old male, diagnosed with type 2 diabetes and pemphigus foliaceus, under treatment with azathioprine and high doses of prednisone, is admitted for epigastric pain, nausea and vomiting. A histological examination was performed in order to diagnose the underlying cause.
Methods: An upper gastrointestinal (GI) endoscopy was performed and tissue samples were taken from the ulcerative lesions of the antral stomach and duodenum. The biopsy samples were prepared for microscopy using paraffin processing techniques and the sections were coloured using a standard hematoxylin-eosin stain. The specimen was microscopically examined and the results obtained were correlated with available scientific literature.
Results: The upper GI endoscopy showed oesophagitis with *Candida albicans,* mucosal erosions in the lower oesophagus and multiple gastric ulcerations covered by fibrin. Upon microscopic examination, active ulceration of the gastric mucosa, areas of necrosis and multiple pluricellular parasites in various stages of evolution located in the gastric pits were found. The parasites had the morphology of *S. stercoralis* and they elicited an inflammatory response primarily consisting of eosinophils and neutrophils. Additionally, scattered alongside the areas of necrotized mucosa, multiple cocci and filamentous structures with features compatible with Candida were identified.
Conclusion: The definitive diagnosis was duodenal infection with *Strongyloides stercoralis,* which had extended to the antral stomach, and bacterial superinfection. In this specific case, the finding was unexpected and incidental. This finding underlines the risk of *S. stercoralis* infection in immunocompromised patients and its presence should be considered in the case of patients from this category presenting with GI symptoms. Furthermore, this case report highlights the role of histopathological examinations in the identification and diagnosis of GI parasites.

E-PS-13-009

Cellular phenomenon of lymphoid cells with Roussel bodies and "flaming" cells in spleen tissue of patients who died of COVID-19

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Background & objectives: Combination of COVID-19 infection and mixed flora in lung tissue and formation of lymphoid cells with Roussel bodies in tissues of the spleen is an incompletely studied phenomenon.
Methods: Autopsy material from 34 spleens of individuals who died of confirmed COVID-19 in 2020 was examined. Material was obtained from 20 men and 14 women who died between the ages of 30 and 91 years. The duration of illness ranged from 3 to 23 days. The material was stained with hematoxylin-eosin. Part of the material was stained by PAS reaction.
Results: Few cells with Roussel bodies were found in red pulp of spleen. Foci of coccus flora in alveolar cavity was combined with depletion of red pulp of the spleen and its focal necrosis in isolated cases. Single large lymphoid cells of "flaming" type, single lymphoid cells with Roussel bodies, single mitoses in cells with Mott cell morphology were recorded in the spleen tissue. Sometimes a rare features of topography was observed for cells with Roussel bodies in the spleen tissue in the form of their central location surrounded by lymphoplasmacytic cells in the form of immune rosette.
Conclusion: Lymphoid cells with Roussel bodies in the spleen of patients who died from COVID-19, in combination with mixed flora in the lungs, can be considered as a morphological criterion reflecting progressive immune system depression with unfavourable outcome of the disease.

E-PS-13-011

Hydatid cyst of the spleen: retrospective study and review of the literature

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Background & objectives: Hydatid disease is a parasitic infection caused by Echinococcus Granulosis. It is a common health problem in many countries. This infection predominantly affects the liver followed by lungs. Splenic localization is rare and may pose a diagnostic challenge for clinicians.
Methods: We diagnosed 7 cases of splenic hydatid cyst between 2013 and 2022, in the department of pathology at Habib Bourguiba University Hospital of Sfax.
Results: Mean age of patients was 37 years-old (extreme: 23-69 years). Six of them were females (sex-ratio:0,16). cysts size varied from 3 to 12 cm, several daughter cysts were found in two cysts. Concomitant splenic, liver and peritoneal cysts were diagnosed in one case and a history of lung cyst was noted in another. Diagnosis was revealed by ultrasound supported by positive serologic tests otherwise CT scan was in favour of epidermoid cyst in one case. Total splenectomy was performed to all patients. Histopathological

examination showed the acellular laminated PAS positive membrane with presence in two cases of granulomatous reaction of the adjacent splenic parenchyma.
Conclusion: Hydatid cyst of the spleen is uncommon but it should be included in differential diagnosis of other splenic cystic lesions such as epidermoid cysts, pseudocysts, splenic abscesses, hematomas and cystic neoplasms of the spleen especially in endemic areas. The standard treatment is total or partial splenectomy combined with the perioperative administration of albendazol.

E-PS-13-012
Peritoneal tuberculosis: a challenging diagnosis
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Background & objectives: Peritoneal tuberculosis is a rare entity representing about 2% of all extrapulmonary forms. Those Patients frequently have findings identical to those with underlying malignancy due to non-specific symptoms and imaging. The aim is to present clinocopathological characteristics of this entity.
Methods: We report a retrospective study of 25 cases of peritoneal tuberculosis diagnosed at our department of pathology between 2005 and 2021.
Results: There were 8 male and 17 female patients, aged between 14 and 47 years with a mean of 41. Physical examination was positive for ascites. Computed tomography (CT) abdomen showed large ascites (n=5), peritoneal nodules (n=2) and mesenteric adenopathy (n=2). The diagnosis was made on peritoneal biopsy in all cases.
In microscopic examination, granulomatous reaction was composed of epithelioid cells and multinucleated giant cells with variable number of lymphocytes. These granulomatous lesions were centred by caseous necrosis in 19 cases overs 25 (76%), the rest were non caseating (24%).
Conclusion: Diagnosis of peritoneal tuberculosis is challenging due to its nonspecific clinical presentation, the limitation of laboratory testing, and the similarities of radiographic and laparoscopic evaluation to other diseases. Microscopic findings are variable and sometimes uncertain, especially with non caseating necrosis. The histopathological examination must be completed with bacteriological studies, mainly when the clinic presentation suggests the diagnosis.

E-PS-13-013
Hemophagocytic lymphohistiocytosis in trephine biopsy of a living post-COVID-19 patient
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Background & objectives: Hemophagocytic lymphohistiocytosis (HLH) constitutes a life-threatening inflammatory syndrome. There are a limited number of sHLH cases in which trephine has been performed in living post-COVID-19 patients. We present an sHLH case diagnosed by trephine biopsy in a living post-COVID-19 patient.
Methods: An 81-year-old man with a past medical history of hypertension, diabetes, and ischemic stroke, was referred to the hospital to evaluate leukocytosis, pyuria, and elevation of inflammatory markers four weeks after recovering from COVID-19. Computed tomography of the abdomen and bone marrow (BM) biopsy were performed. The patient received meropenem, two-packed red blood cell units, and was discharged on cefixime.
Results: Computed tomography of the abdomen did not reveal focal signs of infection or hepatosplenomegaly. Leukocytes and C-reactive protein were gradually decreased. BM smear revealed severe anaemia, lymphopenia, and dysplastic morphologic findings of erythroblasts, neutrophils, and megakaryocytes. Trephine biopsy revealed hypercellular dyserythropoietic marrow, plasmacytosis, lymphocytosis, histiocytosis, hemophagocytosis, and the absence of granulomas or carcinoma. Immunohistochemistry documented a mixed population of T lymphocytes (CD3+) and B lymphocytes (CD20+). Strong positivity for CD68 confirmed histiocytosis. CD138 κ, λ staining proved polyclonal plasmacytosis. Perl's staining showed excess hemosiderin deposits.
Conclusion: Based on our findings, we document sHLH in trephine BM biopsy of a living post-COVID-19 patient and persistent leukocytosis, underscoring the diagnostic value of trephine biopsy in preventing life-threatening conditions such as COVID-19.

E-PS-13-014
COVID-19 and small bowel ischemia: immunohistochemical positivity for SARS-CoV-2 in endothelial and inflammatory intestinal cells. A review of two cases
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Background & objectives: COVID-19 is a major pandemic facing the world today caused by SARS-CoV-2, which can cause multisystem damage. Although SARS-CoV-2 primarily targets lung epithelium cells, there is growing evidence that the intestinal epithelium is also affected.
Methods: First-case. 39-year-old male, admitted for bilateral pneumonia due to COVID-19. On the 13th day-of-hospitalization (DH), he presented paralytic ileus. Abdominal tomography revealed acute jejuno-ileal ischemia. Second-case.65-year-old woman with cough and positive PCR for SARS-CoV-2. One week later she developed abdominal pain and fever; the scan reported small loop intestinal obstruction caused by inguinal hernia. Emergency-surgery was performed in both cases.
Results: In the first case a piece of small intestine 164 cm long was resected; in the second case a segment of small intestine and hernial sac were resected. Both cases had external fibrin plaques and histologically acute intestinal ischemia was observed, with transmural necrosis, vasculitis and serositis with perforation; immunohistochemistry for SARS-CoV-2 (GeneTex) was performed, which was positive in endothelial and inflammatory cells. Both cases presented septic shock secondary to fecaloid peritonitis. The first case developed intestinal failure secondary to short bowel syndrome, multiorgan failure and finally died 58 days after surgery; the second case presented gradual improvement, was discharged at 43 DH and is currently alive.
Conclusion: Although the acute intestinal ischemia of the second-case was secondary to an inguinal hernia, the presence of SARS-CoV-2 was demonstrated by immunohistochemistry; which is compatible with recent studies (Norsa et al, Megan et al) that describe the replication of this virus in the intestinal mucosa; this may worsen the prognosis and lead in some cases to acute intestinal ischemia and worsening of the clinical status (as in the first-case);

therefore, control of digestive symptoms in patients with COVID-19 is recommended.

E-PS-13-015

Primary lymph node actinomycosis, a case report

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Background & objectives: Actinomycosis is a rare chronic bacterial infection caused by Actinomyces species. It typically affects soft tissue of the cervicofacial region, pelvis and lungs. Primary involvement of lymph nodes is extremely uncommon. Only three cases have been reported so far.
Methods: A 41-year-old man with unremarkable medical history presented with a 6-week history of painless cervical lump. Physical examination showed a mobile, non tender, left submandibular lymph node measuring 1.5 cm. The patient denied any history of recent dental extraction or oral manipulations. Neck ultrasound showed no other enlarged lymph nodes. An excisional lymph node biopsy was performed.
Results: Grossly, the lymph node measured 1.3 cm in long axis. The cut surface was white yellow and showed no nodularity or necrosis. Histological examination revealed fibrous thickening of the capsule. Thick fibrous bands were also seen between the lymphoid follicles, as well as rare small characteristic sulphur granules that were positive with Periodic acid Schiff and Grocott stains. Final cultures were positive for Actinomyces. The patient received long-term penicillin G therapy.
Conclusion: Actinomyces is a commensal of oral cavity. After disruption of the oral mucosa, it typically spreads by direct destruction of tissue. Lymphatic spread leading to primary involvement of lymph nodes is extremely uncommon. Awareness of this rare misleading presentation is crucial to avoid erroneous diagnosis. Actinomycosis should be considered in case of persistent lymph node enlargement in patients with poor dental hygiene. Sulfur granules are highly suggestive but not pathognomonic of actinomycosis. Microbiologic examination is necessary for a definitive diagnosis.

E-PS-13-016

The diagnosis of non-tuberculous mycobacterial infections on formalin fixed paraffin embedded tissues: a retrospective analysis

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Background & objectives: The prevalence of nontuberculous mycobacteria infection is increasing around the world with a negative impact on the health system. The histopathological features of mycobacterial tuberculosis and nontuberculous mycobacteria infection are indistinguishable on tissue biopsy, hence the aim for this study.
Methods: This was a retrospective study which consisted of all tissue biopsy from patients suspicious for mycobacterial infection which were diagnosed with granulomatous inflammation from 2018 - 2020. These cases were tested using GenoType Mycobacterium CM/AS assay (Hain Life Sciences; Germany, Nehren) to identify mycobacterial species.
Results: A total of 25 cases comprised the study cohort and consisted of 18 females and 7 males with mean age of 37.78 years. HIV seropositive was noted in 32% (8/25) of the cases. Biopsy sites were as follows: lymph nodes 52% (13/25), pleura 20% (5/25), breast 12% (3/25), testis and stomach 8% each (2/25). Microscopically, all the cases showed necrotizing granulomatous inflammation. Ziehl Neelsen staining was positive in 8% (2/25) of the cases. The identified mycobacterial species were as follows: M. fortuitum (76%), M. avium (4%), M. interjectum (4%), Mycobacterium. spp (16%).
Conclusion: Genotyping of mycobacterial species is very important as the morphological features and Ziehl Neelsen staining were unhelpful to distinguish between mycobacterial tuberculosis and non-tuberculosis mycobacterial infection in this study. Definite diagnosis of mycobacterial infection on paraffin embedded tissue sections has important treatment implication for the patient.

E-PS-13-017

Immunohistochemistry (IHC) for SARS-CoV2 - identification of monoclonal antibodies (mAbs) to nucleoprotein, S1- and S2-spike protein subunits and analysis of differential expression of viral proteins in formalin-fixed paraffin-embedded specimens

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Background & objectives: Proper detection of the viral proteins to SARS-CoV2 is mandatory for the morphological assessment of Covid19-induced pathologic changes. We identified commercially available mAbs to NP, S1, and S2 SARS-CoV2 respectively. A comparative expression analysis was performed in virally infected tissue.
Methods: A tissue-independent testing method for screening mAbs was employed using HEK293 cells transfected with the various viral proteins). FFPE pellets of HEK293 cells transfected with NP, S1 and S2 proteins were generated and used for mAbs testing/selection. MAbs were then tested on SARS-CoV2+ve specimens, and in-situ expression of NP, S1, S2 proteins was compared.
Results: Several commercial anti-SARS-CoV2 mAbs were consecutively tested. Most antibodies did not work in IHC and/or generated unspecific reactivity with various viral proteins. Only 3/10 mAbs proved useful for IHC in FFPE material. The reagents were: mAb 001 (anti-NP; SinoBiological) mAb 1A9 (anti-S2; GeneTex), and mAb 1035206 (Anti-S1; Novus). All mAbs gave also strong and consistent staining in FFPE tissue. Comparative immunostaining in lung autopsy cases showed that NP was most abundant while S1/S2 proteins were less prevalent. Difference was less striking in biopsies. More congruent expression of viral proteins was seen in placenta. Overall the NP was most widely present, while S1 and S2 showed a much more restricted expression
Conclusion: HEK-293 cells transfected with viral proteins are an excellent way to test anti SARS-CoV2 mAbs for specificity and suitability. Most commercial mAbs show unspecific staining and are unsuitable for IHC. Moreover, there are different expression patterns for NP, versus S1 and S2 proteins in infected human specimens. Consequently, presence of SARS-CoV2 proteins may depend on which viral protein was analysed. Therefore, morphological studies of Covid19-related changes are impacted by which viral protein was analysed and may have limited comparability.

E-PS-13-018

Analysis of pathological changes in spontaneous abortions in pregnant women with IgM positive for Dengue, Chikungunya, Zika or with positive treponemal test for syphilis

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Background & objectives: Maternal infections by some microorganisms include several unfavourable outcomes. Therefore, the study aimed to analyse anatomopathological alterations in ovular remains of spontaneous abortions of pregnant women with positive IgM serology for dengue, chikungunya, zika or positive treponemal test for syphilis.
Methods: From June 2020/January 2021, 259 cases of pregnant women in spontaneous abortion were admitted, in which blood samples were collected for IgM ELISA serology for zika, dengue, chikungunya and rapid test for syphilis. Ovular remains were stored and fixed in 10% buffered formalin and sent for anatomopathological evaluation.
Results: Among the cases admitted, regarding IgM, were reagent 17 (7.8%) in dengue, 32 (14.1%) in chikungunya and 9 (3.8%) in zika. In the rapid test for syphilis, 15 (5.9%) tested positive. In Dengue, fibrinoid deposits (p=0.000), syncytial nodes (p=0.001) and calcifications (p=0.034) showed statistical significance with the outcome. In Chikungunya, fibrin thrombus showed borderline statistical significance (p=0.053). In Zika, the prevalent change was poor vascularity, however no findings showed statistical significance. In syphilis, calcifications (p=0.020) and haemorrhagic spots (p=0.057) showed statistical significance, the latter being borderline. In all ovular remnants, it was found a rich inflammatory environment.
Conclusion: The results found in this investigation suggest a direct effect of the aforementioned viral and bacterial infections during the gestational period, particularly in the first 12 weeks of gestation, leading to unfortunate outcomes. Therefore, further studies on the subject are needed to understand the pathogenesis of the identified alterations and their repercussions, since, as observed in other studies, they may be related to early termination of pregnancy or to some complication related to the foetus.
Funding: Research funded by the Government of the State of Ceará, through the Secretary of Science, Technology and Higher Education and the Ceará Foundation for the Support of Scientific and Technological Development (FUNCAP) and the Directorate of Research, Development and Innovation (DPDI) of the University of Fortaleza.

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E-PS-14-001
Short training significantly improves ganglion cell detection using an algorithm-assisted approach

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Background & objectives: Acquiring sufficient teaching material for rare diseases, such as Hirschsprung's disease may be difficult, especially in smaller institutes, limiting training. The Objective of this study is to assess the effect of a short training session on algorithm-assisted HSCR diagnosis.
Methods: Five pathologists reviewed a dataset of 568 image sets (1704 images in total) selected from 50 cases by the DSA, and were tasked with scoring the images for the presence or absence of ganglion cells. The task was repeated a total of three times. Each pathologist had to complete a short educational presentation between the second and third iterations.
Results: The training resulted in a significantly increased rate of correct diagnoses (true positive/negative) and a decreased need for referrals for expert consultation. No statistically significant changes in the rate of false positives/negatives were detected.
Conclusion: A very short (<10min) training session can greatly improve the pathologist's performance in the algorithm-assisted diagnosis of HSCR. The same approach may be feasible in training for the diagnosis of other rare diseases.

E-PS-14-002
Artificial intelligence in dermatopathology: can an algorithm replace the pathologist?

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Background & objectives: Artificial intelligence is a very current topic in this period. We tried to train an AI algorithm using basic histopathological criteria that indicate and differentiate with a good probability a malignant melanoma from a severe dysplastic nevus, starting from WSI.
Methods: The artificial intelligence image processing algorithm used to classify and to enhance anomalies contained in the microscope image is the Fast Random Forest (FRF). The learning process of the algorithm is based on a preliminary classification of cluster of pixels of the same image. The FRF testing provides as output the processed image with coloured enhanced Melanoma pixel clusters.
Results: For five pixel clusters of the same dimensions, occurs a number of about 300 instances (computational cycles) to achieve the maximum precision (equals to 1), with a computational cost of about 2 minutes using a processor Intel® Core™ i5-7200U CPU, 2.71 GHz. The minimum recall performance parameter (near to 0) is achieved about 392 instances. The ROC curve (representing in the plane the true positive rate versus the false positive rate) is matching with the ideal curve of a perfect classifier. The performance indicators confirm the correct setting of the FRF hyperparameters. The FRF images have been processed by following a specific image diagnostic protocol, oriented on reading and algorithm error minimization.
Conclusion: An important tool for melanoma diagnosis is the probability image estimated by the processed FRF output image. The probability image is useful to better discriminate information about ambiguous lesions. A single probability image is referred to a particular class of "defect", and enhances, by the white colour, the defect distribution in the whole analysed image. By knowing the dimension of the acquired microscope image, it is also possible to estimate the defect distribution percentage.

E-PS-14-003
Use of Anki flashcards tool for reviewing pathology and radiology of medicine contents

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Background & objectives: Pathology and Radiology are essential for medical education. Therefore, new study methods are in development, such as electronic flashcards, in order to make the process more dynamic. In this regard, Anki platform has been gaining popularity because it is accessible.
Methods: In this study Anki platform was used, a cross-platform software to develop an electronic pathology/radiology flashcard

database, that can be accessed by PC, iOS and Android. The application of this study was carried out in 102 medical students from University of Fortaleza, being applied to a questionnaire through Google Forms seeking to evaluate the effectiveness of the learning strategy developed.
Results: In a class of 102 students, 63 of them answered the form. More than 90% of the students considered that the flashcards were useful to the consolidation of the contents of Pathology and Radiology, and more than 90% marked that the flashcards contributed to a better revision of the same contents. The flashcards would be stored by 83% of the students to review the same contents in the future, letting the algorithms determine the dates of the next revisions. More than 90% of the students would use this tool to study other modules, and 50 of them would use it in tutoring, another methodology that requires a long-term revision.
Conclusion: From the recent study, it was possible to demonstrate that the methodology used was relevant and useful for developing clinical reasoning based on automated spaced repetition learning focused on pathology and radiology exercises, which were made available on several mobile platforms, making the experience even more dynamic and easy to access. Furthermore, the systematization employed is a facilitator for the long-term consolidation of student knowledge, which in practice was confirmed by the data analysis obtained during the study evaluation.

E-PS-14-004
Application of image analysis based algorithm for quality control of immunohistochemical staining
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Background & objectives: Immunohistochemistry (IHC) is a main tool in today's pathology routine. Common applications include disease classification and biomarkers for targeted therapy. Positive controls are included on each IHC slide, misinterpretation of the staining in the control may lead to inaccurate diagnosis.
Methods: To develop an algorithm for quality control of IHC we trained the algorithm to identify 3 patterns of IHC staining (nuclear, cytoplasmic and membranous). Fifty slides from each category (membranous Her-2-neu, nuclear TTF1, and cytoplasmic Cytokeratin7) were scanned. From these images, we captured 1,645 images, out of which 1,174 images were used for training phase and 471 for validation phase.
Results: The algorithm was able to detect an average 87% of all the relevant stains. Specifically, the algorithm accurately identified 98%, 85% and 78% of membranous, nuclear and cytoplasmic staining, respectively. Misclassification of cytoplasmic staining was mainly due to clear cytoplasm. Misclassification of nuclear staining was due to poor segmentation of adjacent nuclei.
Conclusion: We develop an algorithm that shows high success in classifying staining patterns in scanned slides. Although the algorithm requires mild improvement, we estimate it could be a significant addition to the toolbox of digital pathology and be applied for quality control of IHC in the daily routine practice. Moreover with the correct usage of the algorithm, misinterpretation of the staining and inaccurate diagnosis could be easily prevented.

E-PS-14-005
Homology-based approach for pathological diagnosis of prostatic cancer
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Background & objectives: Prostatic adenocarcinoma (PCa) detection by image analysis from pathological specimens has been attempted. Although the systems based on the AI algorithm are very popular, we propose a newly established unique idea that is called "the homology profile method".
Methods: The digital data from prostate needle biopsy specimens at Ise Municipal General Hospital were binarized for each grayscale (0-255) and calculated the homology index (the Betti number). The several profile, including its maximum value was featured. The staining condition was not in a consideration. The Betti number was calculated by an ordinally note type computer.
Results: The Betti number was calculated for 100 JPEG format images for each of normal, Gleason pattern 3, 4, and 5. From the results of the t-test, the Betti number of PCa was significantly higher than that of normal prostatic glands. ($p<0.0001$). There was also a significant difference in Betti number of each Gleason pattern compared to normal ($p<0.0001$). The Betti number of Gleason pattern 5 was significantly higher than others.
Conclusion: The homology is a mathematical concept that measures "the contact degree" from the images. The homology profile method has not been applied to detect PCa using pathology images. This method is not only useful for detecting adenocarcinoma, but also for detecting Gleason pattern 5 PCa alone. Unlike AI algorithm, our idea is expected to be applicable to medical practice because of its small data size and reduced computation.

E-PS-14-006
Efficacy and efficiency of a mitosis detection tool in invasive breast cancer
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Background & objectives: Mitosis counting is part of the Scarff-Bloom-Richardson (SBR) scoring for invasive breast cancer (IC). We evaluate the benefit of using an AI-based mitosis detection algorithm in the pathologist's workflow.
Methods: Our algorithm has two steps. A RetinaNet detector was first trained on a specially designed mitotic dataset of 4132 patches from 162 Whole Slide Images (WSI) to detect mitosis. An EfficientNetB0 classifier refines these results by removing a part of false positives. Results are displayed in our interactive viewer, Cleo.
Results: 4 pathologists have used the solution on 50 WSI, with and without AI-results displayed. We evaluated the performance (F1-scores, Precisions and Recalls) and the time spent by pathologists on the WSI in both cases. The clinical study is ongoing and final results will be available in June. Actual algorithmic metrics are promising, but do not capture the value brought to pathologists as a proper interactive user interface enriched with the detector output will ease practitioners' task and increase both recall and precision.
Conclusion: To meet pathologists' needs we developed a mitotic detection algorithm trained with routine data along with an interface designed with and for practitioners. Our clinical study will assess whether this tool can help pathologists in their daily practice.

E-PS-14-007
Unsupervised stain adaptation in invasive carcinoma classification for breast histopathology using CycleGANs
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Background & objectives: Generalization is one of the main challenges of computational pathology. Slide preparation heterogeneity leads to poor models' performance on unseen data. This issue is addressed here by comparing approaches based on different cycleGAN usages.
Methods: We build a stain translation device using unsupervised cycleGANs image-to-image translation. Three approaches were compared to a baseline model, their performance were assessed using invasive carcinoma patch classification. The first two approaches use the translation device at inference or training respectively, leading to stain specific models. The last method uses it for stain augmentation to produce a stain invariant model.
Results: Baseline metrics are set by training and testing a model on a reference stain with colour augmentation. The first approach showed improved performance on different stains by 20% AUC compared to the baseline without requiring task specific model re-training. Secondly, we demonstrate that using the stain translation device before model training allows for labelling knowledge transfer between stains. This results in high performance without using any labels for a particular target stain. Finally, the translation device is used for stain augmentation during training, resulting in a stain invariant model with equally good performance on every stain.
Conclusion: Every modality tested in this study improves the baseline without needing labelled data on target stains. We assessed the performances using three medical centres with H&E and H&E&S stainings. The study shows that cycleGAN based domain adaptation methods are solutions to the generalization challenge in computational histopathology.
Such a framework can be used in other applications such as automatic segmentation or object detection.

E-PS-14-008
Detection of microcalcifications in whole slide images: a comparison between image processing and deep learning approaches
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Background & objectives: Microcalcifications are calcium deposits in breast ducts. If the mammographic abnormality reveals microcalcifications, the pathologist should make every effort to identify them. As a help, we present an automatic microcalcification detection pipeline in Whole Slide Images (WSI).
Methods: Epithelial regions are parsed from the WSI into patches that are fed to a classifier. A first proposed image processing-based classifier (Classifier1) detects blurry dark objects as this is the typical aspect of microcalcifications on WSI. The second one (Classifier2) is a convolutional network trained on 164835 patches from a total of 1615 WSI, including 1633 microcalcifications patches.
Results: Classifiers are evaluated based on their balanced accuracy (BAcc), precision (Pr), recall (Re). However, Those metrics are insufficient to capture the value brought to the pathologist. Not every microcalcification must be found, the mere detection of their presence is enough to determine whether the biopsy was well located. To evaluate the pipeline performance, we propose additional metrics. Objects classified as microcalcifications are sorted by classifier's confidence and we compute: the average rank of the first detected microcalcification (Average_Rank), the average number of slides for which a microcalcification is detected among the top 16 objects (Microcal_in_top). Results are: BAcc: 0.79-0.88, Pr: 0.07-0.73, Re: 0.67-0.76, Average_Rank: 8.5-0.7, Microcal_in_top: 0.75-0.83 (format metric_name: metric_classifier1-metric_classifier2)
Conclusion: Our automatic microcalcification detection pipeline could be helpful to pathologists. Two different classifiers can be plugged into the pipeline. The first one is based on image processing techniques and needs a small amount of labelled data to be set up. Although its performance is good, it is outperformed by the deep learning based classifier. Both solutions can be used depending on the availability of labelled data.

E-PS-14-009
Understanding batch variation within a cohort before digital pathology analysis of multiplex immunofluorescence in colorectal cancer
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Background & objectives: To apply two optimised multiplex-immunofluorescence (mIF) protocols (Panel 1-DAPI, Cytokeratin, CD4, CD8, CD3, CD20; Panel 2-DAPI, Cytokeratin, CD4, CD68, FOXP3) to a cohort of colorectal-cancer (CRC) in order to determine effect of batch variation within the cohort using digital pathology.
Methods: mIF protocols were applied to 518 FFPE-CRC sections using an Leica Bond RX autostainer. Each batch of slides was ran with a tonsil control and fluorescent scanning was performed using a Vectra Polaris.
Using QuPath, we performed annotations, cell-segmentation, epithelium-stromal classification and cell classification. Cell features and summary statistics for each mIF channel were exported for quantitative analysis using RStudio.
Results: Mean greys per simulated cell for each biomarker of interest were reviewed in order to determine batch variability. Values for Cytokeratin, DAPI, CD4, CD8 and FOXP3 demonstrated limited variability across the cohort for both panels. In contrast, values for CD20, CD3 in panel 1 and CD68 in panel 2 were found to be batch dependent, affecting 7/15 and 5/15 of panel-specific staining runs. On review, the same florescent dye (Opal570) was used to visualise CD20 and CD68 across both panel designs and therefore most likely to influence batch-dependent, dye-specific background staining. Whilst tumour-stroma classification was adequate in affected batches, biomarker-dependent cell classification was positively skewed compared to adjacent tonsil controls.
Conclusion: This study found that batch artefacts did not significantly impair tissue-specific, mIF epithelium-stromal classification, due to use of an artificial neural network. In contrast, biomarker-specific cell classification using pre-defined intensity thresholds was found to be vulnerable to positive skew in tissue sections from batches where high Opal570 background staining was present. Whilst use of pre-defined thresholds was acceptable for most optimised antibody-opal pairs in both panels, this work indicates the importance of reviewing dye-specific bias prior to mIF image analysis.
Funding: This study was supported by Cancer Research UK. Grant Numbers: C11512, /A20256

E-PS-14-010
Abnormal differentiation of follicular helper CD4 T (TFH) cells in systemic lupus erythematosus; an imaging perspective
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Background & objectives: Deregulated germinal centre (GC) reactivity is a main determinant for the SLE pathogenesis. Emerging evidence suggest that TFH cells may play an important role in this process. We sought to compare GC immune cell subsets between SLE and control GCs.
Methods: Multiplex imaging was applied for the in situ quantitative analysis of GC cell populations in control, selected to express active GCs, (n=4) and SLE (n=4) lymph nodes (LNs). The latest Vectra Polaris system and inForm/PhenoptReports software (Akoya) were used. Luminex analysis was performed in matched serum samples from the SLE individuals.
Results: No difference was found for GC B and CD8 cell subsets analysed. A strong correlation between CD4hiPD1hi TFH and GC B cells was found only in control LNs. Significantly higher numbers of less differentiated (CD4hiPD1hiCD57lo) TFH cells were found in SLE compared to control LNs, a profile associated with significantly higher numbers of CD4hiPD1hiCD57lowGATA3low and lower numbers of CD4hiPD1hiCD57loBcl6hiKi67loGATA3hi TFH cells. A clear trend for larger FDC network area and CXCXL13hi cells within GCs was observed in SLE. Significantly higher extra-follicular IFNa expression, a supporter of initial TFH differentiation, was found in SLE. Among circulating biofactors analysed, a significant correlation between CXCL13 and CXCL13hi GC cells was found in SLE.
Conclusion: We provide evidence for an altered differentiation of TFH cells in SLE, characterized by reduced expression of highly differentiated (CD57hi), potential providers of IL4 (GATA3hi) TFH cells as well as a dissociation between TFH and GC B cells. Whether this reflects an aberrant, not affinity-based development of TFH needs further investigation.

E-PS-14-011
Digital Pathology reporting of breast core biopsies in Malaysia
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Background & objectives: Digital pathology has become an integrated component of primary reporting in Gribbles Pathology for the past two years. During the perpetual COVID 19 pandemic in 2021, most of the core biopsies of breast were reported digitally, away from the office.
Methods: A highly advanced Aperio AT2 slide scanner (Leica Biosystems), approved by FDA for primary reporting, is in usage for routine digital pathology reporting in Gribbles Pathology. A total number of 283 breast core biopsy cases were reported, digitally. Reporting was done as per latest international guidelines along with IHC reporting of hormonal status as per CAP protocol.
Results: Digital pathology reporting of breast core biopsies is as accurate as conventional microscope reporting, and in many instances, more advantageous and precise. With an integrated Dragon Speech software, all cases were reported with ease, without resorting to the conventional microscope for a review. The response and acceptance from the surgeons are rewarding. Measurements of small malignant foci, and interpretation of grade, coupled with digital photography has made the routine reporting more acceptable. Constant and continuous practice has made the digital reporting more dependable, and accurate than conventional microscope reporting. IHC analysis with comparison of different hormonal receptors in a single view is a futuristic outcome of digital reporting.
Conclusion: Digital pathology reporting of core biopsies of breast is simple, dependable, accurate and should be incorporated as a routine primary reporting procedure, where digital pathology is available. IHC reporting is much easier and precise. The accuracy and effectiveness are very advantageous for the current demand of oncology management in many hospitals with tertiary care. This is the initial step taken by Gribbles Pathology for future diagnostic digital pathology and artificial intelligence (AI) in Malaysia.

E-PS-14-012
Classification of histological features based on IHC staining heterogeneity within tumours
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Background & objectives: Haralick texture features are used to quantify image heterogeneity. In this study, the heterogeneity of proliferation (Ki67 staining) and immune cells (CD45 staining) within tumours was used to classify histological characteristics of laryngectomy specimens.
Methods: 85 whole mount tumour slides of 22 laryngeal or hypopharyngeal carcinomas were immunohistochemically stained for Ki67 and CD45 and scored on histological characteristics. The tumour area was annotated in QuPath. Haralick features independent of DAB-intensity were extracted from the isolated DAB-signal and used as input for a principal component analysis (PCA). A support vector machine was fitted for classification.
Results: The PCA included 16 Haralick features (8 from Ki67 and 8 from CD45 staining). The first four principal components (97.2% explained variance) were used to fit a linear classifier. Based on Ki67 and CD45 heterogeneity, only laryngeal vs. hypopharyngeal tumours and cohesive vs. non-cohesive growth showed promising results for classification. The linear classifier resulted in a classification accuracy of 85.9% for laryngeal vs. hypopharyngeal tumours and 76.5% for cohesive vs. non-cohesive growth. A leave-one-patient-out cross validation resulted in an error rate of 0.25 and 0.34 for both classifiers respectively.
Conclusion: This study shows the feasibility of tumour classification by histological characteristics based on the heterogeneity of DAB-stained biomarkers within the tumour. It is a matter of finding the right (combination of) biomarkers for classification by different characteristics and classification of different tumour types. The classifiers created in this study are a proof of concept, since more data is needed to create robust classifiers, but the method shows great potential for automated tumour classification.
Funding: Dutch Cancer Society research grant 10978

E-PS-14-013
A thyroid cytology case report using Google Lens for the diagnosis
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Background & objectives: Pathologists use manual methods to examine samples through a microscope, but new imaging technologies have been designed to assist in the pathology diagnosis. An example is the use of digital cameras from smartphones in combination with artificial intelligence applications.
Methods: We present a case report of a 40-year-old woman, with a personal history of asthma and rheumatoid arthritis, who underwent ultrasound-guided fine-needle aspiration cytology (FNAC) due to increase of the right thyroid lobe. The patient had no associated symptoms and no analytical changes. Ultrasound revealed slight enlargement of the right thyroid lobe, with two nodules measuring 12x9x6mm and 14x13x11mm.
Results: A FNAC was performed, without complications. Cytology revealed a sparsely cellular sediment, with rare follicular cells

without nuclear atypia, lymphocytes and neutrophils, with thin and thick colloid. Numerous filiform structures were identified, with branching at acute angles raising the possibility of a fungal infection, and rare hair follicles. The diagnosis was benign (colloid nodule) through The Bethesda System for Reporting Thyroid Cytopathology. After an exhaustive search by the reference books, it was not possible to determine the species name of these structures. The Google Lens application was used and allowed to select structures with similar morphology, confirming contamination by Verbascum sp. plant (which is indigenous in the patients residential area).
Conclusion: The second cytology did not show the presence of these structures leading to the conclusion that it was a contamination. At the moment, no empirical evidence for using Google Lens in a medical setting is known to the authors. Nevertheless, Google Lens seems to be good for a quick evaluation, as smartphone cameras have become a widespread cost-effective method for pathology image acquisition and this software is freely available in our devices.

E-PS-14-014
A robust, centerwise-adaptive hybrid machine learning approach for HER2 scoring
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Background & objectives: To enable precise human Epidermal growth factor Receptor 2 (HER2) quantification in digital pathology, we propose a hybrid deep- and machine learning approach, which exhaustively localizes invasive cancer in a slide and is adaptive to centerwise HER2 scoring criteria.
Methods: Our dataset contains 350 Whole Slides Images (WSI) comprising 3 scanners. To quantify HER2 expression, we first localize all invasive cancer in a WSI using a U-NET. Then, we use hand-crafted features based on DAB colour devolution to determine HER2 expression in cancer. The slide label is determined by comparing aggregated expression with that of the laboratory's HER2 calibration slides.
Results: HER2 quantification is based on the staining completeness and intensity of all cancer cell membranes in the WSI, where the classes 0, 1+, 2+, and 3+ are distinctive in that specific percentages of cells are stained more intensely than the centre's calibration slides. In practice these properties can only be eyeballed, leading to large inter-observer variability in HER2 slide classification. We compare eyeballing HER2 scoring with our algorithm's evaluation based on clinical guidelines, calibrated on the centre's calibration slides. Our results indicate high algorithm/eyeballing agreement for images with homogeneous HER2 expression within a slide, but less so for heterogeneous expressions.
Conclusion: The results indicate that our AI-based HER2 quantification can come to a different conclusion than expert eyeballing for hard cases. This may be the result of our exhaustive calculation of the total tumour surface, which is used as the denominator to determine the percentage of cells that exhibit HER2 expression. Visual inspection, in contrast, may underestimate HER2 non-expressive invasive cancer areas. In such cases, our approach may improve clinical treatment decisions based on verifiable algorithm outcomes.

E-PS-14-015
Blended learning in histology using a virtual microscope: from adaptation to adoption at the University of Geneva
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Background & objectives: Priscilla Souilé and Jackie Perrin-Simonnot, two collaborators at the Faculty of medicine of the University of Geneva, teach histology using a blended learning model alternating online virtual microscopy and on-site activities to enrich and complete the learnings outcomes.
Methods: The virtual microscopy practical work sessions are given using the open-source CYTOMINE software, integrated with the open-source MOODLE learning management system. The teaching assistants, supervised by the professors, are coaching the students using the virtual microscope and a chat space to exchange questions and answers. Fully online during the COVID pandemic, this pedagogical strategy now also includes face-to-face remediation.
Results: To maintain quality of histology teaching during the COVID pandemic period would have been impossible with a classic model based only on practical sessions in face-to-face using microscopes. Beyond having taken up this challenge, and made it possible, this blended model based on web-based virtual microscopy allowed teachers and students to collaborate with more autonomy, transparency, and traceability, to ultimately having developed more persistent knowledges and skills. Alternating with face-to-face sessions after the pandemic allowed to keep the development of microscope related skills and develop more personalized remediation. This complementarity meets the objectives of both teachers and students.
Conclusion: The histology practical work sessions during the pandemic were quickly adapted to full e-learning based sessions thanks to virtual microscopy. Students, supervisors, and professors founded this virtual environment easy and intuitive, allowing them to quickly switch to new ways of teaching and learning, essential in these troubled times. In addition, it trains students to use tools that foreshadow what will be those they will use in their future career, in an easy and intuitive way.

E-PS-14-016
The application of artificial intelligence in the diagnosis of prostate cancer
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Background & objectives: Prostate cancer (PC) is one of the leading causes of death in men from cancer. Artificial intelligence can reduce subjectivity and improve the effectiveness of diagnosing this disease using fewer resources than the standard diagnostic scheme.
Methods: We have created a mathematical algorithm based on histological image recognition by machine learning and image recognition methods. The input data for training and testing the mathematical algorithm were the results of PC histology obtained by biopsy. The structured vector consisted of nine characteristics of PC cells and one variable that captures benign or malignant tumours.
Results: We have built a categorical functional model of information-extreme machine learning in the form of an oriented graph of sets used in the operation of the diagnostic system in the exam mode. The introductory recognition class is proposed, in relation to which the system of control tolerances for diagnostic features is determined, to choose the category according to the most significant variance of its input training matrix of brightness. With the increasing power of the alphabet of recognition classes, it is advisable to move from a linear structure of input data to a hierarchical one, which will be the subject of further research.
Conclusion: Comparative analysis of the results obtained by the authors allows us to consider the proposed method of information-extreme machine learning as a promising alternative to neuron-like structures in the analysis of large amounts of data.
Funding: This research has been performed with the financial support of grants from the Ministry of Education and Science of Ukraine No. 0122U000773

"Application of artificial intelligence to provide automation and standardization of the Gleason system in the diagnosis of prostate cancer"

E-PS-14-017

An automated deep learning based mitotic cell detection and recognition in whole slide invasive breast cancer tissue images

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Background & objectives: Nottingham Histologic Grading (NHG) is a prognostic indicator in early invasive breast cancer. NHG contains three factors which are pleomorphism, tubular formation and mitosis count. Mitosis recognition plays an important role for NHG estimation and accurate assessment of cancer prognosis.
Methods: Two novel datasets, which include 139.124 nucleis and 9.816 mitoses with annotations, are created and presented. Moreover, a hybrid deep learning framework is proposed for mitosis recognition. To achieve the results, a modified scaled-YOLOv4 algorithm is first used to detect all nuclei in WSIs. Then, a modified-VGG11 model is employed to recognize and localize mitoses in the WSIs.
Results: In comparison to various classification methods, the proposed framework provides the best results for both in-house and other datasets including MIDOG-21 and ATYPIA. In the first experiment, all algorithms are trained and tested on in-house dataset, the proposed framework obtains the best accuracy results than the other classification algorithms with F1-Score of 49. Moreover, the second experiment shows that the created novel dataset contains different characteristics and features than the MIDOG-21 and ATYPIA datasets.
Conclusion: In this work, we propose a hybrid deep learning approach and introduce two new datasets. The proposed framework is compared with different algorithms on various datasets. The results prove that the proposed approach performs better than the other algorithms in both nuclei detection and mitotic cell recognition in WSIs. Further clinical validation studies are needed for clinical implementation of AI based mitotic count.

E-PS-14-018

Comparison of different nuclear segmentation algorithms on the digital image of HER2 FISH labelled breast cancer tissue sample

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Background & objectives: The FISH technique is a frequently used molecular method to visualize well known genetic aberrations. The method provides results of qualitative, quantitative measurements that can be used to identify the genetically affected cells and their proportion in the tumour population.
Methods: The HER2 protein expression status in breast cancer provides a useful working example of tumour heterogeneity. The FISH technique can visualize the HER2 genetic heterogeneity in the breast tissue samples in situ. The fluorescence samples' peculiarity of the signal burning out, therefore the fluorescence digitalization and the demand an objective FISH evaluation results have become a basic requirement in diagnostics.
Results: The WSI imaging provides an opportunity to identify the different HER2 amplified nucleus. The base of the FISH image analysis is the nucleus segmentation. The classical 2D image analysis algorithms have a significant limitation regarding the detection of the overlapped nuclei. The intensity differences between the overlapped nuclei are not significant for define a proper cut line. The inadequate segmentation results incorrect signal assignment. The fluorescence Z layer scanning method opened a new opportunity for the digitalization and analysis of FISH samples. Slicing the sample section into different Z planes give an opportunity 3D image segmentation. AI based StarDist image segmentation algorithm was evaluated for achieve more precise nuclei segmentation.
Conclusion: During our comparison image segmentation test, we found that the breast tissue intratumor HER2 heterogenetic results change considerably using different image processing algorithms. The deep-learning based segmentation algorithm is found to be more robust in versatile image environment resulting in more accurate object segmentation and separation. The novel approach of nuclei segmentation in turn improves the signal assignment process changing the number of signals within each nucleus, thus improving the reliability of the quotient values confirming the amplification.

E-PS-14-019

Development and assessment of single-cell image classification systems for haematological cytomorphology using convolutional neural networks

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Background & objectives: Morphologic classification of leukocytes represents an important step in the diagnostic workup of blood and bone marrow samples for many haematological diseases. Frequency and importance of cytomorphologic evaluation motivate development and evaluation of diagnostic support systems for leukocyte classification.
Methods: Publically available datasets of peripheral blood and bone marrow cytomorphology are described and used in order to train and evaluate sequential models and ResNeXt-based neural networks for leukocyte classification. Performance of the trained networks is evaluated using data from different sources, thus assessing generalizability of prediction performance. Finally, multiple strategies are presented for robustness assessment and explainability of algorithm predictions.
Results: Convolutional Neural Networks developed using publicly available datasets of leukocyte cytomorphology in blood and bone marrow cytomorphology attain the performance of trained cytologists for tasks such as blast recognition in the diagnosis of AML. The overall classification performance critically depends on the training sample number per class. The pattern of deviation from ground truth is similar for algorithms and humans, with consecutive morphologic cell types within a continuous hematopoietic lineage most susceptible to confusion. Explainability methods show that the models map relevant image areas. Analysis of neural network predictions illustrates the importance of augmentation strategies to ensure classifier robustness against staining and scanner setting variabilities and avoid overfitting.
Conclusion: Published expert-annotated datasets of leukocyte morphology allow training of state-of-the-art neural networks for single-leukocyte classification in the diagnostic workup of haematological diseases. For many diagnostically relevant classes, these networks attain a performance level comparable to human examiners. Using explainability methods, image areas relevant for classification can be illustrated, suggesting significant overlap with structures known to be relevant for cytomorphologic classification. Appropriate augmentation strategies allow hardening classifiers against different preanalytical and digitization parameters, thus ensuring robustness and generalizability of network predictions.

E-PS-14-020

A reinforcement learning approach for automated scoring of immunohistochemically stained mismatch repair genes

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Background & objectives: Assessment of the Mismatch Repair (MMR) status is critical for determining the treatment of colorectal cancer (CRC) patients. We propose a novel reinforcement learning (RL) approach that mimics histopathologists for automated scoring of immunohistochemically stained MLH1 and PMS2 slides.
Methods: The proposed framework consists of two components where initially, a soft attention module analyses WSIs at lower magnification (5×) and identifies potential regions of interest (ROIs) for tile extraction. The tiles are fed into the second component, an RL-based retina-inspired hard-attention classification model which further extracts and processes a series of high-magnification patches from each image tile for target prediction.
Results: The proposed method mimics a pathologist analysing only relevant parts of the IHC slides. We compare our approach against random-sampling with RL-classifier and sliding window based tile extraction. We aggregate results using average probabilities of the top 15 tiles from each WSI for final score.
The proposed model achieved superior performance for both biomarkers with F1-scores of 0.88, 0.82 and AUROC of 0.92, 0.88 for MLH1 and PMS2, respectively. Competitive performance was achieved by ResNet-18, achieving F1-scores of 0.72, 0.71 and AUROC of 0.92, 0.93 for MLH1 and PMS2 while worst performance was achieved by random selection method for F1-score 0.66, 0.62 and AUROC 0.67, 0.64 for MLH1 and PMS2.
Conclusion: We demonstrate the effectiveness of our approach, which mimics a pathologist analysing a fraction of a given IHC slide, for scoring MMR markers in CRC. Our method demonstrates comparable performance to standard computational-pathology methods while only processing a tiny fraction of the WSI. To the best of our knowledge, this is the first RL approach to automatically score the MMR markers. We further intend to improve the model by determining the optimal number of image tiles required for each WSI.

E-PS-15 | E-Posters Molecular Pathology

E-PS-15-001

Intratumoural heterogeneity with different resistant subclones in a treatment resistant gastrointestinal stromal tumour revealed through a novel tissue masking technology

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Background & objectives: A 73-year-old man with a history of metastatic small bowel gastrointestinal stromal tumour (GIST) who have undergone liver and small bowel resections was found to have recurrent peritoneal nodules on follow-up despite being on Imatinib. He subsequently underwent tumour resections.
Methods: On histological examination, the nodules composed of sheets of spindle cells and focal epithelioid cells with vesicular nuclei and prominent nucleoli. The tumour was positive for DOG1 and CD117 on immunohistochemistry which confirmed the diagnosis of GIST. It was then sent for next generation sequencing (NGS). NGS revealed KIT exon 17 N822K, exon 17 N822Y and exon 11 N564_P573delinsGSMET mutations.
Results: The heterogeneous molecular findings in conjunction with the variable tumour morphology had raised the possibility of intratumoral heterogeneity (ITH). A repeat sequencing was performed to confirm the findings. Quantumcyte Oncomask technology was used to assist in the sampling of targeted areas for NGS. Three separate lysates on three areas of interest on a tumour section were created based on morphology. The repeated NGS results verified the findings of ITH. Both areas 1 and 2 with spindle cells revealed KIT exon 11 N564_P573delinsGSMET and exon 17 N822K mutations. Area 3 with epithelioid cells showed KIT exon 17 N822Y and exon 17 G803D mutations.
Conclusion: This case demonstrated the utilization of Quantumcyte Oncomask, a novel tissue masking technology in detection of heterogeneous resistant subclones in a treatment resistant GIST. It enables the sampling of targeted areas in a tumour section to increase the cellular purity for molecular sequencing especially for the analysis of tumour heterogeneity which is known to be associated with therapeutic resistance. The presence of different mutation subclones in GIST is also important in guiding oncologists on the treatment choices.

E-PS-15-002

Cellular and cell-free targetable mutations in non-small cell carcinoma: a comparative study

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Background & objectives: Therapeutic relevance of molecular alterations in non-small cell lung carcinoma (NSCLC) is long established with detection in tissue being gold-standard. Insufficient tissue necessitates use of non-invasive approach as an alternative. Targetable mutations in 100 paired (tissue, plasma) samples were evaluated.
Methods: 100 patients with paired (formalin fixed paraffin embedded tissue and plasma) samples from treatment naïve NSCLC cases were tested for EGFR (exons 18, 19, 20, 21), ALK, ROS1 and MET through Realtime PCR. Interpretation was based on the difference in cycle threshold (CT) of reference and mutation (CT mutation – CT reference = ΔCT).
Results: Tissue samples showed mutations in 60 cases [EGFR mutation - 47, ALK rearrangement -12 (one case had concurrent EGFR and ALK alterations), ROS1 fusion - 2]. Plasma samples showed only EGFR mutation in 43 cases. Overall concordance between tissue and plasma was 62% which dropped to 44% in EGFR mutation-specific sub-type. 38% discordance was recorded for EGFR positive tissue samples while 17 cases of plasma samples showed EGFR mutation where tissue was wild. Two cases showed ALK rearrangement in tissue but EGFR mutation in plasma. Overall sensitivity and specificity for all molecular alterations in plasma were 46.7% and 62.5% which increased to 55.3% and 67.9% with respect to EGFR mutation.
Conclusion: Cell free testing for targetable mutations are complementary but not a surrogate marker to tissue biopsies. Realtime PCR is quite sensitive in detecting cell-free mutations, however more sensitive techniques like next generation sequencing and appropriate collection and processing of cell free samples may be be used to increase the detection rate of targetable mutations in NSCLC.

E-PS-15-003

Prediction of biochemical recurrence in TMPRSS2-ERG-positive prostate cancer by neural network based on pathway enrichment

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Background & objectives: Prostate cancer (PCa) is one of the most common diseases in men. Biochemical recurrence occurs in 20-50% of patients after radical prostatectomy. Nearly half of PCa cases are of the TMPRSS2-ERG molecular subtype.
Methods: The study used RNA-Seq data for 154 locally advanced PCa samples from TCGA. Data analysis was performed in the R (v.3.6.3) using the edgeR (v.3.24.3). GSVA was performed using the GSVA package (v.1.34.0) with the GO, KEGG, and Reactome databases. To build a fully connected neural network (FCNN) as a predictive model, the keras and tensorflow libraries were used.
Results: We identified 7 differential enriched biological pathways between groups of biochemical recurrence (BCR) and biochemical recurrence free (BRF) cases within TMPRSS2-ERG-positive PCa: phytol metabolic process (GO:0033306, rs = -0.31), fatty alcohol metabolic process (GO:1903173, rs = -0.31), positive regulation of amyloid fibril formation (GO:1905908, rs = -0.47), heparanase activity (GO :0030305, rs = -0.38), positive regulation of ryanodine-sensitive calcium-release channel activity (GO:0060316, rs = -0.44), centriolar satellite (GO:0034451, rs = 0.34) and Regulation of gene expression in endocrine-committed (NEUROG3+) progenitor cells (R-HSA-210746, rs = 0.49). The model based on combination GO:1905908 + GO:0034451 + GO:0030305 + R-HSA-210746 + GO:0060316 was most promising with AUC = 0.94.
Conclusion: Thus, we have identified changes in regulation of biological pathways that are involved in phytanic acid metabolism, amyloid bodies formation, neuroendocrine transformation, and cell differentiation, evidently inhibiting apoptosis and inducing tumour cell proliferation for BCR group within TMPRSS2-ERG-positive PCa. Based on changes in the above biological pathways, we built the neural network as a predictive model.
This work was funded by the Russian Science Foundation grant no.18-75-10127. This work was performed using the equipment of EIMB RAS "Genome" centre (http://www.eimb.ru/ru1/ckp/ccu_genome_c.php).

E-PS-15-004

Is next generation sequencing the new golden standard for ALK testing? The diagnostic journey of an atypical case

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Background & objectives: Identification of ALK rearrangements in lung adenocarcinomas (LUAD) is done by immunohistochemistry (IHC) followed by fluorescent-in-situ hybridization (FISH). However, multiple discordances between IHC and FISH analyses have been reported. Therefore, a more specific method to identify these alterations is needed.
Methods: We present a case of a patient diagnosed in 2013 with a primary LUAD and in 2018 with a metastatic recurrence. ALK IHC was performed using clone D5F3. FISH analysis was carried out using Vysis ALK Break-Apart FFPE FISH Probe Kit. In 2021 the molecular analysis was carried out by Next Generation Sequencing (NGS) using Archer® FusionPlex Lung panel kit.
Results: In 2013 the right inferior lobe resection showed an infiltrative LUAD, pT2aN0MxL0N0V0. The tumour was ALK-positive on IHC but negative on FISH. Molecular biology analysis was negative for EGFR, KRAS, and BRAF genes.
In 2018 was identified a 9 mm LUAD was histologically compatible with the primary lesion from 2013 pT2aN0MxL0N0V0. The tumour was intensively positive for ALK on IHC but considered negative on FISH. Interestingly, the FISH analysis revealed a loss of the red signal in 75% of the nuclei analysed. Molecular biology analysis remained negative.
In 2021 NGS analysis using the Archer® FusionPlex Lung panel kit (Archer®) revealed an unusual fusion between ALK exon 2–EML4 exon 13.
Conclusion: The unusual loss of the red signal suggested the presence of an atypical rearrangement in the 5' part of the ALK gene which required additional investigation. Using a NGS panel we identified an atypical EML4-ALK fusion which was not detected by break-apart conventional FISH. We highlight the need for a new gold standard for ALK rearrangements testing represented by RNA NGS, a more sensitive approach that could identify patients with rare molecular phenotypes and increase the addressability of targeted therapies.

E-PS-15-005

Extractions made easy: fully automated extraction and quantitation of nucleic acid using Genexus™ purification system and ready to use consumables

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Background & objectives: Reliable nucleic acid (NA) extraction and quantitation can be challenging in most labs due to lack of expertise and processes in place. Here we report fully automated Genexus™ purification system to extract and quantify NA with ready to use consumables.
Methods: Four purification kits with automated workflows were developed to extract NA from FFPE, liquid biopsy, whole blood, PBL, BMA, cells, and tissue samples. An interactive user interface with touch screen allows intuitive run setup with customizable sample information, elution volumes and ability to select onboard quantitation. If opted, extracted nucleic acid is then quantified onboard using a relevant Qubit™ assay.
Results: To evaluate Genexus™ purification system performance, various samples and input levels were tested and compared with existing extraction methods. gDNA (n=140) and total RNA (n=144) were extracted from sample inputs as low as 50 µL. DNA (n=72) and RNA (n=58) was also extracted from FFPE tumour resections as well as CNBs and FNAs. cfTNA (n=24) extractions were performed using up to 8mL of plasma. Study showed comparable NA extraction efficiency and quantitation accuracy to existing MagMax™ kits and manual Qubit™ assays respectively. All extracted NA was successfully used for downstream applications such as quantitative PCR or NGS confirming the high quality of extracted NA.
Conclusion: This report demonstrates the use of Genexus™ purification system to reliably extract and quantify NA from a variety of challenging clinical research samples and across multiple input levels to be successfully used in downstream applications. Ready to use consumables with REACH compliant reagents, fully automated extraction and quantitation allows the Genexus™ purification system to be used with minimum user interaction, training and expertise.

E-PS-15-006

Novel diagnostic value of driver gene transcription signatures to characterise clear cell renal cell carcinoma, ccRCC

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Background & objectives: Describing and explaining cancer phenotypes manifestation of mutation in marker genes should be examined by comparative tools. The approach of this study was a first attempt to use genetic markers to predict transcription related alteration for diagnostics purposes.

Methods: Subsequent to extraction of total RNA from snap-frozen normal and ccRCC tumour sections and reverse transcription, gene doses and expression of the main oncogenic drivers of ccRCC were measured by quantitative real-time PCR method, followed by calculation of absolute and relative quantities of 5 genes. Diagnostic value of the approach was examined by descriptive statistics using SigmaPlot 12.5 software package.

Results: Determining the copy numbers of four tumour suppressors, VHL, SETD2, PBRM1 and BAP1, ccRCC tumorous and normal adjacent kidney tissues did not significantly differ. Moreover, the relative gene expressions of these genes did not correlate with the gene dosages. Our data revealed that the absolute mRNA levels and also the combined transcription profiles of the four aforementioned driver genes, supplemented by p14ARF, were significantly different in the tumorous samples than in normal ones. Using gene expression signature of four driver genes, ccRCC and normal kidney samples can be discriminated with 87 per cent sensitivity and 77% specificity. Besides, the expression of p14ARF can be used as an independent indicator.

Conclusion: We showed that by calculating the median transcription values of the four ccRCC tumour suppressors of 3p25 and 3p21 chromosomal loci – VHL, SETD2, PBRM1, and BAP1 –, complemented that of the p14ARF, normal, and ccRCC tissues can be distinguished. However, proving that these markers can be suitable in the staging of the disease has not been inspected yet. Our results also highlight the importance of examining the manifestation of the genetic alterations lying behind tumour progression.

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E-PS-15-007

Pulmonary Adenocarcinoma: RET mutation in cfDNA NGS interpretation - case report

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Background & objectives: RET fusions through FISH/IHC/RT-PCR limit fusion partners recognition. NGS DNA/RNA allows fusion genes and splicing isoforms discrimination and fusion transcripts quantification. Liquid biopsies are FDA-approved/validated for circulating cell-free DNA (cfDNA) testing in advanced-stage solid sequences/acquired resistance to molecular therapy.

Methods: A 70-years-old woman with Acinar Adenocarcinoma (CK7/TTF1+) dignosis in RU Lobetomy (2018). New lesions on PET-CT in 2019. Biopsy was performed: pulmonary Adenocarcinoma with EFGR mutated - c.2573T>G;p.(Leu858Arg). Erlotinib induced partial response; May 2021 started osimertinib therapy. In 2022, tissue re-biopsy and liquid biopsy were both analysed by NGS.

Results: Tissue biopsy DNA and RNA analysed by NGS showed the following genetic alterations: EGFR (exon 21): c.2573T>G;p.(Leu858Arg) (17%) and MET Amplification (copy number 7,97). Analysis of liquid biopsy by NGS showed the following genetic changes: EGFR: c.2573T>G;p.(Leu858Arg)(1,5%); KRAS: c.175G>A;p.(Ala59Thr)(0,3%) and RET: c.2647G>T;p.(Ala883Ser)(0,1%).

Conclusion: RET fusion occurs in 1–2% of NSCLC, particularly in younger non-smokers and high risk for brain metastasis is established. MEN2B/MEN1/MEN2A germline mutations have to be considered when RET mutations present low allele frequency; tumoral heterogeneity will always be considered if RET mutations in follow up with higher frequency. NGS cfDNA potentiality for actionable RET mutations, identification, as well as resistance mechanisms after initial response/resistence rearranged RET. Non-invasive cfDNA testing simplifies RET-rearranged determination for TKIs follow up, preceding clinical imaging.

E-PS-15-008

Predictive testing in stage-IV NSCLC within a network of collaborating hospitals

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Background & objectives: Molecular diagnostics is not performed for all eligible NSCLC patients. A better understanding of the hurdles that are encountered by healthcare professionals within the care chain is of pivotal importance to improve outcome for lung cancer patients.

Methods: Pulmonary oncologists, pathologists and clinical scientists in molecular pathology in a collaborating network of 4 regional hospitals that submit predictive testing to an academic centre received a questionnaire addressing aspects of tissue availability, turn-around-time, costs and logistics related to predictive testing. Results were discussed with the participating hospitals in a virtual meeting. A written report was returned to the participants.

Results: Interviewed health care professionals were satisfied with the organization of predictive testing, but also identified room for improvement. When a tissue biopsy cannot be obtained (~10% of all stage 3b-4 lung cancer patients), access to comprehensive testing on a liquid biopsy needs to be organized. Molecular testing is preferred over PDL1 and ALK immunohistochemistry when tissue is limited. Although turnaround times for comprehensive analysis of mutations and gene fusions is acceptable (10-15 business days), sample flow and reporting could be further improved to expedite the results. To identify patients who may benefit from adjuvant targeted therapy, predictive testing should be expanded to stage 1-2 in lung cancer patients.

Conclusion: Active discussions between health care professionals are essential to find opportunities to further improve care for lung cancer patients. This study have led to proposals for improvement that will be evaluated in Q4 2022.

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E-PS-15-009

Assessment of gDNA yield obtained from FFPE samples and from scraped histological and cytological slides of patients with lung adenocarcinoma

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Background & objectives: Formalin-fixed and paraffin-embedded (FFPE) samples represent a challenge in recovering genetic material. Our objective is to evaluate the yield of genomic DNA from samples of primary tumour and aspirated lymph nodes extracted of paraffin blocks and from scraped histological/cytological slides.
Methods: Genomic DNA (gDNA) of 156 samples obtained from tumour resection or endobronchial/transbronchial biopsies (n=81) and mediastinal lymph nodes (MLN) obtained by endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) (n=75) between 2011 and 2019 were extracted with the GeneRead® DNA FFPE kit (Qiagen, Hilden, Germany). Of these samples, 61 were from FFPE tissue and 95 from scraped histological/cytological slides.
Results: The average gDNA yield obtained from FFPE samples was 9.45 ng/μL (0.051-53 ng/ μL) for primary tumours (PT) and 2.96 ng/μL (0.04 to 51 ng/ μL) for MLN. In PT samples extracted from scraped histological slides, the average yield was 12.17 ng/ μL (0.051 to 60 ng/ μL) and in samples of MLN from cytological slides was 18.37 ng/μL (0.057 to 217ng/ μL).
Conclusion: To obtain gDNA from scarce FFPE samples is an arduous process, especially in those with low cellularity, archived for more than 5 years, as used in this study. We observed an improvement in gDNA yield from histological and cytological slides regards to FFPE samples. The use of samples obtained from scraped slides seems to be an efficient tool to improve the gDNA yield for application in genomic tests.
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E-PS-15-011

OpenHRD - an open source platform for calculation of homologous recombination deficiency scores from OncoScan microarrays

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Background & objectives: Homologous recombination deficiency is an important biomarker for PARP inhibitor therapy in ovarian cancer. Existing open-source tools lack standardized parameters and require IT expertise. This project aims to establish a web-based bioinformatic analysis system for robust assessment of genomic instability.
Methods: OncoScan-CNV data was obtained from DNA of formalin fixed embedded specimens. The analysis platform uses raw OncoScan microarray images and applies several open-source pipelines such as "Easy Copy Number", "Oncoscan_tools", "Allele-specific copy number analysis of tumours" for the segmentation analysis. HRD calculation was performed by combination of custom R-scripts and the "HRDscore" pipeline. Additionally a commercial diagnostic HRD-test was obtained.
Results: The analysis comparison between several pipelines revealed that the combination of "Easy Copy Number" (EaCoN), and "Allele-specific copy number analysis of tumours" (ASCAT) was the best performing setup for raw data normalization and segmentation, providing similar results to the proprietary Chromosome Analysis Suite software (ChAS, Thermo Fisher).
The OpenHRD pipeline for homologous recombination deficiency (HRD) calculation is a compilation of EaCoN, ASCAT, our custom R-scripts and "HRDscore". It is run with Django Python and Celery Task Queue web frameworks. Subsequently, the application of the fully automated OpenHRD pipeline with standardized parameters revealed a high correlation to results obtained with the commercial Myriad MychoiceDX test in a cohort of ovarian cancer.
Conclusion: Several studies have shown that HRD is a reliable marker for treatment decisions in PARPi therapy. In this study we provided a simple, standardized, web based system to analyse HRD, which is able to process the microarray scan raw image data and generate reliable HRD score values. Initial validation of the HRD platform has been performed in ovarian cancer, and extension to prostate and pancreatic cancer is ongoing.
Funding: This research was kindly supported by AstraZeneca Austria GmbH

E-PS-15-013

Evaluation of PD-L1 expression in various formalin-fixed paraffin embedded tumour tissue samples using SP263, SP142 and QR1 antibody clones

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Background & objectives: Cancer cells can avoid immune destruction through the inhibitory ligand PD-L1. PD-1 is a surface cell receptor, part of the immunoglobulin family. Its ligand PD-L1 is expressed by tumour cells and stromal tumour infiltrating lymphocytes (TIL).
Methods: Forty-four cancer cases were included in this study (24 triple-negative breast cancers (TNBC), 10 non-small cell lung cancer (NSCLC) and 10 malignant melanoma cases). Three clones of monoclonal primary antibodies were compared: QR1 (Quartett), SP 142 and SP263 (Ventana). For visualization, ultraView Universal DAB Detection Kit from Ventana was used on an automated platform for immunohistochemical staining Ventana BenchMark GX.
Results: Comparing the sensitivity of two different clones on same tissue samples from TNBC, we found that the QR1 clone gave higher percentage of positive cells than clone SP142, but there was no statistically significant difference. Comparing the sensitivity of two different clones on same tissue samples from malignant melanoma, the SP263 clone gave higher percentage of positive cells than the QR1 clone, but again the difference was not statistically significant. Comparing the sensitivity of two different clones on same tissue samples from NSCLC, we found higher percentage of positive cells using the QR1 clone in comparison with the SP142 clone, but once again, the difference was not statistically significant.
Conclusion: The three different antibody clones from two manufacturers Ventana and Quartett, gave comparable results with no statistically significant difference in staining intensity/ percentage of positive tumour and/or immune cells. Therefore, different PD-L1 clones from different manufacturers can potentially be used to evaluate the PD- L1 status in different tumour tissues. Due to the serious implications of the PD-L1 analysis in further treatment decisions for cancer patients, every antibody clone, staining protocol and evaluation process should be carefully and meticulously validated.

E-PS-15-014

A rare case of neuroendocrine transdifferentiation in cutaneous melanoma

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Background & objectives: Neuroendocrine transdifferentiation is a rare event in cancer pathogenesis and refers to the phenomenon whereby a non-neuroendocrine malignancy differentiates along the neuroendocrine route. Herein we present a case of neuroendocrine transdifferentation in a primary cutaneous melanoma.
Methods: Case is clinically and pathologically evaluated accompanied by immunohistochemistry. This case treats a 45-year-old male, with a history of a malignant melanoma excised from the left anterior shin in 2015 and multiple in transit metastatic lesions in subsequent years. On follow-up routine radionucleotide imaging studies performed in 2019, he was found to have uptake in a right inguinal lymph node.
Results: Histological analysis showed a tumour with striking neuroendocrine morphology that showed immunohistochemical co-expression of neuroendocrine and melanocytic markers. A retrospective review of the patient's histology confirmed that the original melanocytic lesion was conventional epithelioid melanoma in vertical growth phase with no evidence of neuroendocrine differentiation on morphological or immunohistochemical grounds. Retrospective analysis of two in-transit metastases on the right shin (2017) and the right side of the leg (2019) showed subtle morphological transdifferentiation of the melanocytic tumour with progressively increasing immunohistochemical expression of neuroendocrine markers. BRAF mutational analysis on the first in-transit metastatic lesion, uncovered the 1799T>A (p.Val600Glu) mutation, which mutation has been conserved on the subsequent metastatic groin tumour.
Conclusion: This phenomenon has been best described in high grade prostatic adenocarcinoma, often after extensive therapy, representing a possible treatment resistance mechanism. Neuroendocrine transdifferentation, however, is vanishingly rare in melanocytic neoplasms. De novo neuroendocrine transdifferentiation typically represents an aggressive clinicopathological phenotype. Nonetheless, this patient was kept on dual BRAF inhibitor therapy and remains disease free to date. The mutational evolution of this tumour will be studied by Whole Genome Sequencing to elucidate potential drivers of the neuroendocrine phenotype.
Funding: The Project: "Molecular switch underpinning Neuroendocrine Transdifferentiation in malignant neoplasms – MOLNET" (REP-2021-021) is financed by the Malta Council for Science & Technology, for and on behalf of the Foundation for Science and Technology, through the FUSION: R&I Research Excellence Programme

E-PS-15-015

Precision proteomics for the characterization of follicular-patterned thyroid neoplasms entities

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Background & objectives: Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) are low-risk thyroid lesions most often with RAS-type mutations. The current histological diagnostic criteria are still debated. In this study we'll characterize NIFTP lesions by MALDI-MSI to highlight proteomic signatures.
Methods: Archived FFPE samples from eight NIFTP (5 RAS-mutated and 3 RAS-WT) and one goiter were analysed by MALDI-MSI using rapifleX MALDI Tissuetyper equipped with a Smartbeam 3D laser at 2kHz frequency. Mass spectra were acquired in reflectron-positive mode. Images of FFPE NIFTPs tissues were acquired with 50 µm spatial resolution. CHCA matrix was removed, digested peptides were identified by nLC-ESI-MS/MS.
Results: Considering the proteome of the entire tissue sections, unsupervised segmentation analysis highlighted i) the presence of the nodular lesions that arose in the context of normal thyroid parenchyma, with spectra clustered under separate nodes, ii) under the nodule nods, a further separation enlightened the presence of NIFTP and hyperplastic lesions, with spectra being clustered under separate nodes. The proteomic data complexity was investigated and unsupervised principal component analysis highlighted specific patterns of the two NIFTP entities. ROC analysis highlighted that five ions were able to discriminate RAS-mutated and RAS-WT NIFTP.
These results underline the MALDI-MSI capability of detecting proteomic signatures within regions that are indistinguishable at the microscopic level.
Conclusion: Spatial-proteomics is an outstanding approach to differentiate NIFTPs from other follicular-patterned features and to characterize classic and atypical cases, highlighting the potential role of Matrix-Assisted Laser Desorption/Ionization (MALDI)-Mass Spectrometry Imaging (MSI) technology as a support to traditional pathology.
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E-PS-15-016

The impact of pre-analytical factors on DNA quantification

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Background & objectives: Attaining high-quality genomic DNA is considered one of the most important phases in molecular oncology diagnoses, the aim of our study is to evaluate the influence of cold ischemia and fixation time on the DNA quantity of cancer digestive specimens.
Methods: 32 FFPE blocks of colorectal cancer, liver cancer, Pancreaticoduodenectomy, and gastric cancer tissues were obtained and macro-dissected. We used the following cold ischemia times: less than 1 hour (CIT-1), and 96 hours (CIT-5). 24 hours (FT-1) and one week (FT-4) for the fixation times. We applied a fluorometric procedure (Qubit 3.0) to determine the quantity of the collected DNA samples.
Results: The correlation between normal and tumour tissue was statistically significant for pre-analytical parameters evaluated with a strong influence on tumour tissue. For fixation times, the correlation between both (FT-1) and (FT-4) was significant with $p = 0.059$. For cold ischemia times, the value $p = 0.028$ was significant for both (CIT-1) and (CIT-5). The Qubit detected the lowest DNA concentrations in all prolonged fixation samples (FT-4) with an average of 1,55 ng-µl. The highest DNA concentrations were in samples with less than one hour of cold ischemia duration with an average of 159 ng-µl.
Conclusion: our preliminary research revealed that these pre-analytical parameters have a significant impact on the concentration and DNA quantification, as well as its variation depending on the type of tissue with more marked consequences on tumour tissue.

E-PS-15-017

Monitoring PIK3CA molecular heterogeneity in breast cancer using liquid biopsy

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Background & objectives: Breast cancer is a dynamic disease with continuous clonal selection reflecting singular molecular alterations. This heterogeneity occurs intratumor and even among primary tumours and metastases. This study aimed to assess the role of liquid biopsy for monitoring molecular alterations.
Methods: A 54-year-old woman with infiltrating lobular breast carcinoma was treated with neoadjuvant chemotherapy, radical mastectomy and hormone therapy. Disease was controlled for five years until increased levels of biochemical markers (CEA and Ca15.3) led to the detection of bone metastasis. Molecular characterization of the primary tumour identified H1047R mutation on PIK3CA, which was subsequently followed by digital PCR (dPCR).
Results: Among liquid biopsies, PIK3CA H1047R allelic fraction (AF) remained at low levels and became undetectable during five years. However, disease progressed with elevated tumour markers, new bone lesions and skin metastases. This evident miscorrelation prompted new genomic characterizations. Next generation sequencing (NGS) on a skin lesion showed mutations on TP53 and ERBB2, but no alterations on PIK3CA. NGS analysis on plasma samples revealed three new PI3KCA mutations (E545K with the highest AF, E542K and E726K) and three TP53 mutations. We then performed new dPCR targeting PIK3CA E545K mutation on stored liquid biopsies. This mutation, while not predominant, was the one that correlated best with biochemical and clinical evolution.
Conclusion: Digital PCR on cell free plasma samples allows continuous monitoring of the evolving molecular alterations but do not completely reflect tumour heterogeneity. Clonal dynamics constitutes a major challenge during cancer follow-up, that can be assessed, despite the higher cost, by NGS of plasma or tissue samples.

E-PS-15-018

Assessment of EGFR mutation status in Tunisian series of non-small cell lung carcinomas

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Background & objectives: The epidermal growth factor receptor (EGFR) activating oncogenic mutations are detected in 20% of non-small cell lung carcinomas (NSCLC) and are encountered in exons 18 to 21. We aimed to report the frequency and types of these mutations in our practice.
Methods: EGFR mutation status of 75 formalin-fixed and paraffin-embedded samples of NSCLC was assessed. Mutational analysis concerned exon 18-21 by the ARMS-Scoprion real-time PCR technique using the Therascreen EGFR RGQ PCR mutation kit allowing the detection of 29 somatic mutations in the EGFR gene.
Results: Average age was 55 years with a male predominance (63%). Adenocarcinoma was the most common histological type (93%), followed by squamous cell carcinoma (6%) and adenosquamous carcinoma (1%). Molecular analysis showed that 23% (17 cases) had one or two mutations. Del-exon19, L858R and Insertion were observed with respective frequencies of 65% (11 cases), 23% (4 cases) and 6.67% (1 case). Only one case presented a concomitance of two mutations: L858R and the resistance mutation TKI T790M. Of the mutated cases, 65% (11/17 cases) were female and 94% (16/17 cases) were adenocarcinoma.
Conclusion: The frequency of mutated cases is slightly higher than the frequency already described in a previous study by our team (11.5%) but close to the frequency of mutated cases in the Caucasian population (16%). The most frequent activating mutations are deletions of exon 19 and the L858R mutation of exon 21, the two representing 90% of activating mutations.

E-PS-15-019

About a gastric GIST with co-occurrence of mutations in exons 9 and 11 of the c-kit gene

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Background & objectives: The co-occurrence of two or more mutations in the same oncogene in gastrointestinal stromal tumours (GISTs) is rare and complete pathological response after neoadjuvant treatment with Imatinib is rare.
Methods: We report the case of a 41-year-old woman presenting with abdominal pain. Radiological explorations revealed a gastric mass of 10.5 cm. The histological examination of a biopsy specimen concluded to a GIST. The tumour was locally advanced. The patient had neoadjuvant treatment with Imatinib. Four months after the treatment, the patient was operated with a complete pathological response.
Results: Extraction of DNA was done by Qiagen kit from 4 sections of 10 µm FFPE biopsies. The five hot spot regions comprising the exons and their flanking regions of the KIT gene (9, 11 and 17) and PDGFRA (12 and 18) were analysed. A co-occurrence of 6 coding variations in the KIT gene was observed. Exon 9 indicates the presence of a missense p variation. Ala502Asp which has never been described. On exon 11, five mutations were found, including 2 known (Leu576Pro and Pro577Ser) and 3 others (Gln575Pro, Thr574Pro and Pro577Pro) not described. All variations at exon 17 and exon 12 of PDGFRA were polymorphisms.
Conclusion: Our case showed a concomitance of mutations of exons 9+11 of the KIT gene in a gastric GIST; this co-occurrence is rare and its impact on the response to Imatinib is little known. Pathological complete response is rare in GISTs and generally associated with exon 11 mutations affecting codons 557 and 559, our case carries variations affecting codons 574, 575, 576 and577, plus exon 9 mutation in codon 502. This co-occurrence may be the factor responsible for this good response.

E-PS-15-020

Liquid biopsy: new technical approaches to tumour evaluation

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Background & objectives: Understanding the potential and limitations molecular profiling of tumour based on CTC and ctDNA important for patient stratification. These new tools for diagnosis and prognosis of cancer gives us insight of tumour heterogeneity and evolution, which improves cancer treatment strategies.
Methods: Total of 21 patients were examined by LB. 13 of them with CRC, 5-NSCLC, 3-melanoma. All patients

(STIII-STIVNxM1) with clinical progression after treatment and visceral metastases of tumours, harboring specific mutations. ctDNA concentration were assessed by quantitative acPCR and spectrophotometry. CTCs extraction performed from 20 ml of peripheral blood by cytopheresis in density gradient. CTCs were assessed morphologically and immunocytochemicaly.
Results: Among 10(67%) of 15 patients with stage StIIIM1 after adjuvant chemotherapy (ACT), photodynamic(PDT) and target therapy(TT) mitotic activity of CTCs were detected. CTC DNA concentration was twice as higher then ctDNA concentration and number of apoptotic CTCs were 0-1. Among patients (StIII-StIVIM1) with progression after ACT and stabilization the process after PDT, in 9 (81%) cases CTC DNA concentration was lower than ctDNA concentration, and the number of apoptotic CTC cells were 2-5. Secondary mutation EGFRT780M was detected in 3 (60%) of 5 NSCLC with resistance to TT. Of these, 2 cases with double mutations. The concentration of ctDNA harboring EGFRT780M mutation is higher in cfDNA fraction than i CTC fraction.
Conclusion: Mitotic activity, low percentage of apoptotic cells among CTCs, ctDNA concentration after CTCs lysis is higher than concentration of cell free ctDNA are an unfavourable prognosis (no response therapy). High percentage of apoptotic cells among CTCs and ctDNA concentration after CTCs lysis is less than the concentration of cell free ctDNA is a favourable prognosis. Secondary resistance mutations analysis is more efficacy by ctDNA. The role of CTC for therapy monitoring and prognosis of cancer is more significant than ctDNA.

E-PS-16 | E-Posters Nephropathology

E-PS-16-001
Collapsing glomerulopathy associated with Covid-19 diagnosed one year after SARS-CoV-2 infection: a case report of an emerging entity

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Background & objectives: Collapsing glomerulopathy is one of the most common glomerulopathies associated with SARS-CoV-2 infection. It usually presents as rapidly progressive renal failure within a month of infection and has been associated with apolipoprotein L1 risk alleles, encountered mainly in African patients.
Methods: We report the case of a 29-year-old Caucasian male with a history of kidney transplantation due to end stage renal disease/IgA nephropathy, who presented with renal transplant dysfunction one year after SARS-CoV-2 infection. The patient was subjected to renal ultrasound and DTPA scan that showed mild to moderate glomerular disorder. Additionally, a renal biopsy was performed.
Results: Light microscopy examination revealed two major features: tuft collapse with pseudocrescent formation in two of the four non globally sclerosed glomeruli and focal acute tubular injury. No signs of endarteritis were observed. Immunofluorescence staining for C1q, C3d, IgA, IgG, IgM and κ/λ light chains was negative. Immunohistochemistry for C4d was also negative on peritubular capillaries. Considering patient's history, the diagnosis of collapsing glomerulopathy associated with COVID-19 was made.
Conclusion: Kidney involvement is frequent in patients with SARS-CoV-2 infection with collapsing glomerulopathy being the most common among glomerulopathies. However, there is little information over the presentation of these entities in transplant patients. Our case report describes a biopsy-proven collapsing glomerulopathy occurring in a kidney transplant Caucasian recipient with a low-risk apolipoprotein L1 donor background (father) and a SARS-CoV-2 infection one year earlier. Our histological findings in the kidney allograft were similar to those described in native kidneys of COVID-19 patients.

E-PS-16-002
A tale of a transplant: renal allograft granulomatous interstitial nephritis in early post-transplant period

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Background & objectives: Granulomatous interstitial nephritis in the early post-transplant period is an uncommon cause of kidney dysfunction reported in <1% of renal allograft recipients. Accurate diagnosis and determination of aetiology are important due to consequences of altering immunosuppression in early post-transplant period.
Methods: 31-year male with ESRD(unknown cause) received ABO compatible live related renal transplant and was given basiliximab induction followed by methylprednisolone, mycophenolate mofetil and tacrolimus for maintenance immunosuppression. Graft function was slow with gradual reduction in urine output,Day0 (5,500 ml) to Day3(2400ml) and rise in serum creatinine(3.0mg/dL on Day0 gradually to 4.0 mg/dL on Day3) and developed graft tenderness by Day3.
Results: Urinalysis showed 2+ proteinuria and 70-80 WBCs per high-power field. A transplant kidney biopsy revealed multiple small non-necrotising epithelioid cell granulomas suggestive of granulomatous interstitial nephritis. There was no evidence of acid-fast bacilli and Gomori-Methenamine silver stain was negative for fungal profiles. There was evidence of patchy acute tubular injury in the form of epithelial simplification and reparative basophilia however, no viral cytopathic changes were seen in the tubules and immunohistochemistry for CMV and SV40 large T antigen were negative. No definitive evidence of cellular or humoral rejection was seen in the biopsy. C4d stain for humoral rejection was negative. Overall a drug-induced cause was favoured.
Conclusion: Drug-induced granulomatous nephritis in allografts has been reported from day8 to day720 post-transplantation. This is one of the index cases showing granulomatous interstitial nephritis post-operative Day4 with the likely culprit being sulfonamides. The graft function significantly improved after stopping all the potential offending medicines. Although geographically, tuberculosis is the most common cause of granulomatous interstitial nephritis in countries like India accurate determination of the cause is of utmost importance for early recovery and long-term graft survival.

E-PS-16-003
Histological findings in a prospective cohort of transplant patients with screening for development of donor-specific antibodies

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Background & objectives: Donor specific antibodies (DSA) predispose kidney transplant patients to antibody mediated rejection (AMR). AMR is a leading cause of graft loss. We prospectively studied the histological features in biopsies taken at the time of appearance of a DSA.
Methods: All patients transplanted in our centre between January 2019 and November 2021 were screened (at 1,2,3,6 and 12months post-transplantation and then every year) for the development of

DSA. All patients who developed a de novo DSA were offered a biopsy. We report here histological findings in these biopsies using the Banff classification.
Results: Out of 570 consecutive transplant patients, 82 develop DSA at mean 42 days (+/- 106 days) post-transplant (14.4%)(39% Class I, 40% class II, 21% class I + class II). 57/82 patients had a biopsy at a median of 33 days (+/- 114) post-DSA detection. 47% did not show any histological features of rejection, 30% showed histological features of AMR (either suspicious for or definite AMR), 16% showed only histological features of T cell-mediated rejection (TCMR) (either borderline and TCMR) and 7% had histological features of both AMR and TCMR.
Conclusion: In a prospective cohort of patients with de novo DSA, 53% of those investigated with a biopsy showed histological features of rejection (including incomplete/suspicious features). Next steps will involve molecular analysis of those biopsies.

E-PS-16-004
The importance of renal biopsy in haematological neoplasms. A particular diagnosis
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Background & objectives: Angioinmunoblastic T-cell lymphoma (AITL) is a rare form of peripheral T-cell lymphoma , wich can have renal involvement. The aim of this case is to emphasize the importance of renal biopsy for diagnosis of hematologic systemic diseases with renal manifestations.
Methods: We report a man (48 yo) with diffuse lymphadenopathy and B symptoms, proteinuria (9g/24h), hypoalbuminemia (2,2 g/dl) and hyperlipidemia (LDLc 134 mg/dl) - Nephrotic Syndrome, NS-. Other findings were kappa light chain elevation, high kappa/lambda ratio, elevation of IgG, and eosinophilia. The histological study included renal, axilar adenopathy and bone marrow biopsy.
Results: The biopsy of an axilar adenopathy showed a monomorphic infiltrate of lymphoid cells, positive for Epstein-Barr virus (EBV), yet not conclusive, and follicular dendritic cell hyperplasia. The renal biopsy showed monomorphic proliferation of highly pleomorphic atypical T-cells (CD3+), with PD1 expression, and with polytypic plasma cells. The infiltrate affected the interstitium, without glomerular or tubular involvement. These cells were positive for MUM1 (marker of activated T-cells and plasma cells). The cells infiltrating both lymph node and renal interstitium showed TCR rearrangement, yet these were a minor group in the lymph node compared to those found in the renal biopsy. The bone marrow biopsy had not lymphoid cells infiltrate.
Conclusion: AITL are aggressive and account for less than 1% of all lymphomas, and are associated to EBV in more than 80% of all cases. Several forms of renal involvement have been described, but they are very rare. Renal infiltration was described twice in the literature, both associated with cutaneous rash and splenomegaly. NS due to renal infiltration only has been described once. Four cases of NS secondary to glomerulopathy associated with this entity have been described.

E-PS-16-005
Renal biopsy findings following complement C5 inhibitor Ravulizumab treatment in a patient with C3 glomerulonephritis
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Background & objectives: C3 glomerulonephritis is attributed to the dysregulated alternative complement pathway. The continuous C-activation can be blocked with monoclonal antibodies against C5. We present a patient's renal biopsies with histologically and serologically proven C3 GN before and after C5 inhibitor treatment.
Methods: A 17-year-old, obese (BMI: 39,8kg/m2) Caucasian male patient was hospitalized for nephritic syndrome. Two years earlier, he had been diagnosed with C3 GN. Eculizumab treatment was effective, however, haematuria and proteinuria recurred after conversion to Ravulizumab. A renal biopsy was performed. Besides routine immunofluorescence, the slides were also evaluated for IgG subtypes. The findings were compared with previous pretreatment biopsies.
Results: Active disease with diffuse-global endocapillary hypercellularity and membranoproliferative pattern was observed; 5% of the glomeruli exhibited fibrocellular crescents. Confluating deposits were seen along the capillary loops. Regarding IF, similarly to the pretreament biopsies, diffuse-global mesangial and peripheral C3 positivity was present. In addition, IgG2, IgG4 and restricted kappa deposition was seen in similar location as C3. EM demonstrated increased amount of mesangial, intramembranous and subendothelial deposits, which segmentally exhibited more dense, powdery-like appearance. There was a mild increase in Total Renal Chronicity Score (1/10 to 3/10). Complement serology tests found increased alternative pathway activity and consumption, confirming ineffective terminal complement blockade. Considering the obesity, the dosage of Ravulizumab was increased.
Conclusion: We demonstrated a patient with novel IgG2-IgG4-kappa positivity in the same distribution as the deposited C3 following Ravulizumab treatment. This immunophenotype and the powdery deposits on EM may correspond to the monoclonal antibodies binding to the terminal complement components. We imply that because of the increased body weight, the drug was possibly consumed by the accumulated complement. To our knowledge, this is the first documented case demonstrating the morphological effects of C5 inhibitor treatment in the European literature.

E-PS-16-006
An atypical case of melanin deposition in kidney
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Background & objectives: Pigment deposition in kidney may result from various conditions most commonly due to rhabdomyolysis, intravascular hemolysis and cholestasis. Melanin deposition in kidney is a rare condition that is encountered in course of diffuse cutaneous melanosis in metastatic malignant melanoma (MM).
Methods: We report a 28-year-old female patient presented with headache and high blood pressure with no significant previous clinical history. Physical examination was normal. Laboratory tests revealed very high level of serum creatinine (9.8 mg/dL). Urine analysis showed neither proteinuria nor haematuria. Renal biopsy was performed to clarify whether the kidney injury is acute or chronic.
Results: Kidney biopsy revealed 17 glomeruli, which of 3 was globally sclerotic and acute tubular injury with regenerative changes in a background of interstitial fibrosis, tubular atrophy. Tubular epithelium were filled with golden-brown granular pigment which was confirmed to be melanin by Masson-Fontana. There were no atypical/malignant cells in the tissue. The biopsy was reported as acute tubular injury with diffuse tubular melanin deposition in scarred kidney, and it was recommended to investigate the patient systemically for a potential MM focus. However,

none of the clinical/radiological examinations revealed any mass lesion that could favour MM. It has been more than 2 years of follow up that the patient is still stable.
Conclusion: According to literature review, relevant published reports presented melanin deposition in kidney as a manifestation of diffuse cutaneous melanosis. However our unique case shows that it is not always associated with MM. This finding makes it even more difficult to understand the physiopathogenesis of melanin deposition in tissues in the absence of concomitant tumour component.

E-PS-16-007
An unusual case of diffuse lupus nephritis with features suggestive of overlapping cryoglobulinemic glomerulonephritis
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Background & objectives: Cryoglobulinemic vasculitis can be associated with many diseases such as tumours, infections or autoimmune processes. Even though features of cryoglobulinemic vasculitis have been rarely described in patients with lupus, the exact link between the two diseases remains unclear.
Methods: A 39-year-old female was admitted in our nephrology unit for nephrotic syndrome. Blood tests showed low C3 and C4 and positive ANA, anti-Ds-DNA, anti-SSA and SSB. Serum cryoglobulins were negative. A kidney biopsy was performed and the tissue was divided for light microscopy (LM), immunofluorescence microscopy (IF) and electron microscopy (EM).
Results: LM showed 8 glomeruli with PAS+ hyaline thrombi in most capillary loops, marked thickening of capillary walls and mild segmental endocapillary hypercellularity. Rare glomeruli had segments of tuft sclerosis. IF showed "full house" staining. EM showed dense deposits that were in the mesangial areas, intramembranous, subendothelial and subepithelial. Some deposits had a vague microtubular structure on high magnification. A diagnosis of diffuse lupus nephritis (class IV) with features suggestive of associated cryoglobulinemic glomerulonephritis was made. The patient was started on intravenous cyclophosphamide. After six months of induction therapy, remission of the nephrotic syndrome was obtained and maintenance therapy with azathioprine was initiated.
Conclusion: This case represents an unusual case of diffuse lupus nephritis. The massive intracapillary deposits ("hyaline thrombi") and also the vague microtubular structure observed in some of the deposits using high magnification on EM raises the possibility of concurrent cryoglobulinemic glomerulonephritis. It is well known that mixed cryoglobulinemia can be present in patients suffering from lupus, but the exact impact that this has on the findings observed on the kidney biopsy of lupus patients is not well established.

E-PS-16-008
Late post-transplant focal segmental glomerulosclerosis after covid-19: causal factor or recurrence of primary disease?
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Background & objectives: Focal segmental glomerulosclerosis (FSGS) is an histopathological pattern common to various underlying aetiologies. Primary FSGS is a podocytopathy that frequently recur on early post-transplant stage. In patients with covid19 and proteinuria, collapsing variant of FSGS is the most common lesion.
Methods: We present a 20-year-old man with end-stage kidney disease of unknow ethiology, who underwent kidney transplantation in 2015. He has a history of COVID-19 infection in 2020, and developed FSGS 6 years after transplantation.
Results: One of the most common kidney lesion related to SARS-COV2 infection is FSGS, especially in its collapsing and perihilar forms. In most cases, recurrence of primary FSGS occurs in the first two years after transplantation, especially within the first days and even immediately after the surgery. However, it also may appear on later stages (>3 months), but being extremely infrequent in its very late form (years).
Conclusion: Despite being a very rare event, the possibility of a recurrence of primary FSGS presented in this case (more than 6 years after kidney transplantation) is a plausible option that must be taken into account, given that it is not known the primary underlying disease of the patient. On the other hand, it would be imprudent to completely ignore the role that COVID19 infection might have played on the development of the FSGS.

E-PS-16-009
Tubulointerstitial nephritis and uveitis (TINU) syndrome: a case series
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Background & objectives: TINU syndrome is a rare, immune-mediated entity, characterized by oculorenal inflammation. Diagnosis requires exclusion of all other causes of tubulointerstitial nephritis (TIN). We present a case series with clinical, laboratory and renal biopsy findings denotative of TINU syndrome.
Methods: Five patients experienced ocular and renal manifestations, defined by bilateral uveitis and photosensitivity, along with decline of renal function. In three patients, increased serum creatinine was accompanied by non-nephrotic range proteinuria. The rest of the laboratory evaluation was normal apart from the presence of elevated CRP and erythrocyte sedimentation rate (ESR) levels. All patients underwent renal biopsy.
Results: Histological evaluation revealed interstitial inflammatory infiltration consisting mainly of lymphocytes, with a T-cell predominance, along with several macrophages. Inflammation severity varied among different patients, with some showing scarce foci of immune cell clusters, while others demonstrated a dense, diffuse interstitial infiltration. Interestingly, in one case, a granulomatous pattern, characterized by multiple non-necrotic, ill-defined granulomas was detected. Tubulitis was also encountered in some patients. A divergence was also noted regarding chronicity index, with different levels of tubular atrophy, interstitial fibrosis and global glomerulosclerosis among different cases. Intrestingly, in one patient, electron microscopy revealed scattered granular electron-dense-deposits along some tubular basement membranes creating differential diagnostic issues with anti-TBM and immune-complex TIN.
Conclusion: Our cases seem to represent distinct progressive steps within the continuum of disease evolution. Patients with more prominent inflammation might represent a more initial state, while those with more severe chronicity index, probably depict more advanced stages. The predominance of T-cells predicates a cellular-mediated-autoimmune mechanism, as the driving force of the disease occurrence. Interestingly, medical history in one of our

patients included preceded lymphocytic meningitis and daily use of cannabinoids, which have been reported as triggering factors for TINU syndrome.

E-PS-16-010

Tubulointerstitial nephritis and eosinophilia in renal biopsy. Prognostic marker?

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Background & objectives: To determine whether the presence of eosinophils in renal biopsy and haematuria is associated with a worse renal prognosis in patients with tubulointerstitial nephritis (TIN).
Methods: Retrospective observational study in 79 (41 were women) patients diagnosed with TIN by renal biopsy between 2000-2020. The patients were classified: presence/absence of eosinophils in the renal biopsy and haematuria in the urinary sediment. Clinical-analytical and histopathological variables were analysed, as well as an analysis of renal survival (GFR<60 ml/min/m2) in the study follow-up (36.5 months).
Results: Antibiotics was the most frequent cause (34.2%). At the time of biopsy, 58.2% of patients had haematuria and 37.7% of patients showed eosinophils on biopsy and had a more severe acute renal failure (ARF). The combination of the groups of esoinophilia in the biopsy and haematuria revealed: 72.4% of the patients with eosinophils in the biopsy presented haematuria, and higher Cr elevation (4.12±2.1 vs 2.96±1.49, p=0.016), proteinuria [21.58 (6.8-86.6) vs 0.12(0.01-2.77) g/24h, p=0.001]. On the other hand, 45.7% of patients in the haematuria group had eosinophils in the biopsy. 45.7% of patients in the haematuria group had eosinophils in the biopsy and 13% had peripheral eosinophilia.
Conclusion: Patients with NTI who present eosinophilia in the biopsy and haematuria present a more severe renal failure. The analysis of these parameters could be useful when predicting complications in these patients. Eosinophilia has traditionally been considered a factor that is invariably present in renal biopsies and in peripheral blood, a fact that is not confirmed in our study.

E-PS-16-011

The usefulness of IgG4 immunohistochemical staining in differentiation of idiopathic and secondary membranous nephropathy

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Background & objectives: No reliable biomarker has yet been identified that could be used in the differential diagnosis of idiopathic and secondary forms of membranous nephropathy (MN), but it has been shown that IgG4 is the dominant IgG subclass in idiopathic MN.
Methods: Here we performed IgG4 immunohistochemical staining (IGHG4/1345, Abcam, 1: 100), on 50 kidney biopsy paraffin sections (18 idiopathic and 32 secondary MN). All cases with fine-granular IgG4 deposits along the glomerular basement membrane were pointed out as positive. Sensitivity and specificity were calculated.
Results: The IgG4 was expressed in glomeruli in 16/18 idiopathic MN (89%), and in 7/32 secondary MN (22%). Overall, the sensitivity of IgG4 for the diagnosis of idiopathic MN was 88.9%, while the specificity was 78.1%. Among secondary MN with positive IgG4, patients had known haematological/immunological disorders (plasma cell dyscrasias or IgG4- related disease). The absence of IgG4 was related to all other known secondary causes of MN (systemic lupus erythematosus or malignant non-haematological diseases).
Conclusion: IgG was not absolutely specific for the diagnosis of idiopathic membrane nephropathy, but the spectrum of secondary etiological factors leading to a positive finding is clearly narrowed (plasma cell dyscrasias or IgG4- related disease). Nevertheless, IgG4 negative idiopathic MN is not frequently observed, but the negative IgG4 finding in patients without any evidence of secondary cause at the time of diagnosis, should not sharply exclude possible upcoming secondary aetiology.
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E-PS-17 | E-Posters Neuropathology

E-PS-17-001

Novel CLPTM1L-TERT fusion in an IDH-wt WHO Grade 4 left frontal glioma radiologically masquerading as a pilocytic astrocytoma

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Background & objectives: A previously well 24-year-old man presented with altered mental status. Magnetic resonance imaging revealed a FLAIR mildly hyperintense well circumscribed intra-axial cystic lesion with a T1w isointense solid component showing possible haemorrhage. Radiological impression was pilocytic astrocytoma.
Methods: The resected lesion was examined histologically and extensively interrogated with immunohistochemistry which included GFAP, IDH1, ATRX, p53, Ki67, EMA, CD34, NeuN, neurofilament, SOX10, BRAF V600E, L1CAM, P65 and H3G34R. Further molecular studies included FISH analysis for 1p/19q co-deletion, IDH sequencing, MGMT MS-PCR for promoter methylation and Archer Fusionplex sequencing.
Results: The highly vascularised glial neoplasm showed variable morphology of ependymomatous differentiation, pilomyxoid astrocytoma and oligodendroglioma. Rosenthal fibres and eosinophilic granular bodies were not seen. High grade features such as mitoses, necrosis and microvascular proliferation were noted. The lesion showed GFAP positivity, IDH1-wildtype, conserved ATRX, weak p53 staining and rare EMA perinuclear dot-positivity. Ki67 labelling was 30%. There were no features of a neuronal differentiation. Patchy BRAF V600E and L1CAM staining was noted but P65 and H3G34R staining were negative. The lesion was 1p/19q intact, negative for mutations in IDH1 and IDH2, and MGMT promoter non-methylated. Archer Fusionplex revealed gene fusion between exon 16 of CLPTM1L and exon 2 of TERT.
Conclusion: This was an intriguing glial neoplasm in a young patient, harbouring a unique gene fusion. Single nucleotide polymorphisms at the CLPTM1L-TERT 5p15.33 locus have been described as risk factors for malignancies of the lung, breast and pancreaw. Here, we describe a novel fusion between these 2 genes in a malignant glioma.

E-PS-17-002

Pleomorphic xanthoastrocytoma BRAF wildtype, grade 3 – an unique entity in a young patient

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Background & objectives: Pleomorphic xanthoastrocytoma is a circumscribed astrocytic glioma that generally occur supratentorially, more frequently in young patients. BRAF V600E mutation and homozygous CDKN2A and/or CDKN2B deletion are common alterations in this entity that also presents a DNA methylation profile.
Methods: We report the case of a 19-year-old woman that presented headache, nausea and visual hallucinations. Imagological study revealed an expansive lesion in the left temporal lobe with hyperintense signal on T2-weighted image and postcontrast enhancement on MRI. Adjacent oedema was slightly pronounced. Surgical ressection was performed.
Results: Histopathological examination showed a neoplasia with solid and non-invasive growth pattern, predominantly composed of multinucleated giant cells with pleomorphic nuclei, frequent intranuclear pseudoinclusions and prominent nucleoli. There were also large epithelioid cells with eosinophilic and dense cytoplasm, hyperchromatic central nuclei and astrocytes filled with lipid droplets resembling xanthomatous cells. Ocasionally rhabdoid cells with eccentric nuclei and eosinophilic granular bodies were observed. Mitotic activity represented 13 mitoses/10 HPF. A moderate lymphocytic perivascular infiltrate and reticulin deposition were present. Immunohistochemistry revealed diffuse positivity for vimentin and focal for GFAP, OLIGO2, MAP2, EMA, CD34, neurofilament and synaptophysin. Ki67 was 10-15%. BRAF V600E was negative at immunohistochemistry and by sequencing analysis.
Conclusion: The diagnosis was pleomorphic xanthoastrocytoma (PXA), grade 3 and BRAF wildtype. Although with better prognosis than specific gliomas, especially at young age, PXA frequently recurs. A high mitotic activity and necrosis have also been associated with worse prognosis. About 80% of PXAs harbour BRAF V600E mutation but this finding is not present in our case. However, the DNA methylome profile confirmed the diagnosis.
The patient has been submitted to radiotherapy, followed by chemotherapy, revealing a better clinical outcome.

E-PS-17-003
One year of neuropathology during the pandemic - a review of central nervous system tumours diagnosed at the Bagdasar-Arseni Hospital, Bucharest during 2021
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Background & objectives: 2021 was another year straining the healthcare system in Romania, which was also reflected in the pathology field.
We have reviewed all the central nervous system (CNS) tumours diagnosed by our team throughout this year.
Methods: All tumour cases have been examined by light microscopy using the standard hematoxylin and eosin stain and diagnosed according to the WHO revised 4th edition classification (2016). Several of these tumours were examined during intraoperative consultation as both frozen sections and squash/smear technique using the toluidine blue stain. For the sake of this study, traumatic and inflammatory lesions were excluded.
Results: A total of 749 CNS tumours were diagnosed by our department in 2021, consisting of 569 primary and 180 metastatic lesions. 605 tumours were located to the brain while 144 were spinal. Only 50 of the spinal tumours were primary. The most common brain tumours encountered were diffuse gliomas consisting of 158 cases, out of which 126 were diagnosed as glioblastomas. Other glioma types, as well as glioneuronal tumours were rare, consisting of 34 cases. Meningiomas of both brain and spine were more frequent accounting to 156 and 13 cases respectively. Pituitary adenomas, embryonal tumours and schwannomas were also significantly encountered. 449 intraoperative consultations (frozen sections and squash/smear) were performed.
Conclusion: While tumour diversity encountered throughout the year is consistent with global epidemiology, a few variations were noticed. These were likely influenced by the temporary restrictions and availability of ICU beds during the pandemic waves. While surgery for metastatic lesions remained consistent, primary tumours, especially lower grade ones, were affected. A decrease of paediatric cases was also observed. About 60% of diagnosed tumours benefitted from intraoperative consultation.

E-PS-17-004
Simple subependymal cyst derived from the floor of the third ventricle: a case report of an extremely rare midbrain location
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Background & objectives: Ependymal cysts are rare benign lesions that occur mostly in the lateral ventricles or less commonly into the subarachnoid space and the brain parenchyma. The third ventricle is a very rare location, let alone the midbrain and the periaqueduct area.
Methods: We report the case of a 3-year-old male who presented at the emergency department with symptoms of acute hydrocephalus. Brain imaging tests revealed a dilation of the third and lateral ventricles and the patient underwent endoscopic brain surgery. A thin-wall, transparent cystic lesion was found to originate from the floor of the third ventricle obstructing the aqueduct of Sylvius.
Results: A part of the cystic wall of 0.5 cm in maximum length was biopsied and sent for pathological examination and immunohistochemical analysis. Microscopically the tissue was composed of multiple layers of a three-structured membrane. A thin aggregate of collagen fibres was lined on one side with a zone of glioependymal cells and on the other with a single stratum of flattened cells of unknown origin. Immunohistochemical markers S100 and vimentin were positive on both types of cells, while EMA, GFAP and CK7 were positive only on ependymal zone. General proliferation marker ki67 showed positivity for circa 3% of glial cells. Consequently, the diagnosis of a simple subependymal cyst was established.
Conclusion: To our knowledge, until now there have been reported only 2 cases of midbrain ependymal cysts, both of which occurred in adult patients. Cysts recognized in the third ventricle are usually colloid rather than ependymal. Notably, there is a gap in literature with regards to detailed histological description and immunohistochemistry of benign ependymal lesions. Our case report contributes to medical knowledge presenting an extremely rare entity and posing questions about the cytological features, origin and type of lining cells involved.

E-PS-17-005
Anatomical distribution of cancer stem cells between enhancing nodule and FLAIR hyperintensity in supratentorial glioblastoma: time to recalibrate the surgical target?
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Background & objectives: We investigated the expression and distribution of SOX-2-positive and CD133-positive cancer stem cells both in the enhancing nodule (EN) and in the FLAIR hyperintensity zones on a surgical, histopathological series of 33 glioblastomas (GBMs).
Methods: The inclusion criterion was the intraoperative sampling of different tumour regions by Neuronavigation and positivity to intraoperative 5-ALA fluorescence. 33 patients (20 males and 13 females with a mean age at diagnosis of 56 years) met the inclusion criterion. A total of 109 histological samples were evaluated, 52 for ENs and 57 for FLAIR hyperintensity zone.
Results: Considering the quantitative distribution of levels of intensity of staining (IS), ES (extent score) and immunoreactivity score (IRS), no difference was found between ENs and FLAIR regions for both the SOX-2 biomarker (respectively, IS p=0.851, ES p=0.561, IRS p=1.000) and the CD133 biomarker (IS p=0.653, ES p=0.409, IRS p=0.881).
Conclusion: This evidence suggests to recalibrate the target of surgery for FLAIRECTOMY and 5-ALA could improve the possibility to achieve this goal.

E-PS-17-006
Frontal intraosseous leiomyoma: an unusual case in a 15-months infant
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Background & objectives: Leiomyomas are benign tumours arising from smooth muscle cells. Intraosseous occurrence of leiomyoma is extremely rare with less than 35 cases reported in the literature. Throught this case report, we aim to discuss clinicopathological aspects of this entity.
Methods: We present a case of frontal intraosseous leiomyoma (IL) occurring in a15-mounths infant.
Results: A 15-month-old female infant presented with an undwelling lump on the forehead. Clinical examination revealed a well defined and firm swelling over the forehead. Plain radiography showed a well-defined osteolytic lesion. Histologically, the tumour was localized in the spongious bone. It was composed of moderately cellular spindle cells arranged in orderly intersecting fascicles, with abundant eosinophilic cytoplasm and elongated blunt ended "cigar-shaped" nuclei. The cellular atypia was inconspicuous. No necrosis was found. There were one mitosis. Immunostaining showed positivity for smooth muscle actin and Caldesmone. The Ki67 index was estimated at 4%. The diagnosis was consistent with an intraosseous leiomyoma. A surgical treatment was performed with a wide margin's excision.
Conclusion: IL are extremely rare tumours. To the best of our knowledge this is the first reported case occurring in the frontal bone. IL are more common in younger patients. The diagnosis of this tumour is challenging due to its extraordinarily rare incidence and the absence of pathognomonic radiological signs. It is mainly based on histopathologic examination and immunochemistry. Further studies are needed to study the behaviour of these tumours and their reccurence rates.

E-PS-17-007
Myxopapillary ependymoma: a case report and literature review
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Background & objectives: Ependymomas are rare tumours originating from neuroepithelial cells. While these tumours mainly occur within the central nervous system (CNS), there are occasional reports in children and young adults with primary tumour occurrence outside of the CNS.
Methods: A 63-year-old man presented with a palpable soft tissue mass of 12mm of the sacrococcygeal region of several months of evolution. Magnetic resonance imaging revealed a 12mm mass. He underwent a surgery with histology revealing a myxopapillary tumour.
Results: Histology study showed a myxopapillary tumour. The tumour is composed of some papillary structures formed by vessels encircled by basophilic myxoid and collars of cuboidal tumour cells which demonstrate strong GFAP positivity and CKAe1-Ae3. The patient underwent surgery and postoperative magnetic resonance imaging (MRI) of pelvis taken four days after the surgery demonstrating no evidence of residual tumour, recurrence or metastatic disease to the pelvis.
Conclusion: Reviewing the literature, we found that the mean patient age at the time of tumour symptomatic occurrence is 47 and the entire medullary conus was involved in 57,1% of the patients. Younger age, preoperative functional capacity, lesser initial neurological deficit, tumour location, size and the extent of resection as well as adjuvant radiotherapy were identified as significant factors influencing better outcome.

E-PS-17-008
Aggressiveness of astrocytoma IDH-mutant
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Background & objectives: Astrocytoma IDH-mutant is a distinct neoplastic entity with different aggressive behaviors depending on the histopathological grade. This pathology remains a challenge for the pathologist, neurosurgeon and oncologist. We describe the characteristics and an analysis of their aggression through ancillary studies.
Methods: We conducted a ten years retrospective descriptive study of patients diagnosed in our institution with grade 2, 3 or 4 astrocytomas. Immunohistochemical and cytogenetic tests were performed to stratify the cases according to the IDH gene. The data were entered into SPSS Statistics where they were analysed according to demographic and diagnostic parameters, assessing tumour aggressiveness.
Results: We identified 59 cases, most of them were found in the fifth decade of life (30.51%), more common in males (52.54%). The most common histopathological grade was grade 4 (81.36%). Imaging examinations had an accuracy of 92%. The lesion had a diameter of more than 25 mm (88.14%). The average tumour volume was 80.48 mm3, producing displacements of the midline by an average of 8.69 mm. We noticed a higher average survival rate in females (6.5 months) compared to males. The main prognostic factors identified were: Ki-67 index ($p<0.001$), histopathological grade ($p<0.001$), age at diagnosis ($p=0.040$), presence of tumoral residue ($p=0.037$) and intensity of the IDH1 R132H immunoreaction ($p=0.002$).
Conclusion: We noticed that astrocytomas can appear at any age, not having a specific topography and despite the regional effects, the symptoms do not reveal the degree of aggression. Our study indicated the main negative prognostic factors that are associated with low life expectancy. Thus, the results of our study bring new, up-to-date data to the literature on the characteristics

and evolutionary potential of these lethal tumours of the central nervous system.
Funding: This work was supported by "Ovidius" University of Constanta through the grant no. 3/21.10.2021.

E-PS-17-009
Accuracy of anti-PHH3 antibody in meningioma grading
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Background & objectives: Proliferative potential is an important criteria for meningioma grading. Phosphohistone-H3 has been suggested as a valid proliferative marker in many tumours. We aim to evaluate the efficiency of anti-PHH3 antibody as a grading tool for meningiomas.
Methods: A retrospective study on a series of 40 meningiomas diagnosed from March 2020 to April 2021 at the Pathology Department of the Military Hospital of Tunis was performed. We compared grade variability according to the mitotic count on H&E stained slides and on PHH3 stained slides.
Results: A highly significant correlation was found between mitotic count on PHH3 stained slides (PHH3-MI) and mitotic count on H&E stained slides (H&E-MI). PHH3-MI was higher than H&E-MI in 47.5% cases. A significantly higher sensitivity in the PHH3 counting method was reported in our study. It resulted in an overall upgrading rate of 22,5%; six grade 1 meningiomas upgraded to grade 2, and two grade 2 cases upgraded to grade 3.
Conclusion: Our study findings, conforming to the literature, revealed that PHH3-MI is more reliable and accurate in mitotic figures counting in meningiomas than conventional MI. It exhibited a high sensitivity in tumour grading, reported by an upgrade within 22,5% of the cases. Therefore, it might be used as a reliable tool for meningiomas' grading. Nonetheless, larger studies are obviously needed to obtain a definite conclusion on whether this method should replace the conventional H&E-based MI-method for meningioma grading.

E-PS-17-010
A case of type 2 neurofibromatosis
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Background & objectives: Type 2 neurofibromatosis (NF2) is an autosomal dominant syndrome that primarily affects the central and peripheral nervous system, characterized by neoplastic and hamartomatous proliferations of Schwann cells, meningothelial cells, and glia.
Methods: We report a 27 years old female, showing multiple tumours in the posterior cranial fossa, having a history of multiple meningiomas and one ependymoma.
Clinically, the patient complained of vertigo, headache, balance disorders, bilateral hearing loss. The clinico-radiological diagnosis of multiple intracranial meningiomas including one with petroclival location, and one with transverse sinus insertion has been established.
Results: Transverse sinus tumour was confirmed microscopically and immunohistochemically as a fibrous meningioma, and showed strong positivity for EMA, Vimentin and PR, with increased ki67 index (6% in hotspot), that can be associated with an aggressive biological behaviour. Petroclival tumour proved to be a Schwannoma, microscopically showing a biphasic pattern with Antoni A and Antoni B zones, immunohistochemically showing strong positivity for S100 and negativity for EMA, PR and BCL2. Given the previous and current morphopathological diagnoses of multiple meningiomas, an ependymoma and a schwannoma, the criteria (NIH / Manchester) for the classification of NF2 were met. Genetic testing and counselling for NF2 were recommended.
Conclusion: In patients with NF2 it was acknowledged an increased frequency of high-grade meningiomas, making it important to distinguish between a meningioma and a schwannoma, the histology and immunohistochemistry being useful tools when there is no family history.
The morbidity of NF2 patients is significant and the clinical manifestations can vary from progressive deafness due to vestibular schwannomas, other central nervous system deficits and craniospinal neuropathies (including blindness) from multiple meningiomas. For these reasons, an accurate and early diagnosis is essential.

E-PS-17-011
Supratentorial ependymoma, ZFTA fusion-positive: report of a new entity
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Background & objectives: In the 5th edition (2021) of the WHO classification of CNS tumours (WHO CNS5), Ependymomas should be classified according to a combination of histopathological and molecular features as well as anatomic site (supratentorial, posterior fossa and spinal).
Methods: We present a case of supratentorial ependymoma (SE), ZFTA fusion-positive (SEZFTAF) to describe the clinicopathological features and molecular alterations of this rare new entity. A 5-year-old girl, with no medical background, was presented to neurosurgery department for seizure and a month-long history of headache and vomiting. On examination she was conscious and oriented to time and place.
Results: MRI demonstrated a right frontal solidocystic mass measuring 50x44x35mm. The tumour showed strong and inhomogeneous enhancement in their solid components after intravenous gadolinium injection. The patient underwent gross total resection of the lesion through right frontal craniotomy. On histological examination, the lesion was well demarcated from adjacent brain. It was composed of cells characterized mainly by round uniform nuclei with speckled chromatin and poorly defined fibrillary cytoplasm. Mitotic activity was significant with the presence of vascular proliferation and some necrotic changes. In immunohistochemical study, tumour cells were positive for GFAP and EMA. We noted a nuclear accumulation of p65 porotein. The tumour was graded 3 according to the WHO CNS5.
Conclusion: Most of the SE ZFTAFP tumours arise in the parietal or frontal lobe as in our case. These tumours affect primarily children. They Show varying degrees of anaplasia and have been regarded as WHO CNS5 grade 2 or 3 on this basis. The term "anaplastic ependymoma" is no longer listed. SE ZFTAFP show nuclear accumulation of p65 protein and cytoplasmic expression of L1CAM. Immunoreactivity for p65 has been found to have a slightly higher specificity.

E-PS-17-012
Glioblastoma associated with a primitive neuroectodermal tumour of the brain as a poorly differentiated dimorphic malignant tumour in a 38-year-old man. A rare case report
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Background & objectives: Among tumours of the CNS, a combination of glioblastoma and a primitive neurodermal tumour in young people is extremely rare. Intravital diagnosis of this type of tumour is difficult due to the difference in clinical and morphological picture.
Methods: We present a case of a 38-year-old male with an intravital diagnosis of glioblastoma associated with a primitive neuroectodermal tumour of the brain. Due to the dimorphic structure of the tumour, the diagnosis was difficult, confirmed by histological and immunohistochemical studies at two independent hospitals. Despite treatment, the patient died. An autopsy with histological and immunohistochemical examinations was performed.
Results: An autopsy revealed flabby brain tissue in the focus of the removed tumour of the frontal lobe of the right hemisphere of the brain, as well as multiple metastases in the pia mater and cerebellum. The subependymal and paraventricular regions (including basal nuclei) was affected as well. There was also an oedematous pia mater of the spinal cord with a total lesion with massive compression of the spinal nerves. Histologic examination of tumours showed high cellularity with a perivascular arrangement of polymorphic cells. The tumour has many vessels of various calibers, proliferation of thin-walled vessels, areas of necrosis. There are more differentiated areas resembling multiforme glioblastoma in structure.
Conclusion: This case reminds us that in the presence of clear clinical symptoms of one type of tumour, a mixed type of tumour of central nervous system should not be excluded, which may affect therapy.

E-PS-17-013
FET-CREB fusion positive intracranial mesenchymal tumour: a case report
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Background & objectives: Intracranial mesenchymal tumour with FET-CREB fusion, a provisional entity in the 2021 WHO blue book, is defined by gene fusions of the FET family of RNA binding proteins (EWSR1/FUS) to the CREB family of transcription factors (CREB1/CREM/ATF1).
Methods: We present a 24-year-old male patient, who presented with headache, dizziness and dysarthria. MRI revealed cerebral oedema and 23 mm sized, contrast enhanced mass in the right parieto-occipital region. Patient underwent craniotomy and total excision of the mass was done. Tumour was diagnosed as angiomatoid meningioma in another centre and brought our institution for a second opinion.
Results: On morphological assessment, tumour had a myxoid and oedematous stroma with vascular structures having hemangiopericytic pattern and focal chicken-wire appearance. Neoplastic cells have elongated nuclei with vesicular chromatin pattern and spindle shaped cytoplasm. Cytological atypia and necrosis were absent. Mitosis was counted as 2/10 HPF. Immunohistochemically, tumour cells were diffusely positive with EMA, desmin, GLUT1 and focally positive with CD99; while negative with GFAP, STAT6, MUC4, CD34, synaptophysin and S100. Fluorescence in-situ hybridization was performed, revealing EWSR1 rearrangement. These findings suggested the diagnosis of intracranial mesenchymal tumour, FET-CREB fusion positive.
Conclusion: Here we presented EWSR1 rearranged, intracranial myxoid mesenchymal tumour, compatible with this diagnosis. Intracranial mesenchymal tumours with FET-CREB fusions, previously described as intracranial angiomatoid fibrous histiocytoma and intracranial myxoid mesenchymal tumour (IMMT), are a newly described group of tumours and mostly seen in paediatric patients and young adults. They are characterized by fusion of a FET family gene (EWSR1/FUS) to the CREB family of transcription factors (CREB1/CREM/ATF1). Clinical course, morphological features and genomic landscape is still unclear.

E-PS-17-014
Brain metastasis of exceptional origin: retrospective study in a single institution
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Background & objectives: The most common primary tumours of brain metastasis (BM) are lung cancer, breast cancer, melanoma, colorectal and renal cancer. BM of exceptional origin (BMEO) are poorly documented. In this study, we aim to report our experience about BMEO.
Methods: We performed a retrospective study of BM diagnosed at our department over a period of 10 years (January 2010-December 2019). BM of pulmonary, colonic, mammary, renal and melanic origin were excluded. At all, 27 cases of BMEO were included in our study.
Results: The median age of patients was 54 years. The study included 21 men and 8 women. Lesions were solitary in 15 cases and multiple in 12 cases. Tumours were located in the supratentorial region in 13 cases. A history of a previously known cancer was found in 25 cases. Eleven patients underwent surgical resection. The most common primary sites of BM were thyroid and prostate (four cases each), followed by bladder, ovary and bone (Three cases each) and testis and buccal mucosa (Two cases each). The other primary sites were oesophagus, pancreas, upper urinary tract urothelial, mediastinum, adrenal gland and palatine tonsil (one case each).
Conclusion: Despite advances in imaging methods, there are no pathognomonic features that distinguish BM from primary malignant brain tumours or nonneoplastic conditions. Therefore the standard of diagnosis of BM remains pathological examination. Immunohistochemical and molecular analysis are helpful to make appropriate diagnosis. Correlation of histological findings with clinical and imaging results is necessary.

E-PS-17-015
Two cases of MN1-PATZ1 rearranged neuroepithelial tumours with different histopathological and clinical features
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Background & objectives: PATZ1-fusion is a rare molecular event among central nervous system neoplasms, which have recently been reported in a subset of glial/glioneuronal tumours mainly affecting young patients. Hereby, we present two cases of MN1-PATZ1 rearranged neuroepithelial tumours with different clinicopathological characteristics.
Methods: A retrospective departmental study investigating 931 paediatric and young adult neuroepithelial tumours identified two previously unclassified gliomas harbouring MN1-PATZ1 fusion, confirmed by multimodal panel and methylation profiling (DKFZ, Brain tumour methylation classifier v12.5).
Results: A 24-year-old woman (Case 1) presented with a contrast-enhancing left frontal mass. Histology showed a

hypercellular glioma with brisk mitotic activity, palisading necrosis and microvascular proliferation. Case 2 was located in the parietal lobe and presented with seizures in a 10-year-old boy. The tumour was well-demarcated and displayed bizarre-looking giant cells and perivascular pseudorosettes. Mitotic figures were scarce but glomeruloid vessels were noted. Focal astroblastomatous features and abundant eosinophilic granular bodies were seen in both cases. Both patients underwent macroscopic resection and chemo-radiotherapy. In Case 1, the tumour recurred in 9 months, and the patient died 14 months after first admission. Case 2 is tumour-free after 23 months of follow-up.
Conclusion: Neuroepithelial tumour, PATZ1-fusion is a molecularly defined provisional CNS tumour type which might be under-recognised due to its broad morphological spectrum and inconclusive immunoprofile. The biological behaviour of this tumour is yet poorly understood ranging from very aggressive clinical behaviour (Case 1) to more stable diseases with a risk of late recurrence (Case 2).

E-PS-17-016
Confusing intracranial calcified lesion
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Background & objectives: Calcifying pseudo neoplasm of the neuraxis (CAPNON) is a rare, fibro-osseous lesion that can occur anywhere in the central nervous system with 150 reported cases. It's exclusively diagnosed by pathological examination. We describe a case of CAPNON mimicking an oligodendroglioma
Methods: A 56 -year-old female presented with 2 years history of recurrent holocranial headache and dizziness which have worsened in the preceding month. Physical and neurological examinations revealed no obvious abnormalities. Magnetic resonance imaging (MRI) of the brain showed a complex calcified and cystic mass, measuring 40x32 mm in size, in the right frontal lobe. An oligodendroglioma was suspected.
Results: Frontal craniotomy was performed and the entire mass was excised. Grossly, the 2.5-cm-sized lesion was a homogeneous, calcified mass without identifiable compartments. Histologically, the lesion consisted of glial tissue containing amorphous lamellar calcification with myxoid matrix in the background. The calcifications had concentric circular structure. In some places, osseous metaplasia was present. Around the lesion, peripheral palisading spindle to epithelioid cells was noted. Final diagnose is Calcifying pseudo neoplasm of the neuraxis. At follow up 1 year later, the patient was in a good condition and reported no discomfort.
Conclusion: Calcifying pseudo neoplasm of the neuraxis is a rare, slow growing benign lesion that should be included in the differential diagnosis of intracranial calcified lesions to avoid improper treatment. This entity mimics many calcifying intra-axial lesions as ganglioglioma, oligodendroglioma, and infections like tuberculosis.

E-PS-17-017
When the biomarkers decrease and the tumour increases: a case of intracranial growing teratoma syndrome
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Background & objectives: Growing teratoma syndrome(GTS) is a rare clinical entity, which has been diagnosed in patients with intracranial germ cell tumour(GCT) who present a paradoxical enlarging of the original tumour despite the normalization of tumour markers during or after appropriate systemic chemotherapy.
Methods: A 17-years-old male was admitted to Neurosurgery Department, after a diagnosis of an intracranial space-occupying lesion, made during the study of 5-month-long polydipsia and polyuria and diplopia. On MRI, the mass was well-demarcated, midline, involving the pineal area. Laboratory studies revealed elevated alpha-fetoprotein and beta-human chorionic gonadotropin, in the cerebral spinal fluid and blood. Ventriculoendoscopy and biopsy were performed.
Results: The biopsy was a fragment of 0.5 cm that showed the presence of a germinoma, constituted by a poorly cohesive tumour of round medium-size cells, with positive immunostaining for C-Kit and OCT4. Three cycles of systemic chemotherapy were given (cisplatin, ifosfamide, etoposide). The tumour markers normalized, however the GCT had a volumetric enhancement. The patient underwent an occipital craniotomy for resection of the pineal tumour. Macroscopically, the tumour measured 3.0x2.0x1.5 cm and the histopathologic study revealed the presence of mature teratoma, composed of cysts lined by respiratory epithelium and mature neural tissue. Surprisingly, a foci of 0.3 cm of germinoma was found, with the same histological features described previously.
Conclusion: The uncommon enlarging residual masses after treatment of intracranial GCT despite the concurrent normalization of tumour markers should warn for a possible GTS. GCT containing immature teratoma appears to be associated with a higher risk of developing GTS, once the chemotherapy induces the transformation of immature cells into mature teratoma.

E-PS-17-018
WHO 2021 histopathological grading of atypical and anaplastic meningiomas
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Background & objectives: As the WHO Central Nervous System was published in 2021, changes had been done in the grading of meningiomas. In this study, we aimed to grade the atypical and anaplastic meningiomas and evaluate the prognostic value of histopathological parameters.
Methods: Out of 316 patients diagnosed with meningioma, forty-three cases were diagnosed as atypical or anaplastic meningioma. All the slides of the cases were re-evaluated by a senior pathologist and a pathology resident for the grading parameters. Other than 4 patients that passed away perioperatively all the patients were followed up and the mean follow-up period was 42.8±33 months.
Results: According to the new WHO grading system, 40 of the cases (95%) were graded as 2, and two cases were graded as 3. The special morphological meningioma subtypes were associated with spontaneous necrosis, higher mitosis, and the absence of prominent nucleoli (P=0.01, P=0.02, P=0.04). Small cells feature was associated with mitosis criteria and no brain invasion (P=0.04, P=0.02). Spontaneous necrosis was correlated with higher mitosis (P=0.02). As no significance was found between histopathological grading parameters and recurrence-free (RFS) or overall survival (OS), in the subgroup of brain invasive meningiomas increased cellularity showed a better RFS (P=0.021). Spontaneous necrosis in brain invasive meningiomas worsened OS (P=0.049).
Conclusion: In grade 2 and 3 meningiomas, as brain invasion and increased cellularity were the commonest and favourable findings, this study suggests that the spontaneous necrosis feature has an important prognostic significance in the brain invasive subgroup. While none of the histopathological parameters made a greater

prognostic difference in this small group of cases; TERT promoter mutation and homozygous deletion of CDKN2A and/or CDKN2B become more needed to foresee the disease progression.

E-PS-17-019

Low-grade glioneuronal tumour with neuropil-like islands and FGFR1 mutation, a case report

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Background & objectives: Glioneuronal tumour with neuropil-like islands (GNTI) is a rare tumour entity that is described mainly in adults with very few cases reported in pediatrics that are molecularly tested.
Methods: An 8-year-old female presented initially in 2016, at the age of 1-year, with seizures and was found to have a left frontal mass, for which she underwent craniotomy. In 2018, she presented with recurrence and in 2021 she presented with a second recurrence. No chemotherapy or radiotherapy was administered.
Results: A review of the original pathology material as well as of the first and second recurrence shows similar features. There is proliferation of monotonous round cells with clear cytoplasm, separated focally by fine vasculature and in other foci by proliferating vessels, with occasional mitotic figures. These foci are positive primarily for GFAP. Other foci show islands of neuropil surrounded by cells with clear cytoplasm that stained for Synaptophysin and focally for NeuN. The final diagnosis was a low-grade glioneuronal tumour with neuropil-like islands.
Examination by Nanostring confirmed the presence of FGFR1 tyrosine kinase domain duplication (TKDD).
Conclusion: FGFR1 TKDD is known to be implicated in paediatric low-grade glioneuronal tumours, including DNET. Glioneuronal tumour with neuropil-like islands is another morphological variation along the spectrum of tumours characterized by FGFR1 mutations. This has important implications for confirmation of the diagnosis as well as being predictive of response to FGFR inhibitors.

E-PS-17-020

Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease): a rare case report

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Background & objectives: Dysplastic gangliocytoma of the cerebellum (DFG), also called Lhermitte-Duclos Disease, is a rare lesion of the posterior fossa consisting of a diffuse hypertrophy of the cerebellar cortex. It is one of neuronal and mixed neuronal-glial tumour, WHO grade I disease.
Methods: A 26-year-old man, with no history, consulted for a progressive vertigo and headache, with nausea and vomiting for 7 days. During the physical examination, the vital signs were stable. The patient displayed ataxia with wide-based gait. No nystagmus. Brain MRI showed an intra-parenchymal lesion of the left cerebellum, isointense on T1- and T2-weighted sequences. No prominent enhancement.
Results: Surgical resection was proposed because of size, the undetermined nature of the lesion and the supposed impact on expansion of the cerebellum. The patient underwent tumour resection. The histopathological examination showed an abnormal architecture of the cerebellar cortex: dysplastic Purkinje cells were present in the granular layer and in the underlying white matter. The molecular layer was replaced by larges axon bundles. No mitosis or necrosis was be seen. Ectatic vessels and calcifications were present. Ki67 was inferior to 1%. In immunohistochemistry, dysplastic cells were synaptophysin and GFAP positive. The diagnosis of a dysplastic gangliocytoma of the cerebellum was confirmed.
Conclusion: DGC is a rare and benign brain tumour. It has both neoplastic and hamartomatous characteristics. It frequently presents in young adults. The pre-operative diagnosis proves to be a challenge. On MR, Tiger-strip sign is characteristic but is not always seen. The prognosis is good if total resection can be achieved. Further molecular examinations of PTEN gene mutation is recommended. Adult-onset of DGC is considered to be a pathognomonic criteria of Cowden syndrome characterised by mutation of PTEN gene.

E-PS-17-021

Cerebellar liponeurocytoma: clinical and pathological analysis

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Background & objectives: Liponeurocytomas are rare and slow-growing tumours located predominantly in the cerebellum. Our aim is to present a new case of liponeurocytoma and describe its epidemiological, clinical and pathological features, as well as management strategies.
Methods: We describe a new case of liponeurocytoma diagnosed in the Rabta hospital, Tunis, Tunisia.
Results: We report the case of a 38-year-old woman without particular pathological antecedent with a few months history of headache and dizziness, aggravated since 2 days by signs of increased intracranial pressure and cerebellar dysfunction. The Computerized Tomography practiced in emergency showed a subtentorial space occupying mass, heterogeneous, exhibiting the attenuation values of fatty tissue, with hydrocephalous upstream. The patient has been operated. The histopathological and immunohistochemical studies concluded a cerebellar liponeurocytoma.
Conclusion: Cerebellar liponeurocytoma is a rare neoplasm with distinctive morphologic features. It typically involves the cerebellar hemispheres of middle-aged to older adults. The tumour is composed of a uniform population of neurocytic cells possessing round to oval nuclei and pale to clear cytoplasm. A variable degree of lipidization of the tumour cells is present, lending a resemblance to mature adipose tissue.

E-PS-17-022

Atypical presentation and no concordant methylation class of a paediatric high-grade astrocytoma with piloid features (HGAP)

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Background & objectives: High-grade astrocytoma with piloid features (HGAP) is an uncommon new tumour entity of the central nervous system, extremely rare in paediatric population. Characterized by distinct DNA methylation profile, CDKN2A/B deletion, MAPK pathway alterations and ATRX mutation and/or loss of expression.
Methods: We describe the case of a 7-year-old boy with no relevant medical history, admitted in our hospital due to a raised intracranial pressure, secondary to hydrocephalous. Cerebral magnetic resonance imaging revealed a hypothalamic-optical

well-circumscribed solid/cystic tumour, with peduncle invasion and normal extension studies. An endoscopic surgical cyst fenestration and Monroe liberation was performed, together with an endoscopic biopsy for diagnosis.
Results: Paraffin sections stained with haematoxylin-eosin demonstrated a moderately cell-dense neoplasm with piloid astrocytic histological features presenting Rosenthal fibres. Vascular hypertrophy with glomeruloid proliferation and high mitotic activity (9 mitosis/10 HPF), were observed. Immunohistochemistry revealed loss of ATRX expression in 90% of neoplastic cells with positive staining for Olig2, PGFA and H3K27me3, and negative staining for LIN-28A, H3K27M, p53 and IDH1, with a ki67 proliferation index of 30%.
The methylation class was of diffuse leptomeningeal glioneuronal tumour (DLGNT) with a concordance score of 0.57. For further analysis, next generation sequencing (NGS) was performed, demonstrating ATRX mutation; CDKN2A/B deletion, codeletion of 1p/19q; and absence of KIAA1549-BRAF fusion, BRAFV600E and IDH mutation.
Conclusion: Histopathological features of high-grade astrocytoma with loss of nuclear ATRX expression, suggested HGAP. Considering the low score value of DLGNT methylation class and the close molecular segregation described in both entities, we extend the study through NGS. This approach enabled us to confirm the presence of a mutation in ATRX and the deletion of CDKN2A/B, endorsing the diagnosis of HGAP. We believe that integrated histologic and molecular analysis is essential to enable accurate diagnosis of this rare brain tumour.

E-PS-18 | E-Posters Ophthalmic Pathology

E-PS-18-001
Pseudoglandular hyperplasia of the conjunctiva: report of a rare entity

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Background & objectives: Pseudoglandular hyperplasia of the conjunctiva (PHC) is a rare benign pseudo tumoral lesion which arises preferentially in conjunctiva fornix and/or tarsal. We report here a new case of this rare entity, review its histopathological features and discuss its differential diagnoses.
Methods: The morphologic findings of PHC of the right eye occurring in a 65-year-old man were reported with a review of the related literature.
Results: The patient consulted for a swollen pediculated conjunctiva mass. MRI revealed a well-limited hypervascular nodule, in the right upper palpebral conjunctiva, measuring 12 x 10 x 13 mm. Surgical excision was performed. On microscopic examination, the specimen received was covered with a regular stratified squamous epithelium containing numerous goblet cells. The epithelium realized invagination into the stroma with formation of pseudoglandular or pseudoadenomatous structures of various sizes. The surrounding stroma contained inflammatory cells with blood vessels. The lesion was focally ulcerated. There was neither nuclear atypia nor mitosis. The diagnosis of PHC was retained.
Conclusion: PHC has distinctive histological features. It is defined as a proliferation of the conjunctival epithelium with prominent glandular structures. Clinical presentation and radiological features are not specific. Diagnosis is based on pathology analysis. PHC has good prognosis. Awareness of this entity is crucial to distinguish it from well-differentiated adenosquamous carcinoma to ensure the appropriate treatment. The absence of an infiltrative growth pattern and cytologic atypia with mitoses lead for PHC diagnosis.

E-PS-18-002
Spindle cell haemangioma, an unusual presentation

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Background & objectives: Spindle cell haemangioma (SCH) is a benign vascular tumour that occurs in the dermis or subcutaneous tissue of the hands and feet of young adults. SHC is occasionally associated with Maffucci syndrome, Ollier disease, and Klippel–Trenaunay syndrome.
Methods: An 18-year-old male patient presented with a mass near the lacrimal gland in the left orbital region. Magnetic resonance imaging revealed a 7x13 mm nonspecific mass lesion in the left lacrimal gland localization with contrast enhancement. An excisional biopsy was performed from the masses in the left orbital region and sent to pathology.
Results: Gross examination of the surgical specimen showed the 1.5x1.4x1 cm haemorrhagic lesion. Microscopic examination revealed two different components, thin-walled, large cavernous spaces and spindle epithelioid endothelial cells. There were 1-2 mitotic figures per 10 high-power field. Cellular atypia, atypical mitosis, necrosis, and pleomorphism were not observed. Immunohistochemical examination revealed a positive reaction with CD31 and CD34 in cells lining the vascular spaces.
Conclusion: The case was diagnosed as SCH. SCH is very unusual tumour in the orbital region. SCH should be considered as one of the differential diagnosis in vascular tumours of the orbit. Therefore, immunohistochemical examination should be performed to differentiate it from tumours such as orbital cavernous venous malformations, Kaposi's sarcoma, angiosarcoma and epithelioid haemangioma.

E-PS-19 | E-Posters Other Topics

E-PS-19-001
Slide-free imaging of fresh bulk H&E-stained tissue using multiphoton microscopy

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Background & objectives: Frozen sectioning is the gold standard for intraoperative histopathological examinations. We propose a laser-based microscopy technique to image bulk tissue directly in the operating theatre without having to freeze or section the tissue.
Methods: We develop a laser-based multiphoton microscope intended for the special working conditions in the operating theatre. The feasibility of the microscopy system is evaluated using bulk porcine tissue samples which are stained with haematoxylin and eosin (H&E). The fresh bulk tissue is stained using a 6-7min H&E quick staining protocol and directly investigated under the microscope.
Results: We obtain images of bulk unsectioned H&E-stained tissue within 15min. The laser microscopy technique evaluates the morphological structure at or slightly below the surface of the tissue. The H&E distributions in the tissue are recorded separately and can therefore also be evaluated individually. The images are inherently digital and can be analysed remotely by a pathologist and prevent delays due to sample transport to the pathology lab.

The images are compared to both formalin-fixed paraffin-embedded and frozen sections of the same organ and the speed of the measurement is evaluated.
Conclusion: Our self-built multiphoton microscope can create H&E images of fresh bulk tissue without freezing or sectioning. A quick staining protocol has been developed to achieve a competitive imaging speed. The technique offers a fast alternative to the frozen section workflow avoiding delays by transporting the tissue to the pathology lab. We will start a clinical study on basal-cell carcinoma to evaluate the diagnostic accuracy and try analysing our digital image data by modern AI algorithms in the future.

E-PS-19-002
Three-dimensional observations of metastatic cancer cells in body fluids using label-free optical diffraction tomography
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Background & objectives: Label-free optical diffraction tomography (ODT) can overcome the limitation off conventional cell imaging technologies. Rapid diagnosis of metastatic carcinoma in body fluids is necessary for deciding a stage. We evaluated the metastatic cancer cells using ODT as a diagnostic tool.
Methods: Two kinds of primary cultured cells of pulmonary adenocarcinoma and gastric adenocarcinoma were used as control group and ten body fluid samples containing metastatic carcinomas, such as pleural fluid and ascites were used as experimental group. Reconstruction of a three-dimensional (3D) refractive index (RI) map using ODT. Tumour volume and three dimensional morphology were observed through 3D optical method.
Results: All cancer cells presented prominent nucleoli, less cytoplasm, and mostly uniformed nucleus. The average volume of the gastric adenocarcinoma cells and pulmonary adenocarcinoma cells was 5169.3um3 and 3939.3um3, respectively. The surface of the cells was varied and it was generally uneven accompanying process or blebs rather than smooth.
Conclusion: There is no study comparing cancer cell cyto-morphology using ODT so far. Since there is no staining process after obtaining the body fluid, rapid identification and confirmation of metastatic cancer cells may be possible through body fluids from the patients' bed side.

E-PS-19-003
Modifying bioeffects of posturan incorporation
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Background & objectives: The long-term bioeffects of depleted uranium after incorporation are of considerable interest from the standpoint of its endogenous effects and in order to identify the reactivity of target organs.
Methods: Fragments of biopsy material of the parotid gland and jejunum from 135 mature male rats were used. Reactions to dehydrogenases were carried out on cryostatic sections of the parotid gland. Intraepithelial lymphocytes and mucosal barrier were detected on paraffin sections of the jejunum stained with hematoxylin and alcyan blue.
Results: Three and six months after a single incorporation of depleted uranium in the parotid gland, a prolonged bioeffect of changes in the light-optical density of dehydrogenases was noted. In acinuses, the indicators were significantly higher than the control ones. There were no differences from the control in the striated excretory ducts. However, there was a significant increase in their extent, stating atypical regeneration and an increase in the viscosity of the secretion. Destructive changes of acinuses are noted. The dynamism and depth of penetration of lymphocytes into the jejunum epithelium determined the specificity of the microenvironment for antigen recognition and correlated with severity of the barrier properties of mucin gel.
Conclusion: The results of the study have identified a pathogenetically significant role in the realization of depleted uranium bioeffects. Persistent changes in the parotid gland were a reflection of a violation of the formation and excretion of secretions, suggesting a change in the microflora in the oral cavity, and an increase in the density of the mucosal barrier in the jejunum. The multidirectional nature of the changes revealed a prolonged pattern of reactions characterizing the cumulative radiotoxic bioeffect of depleted uranium.

E-PS-19-004
Conceptions of learning factors in undergraduate medical students. Teaching directed by threshold concepts
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Background & objectives: Students' cognitive perceptions (SCP) are considered important variables for high-quality learning. In this study, SCP were used to identify histopathological threshold concepts (TC) in medical curricula. The objective is to analyse the perception of medical students' about TC in Pathology.
Methods: A questionnaire was developed and validated to characterize SCP of CT in pathology. A sample of 180 medical students' participated in the study. Different items were evaluated by means of a Likert-type scale (1-5) on their consideration of each CT in pathology. Statistical analysis was performed (Student's t test) comparing the values by gender and the differences between different sections.
Results: The result of questionnaires related to morphostructural TCs was very distributed in the interval from 1 to 5, being the mean value 3.2/5. CT related to two-dimensional microscopic identification were scored 4.2/5. Additionally, students identified CT related to the general histogenesis of neoplasms as critical to understanding and learning in pathology.
Conclusion: The identification of threshold concepts through students' perceptions is potentially useful to improve the teaching and learning process in health sciences curricula. The differences observed must be taken into account in the organization in the teaching programming of the Pathology subject and in the entire Medicine degree, to guarantee an autonomous learning process based on specific competencies.

E-PS-19-006
Pathological anatomy as an innovative teaching experience in biology students
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Background & objectives: Histological image analysis plays a role in studying pathological alterations in diseases, especially in practical

teaching. To know the degree of satisfaction and the usefulness of an innovative practice in a non-medical subject in collaboration with a Pathology Unit.
Methods: 48 students carried out a practical activity of viewing digitized human biopsies. Students observe biopsy images of a pathology according to its cellular alteration and corresponding pathology was selected. On each image, they identified the tissue/organ, the "residual" histological structures and their alterations. This activity was evaluated by an anonymous survey on a Likert scale (0-5).
Results: The survey was answered voluntarily by 85.48% of the students enrolled in the subject, of which 24 were women (58.5%), 16 men (2.4%) and 1 person without assigned gender (2.4%). The responses were grouped into 3 blocks: 1) evaluation of the methodology used with a mean score of 4.31; 2) usefulness of the activity, which obtained a mean score of 4.41; 3) general evaluation of the innovative teaching practice where 53.6% (22) had an excellent opinion of it, 43.9% (18) acceptable and 2.5% (1) fair.
Conclusion: The interpretation of histopathological images has been a teaching innovation highly valued by the students. The teaching strategies must be implemented in different subjects of the study plans to promote an adequate interaction between health and non-health professionals as a projection to a more transversal university teaching.

E-PS-19-008
Male breast cancer with synchronous renal cell carcinoma: a rare presentation
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Background & objectives: Male breast cancer (MBC) is rare. Synchronous MBC with other types of cancers is exceptional. We report a case of male synchronous breast and renal carcinoma, and we highlight the clinicopathological features of this rare association.
Methods: A 60-year-old male smoking patient followed for mental retardation complained of a left breast mass. On questioning, he did not report any other urinary-associated symptoms.
Results: A breast biopsy concluded to an invasive breast carcinoma. Thoracoabdominal computed tomography showed bilateral pulmonary micronodules and a mass of the left kidney measuring 7cm x 6,8cm, containing heterogeneous enhancement calcifications. The patient underwent breast radical surgery with axillary lymph node dissection and postoperative staging was T4b N1. Thus the patient was referred to the urologic department for renal surgery before adjuvant chemotherapy for the breast cancer. A left nephrectomy was done. The pathological examination concluded to papillary renal cell carcinoma type 1 with nuclear grade 2 and absence of associated breast carcinoma contingent. The patient underwent adjuvant chemotherapy for the breast cancer with regular follow-up.
Conclusion: Synchronous tumours with MBC are rare and to our knowledge, this is the first case reporting synchronous MBC with kidney tumour. Few studies reported the tendency of papillary renal cell carcinoma subtype to be associated with multiple neoplasias. Therefore our case enriches the data to perspective studies of synchronous cancers associated with certain histologic subtypes and could be a clue to detect cancers most frequently associated with certain histologic types.

E-PS-20 | E-Posters Paediatric and Perinatal Pathology

E-PS-20-001
Nephroblastoma associated with nephroblastomatosis: a study of 6 cases
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Background & objectives: Nephroblastoma associated with nephroblastomatosis is a rare embryonal renal disease with a high incidence in children under 5 year-old. Nephroblastomatosis is regarded as precursor lesion of nephroblastoma. The aim of our study is to recall the anatomo-clinical features .
Methods: A total of six cases of nephroblastoma associated with nephroblastomatosis diagnosed at the Department of Pathology of University Hospital in Monastir and treated in the Pediatric Surgery Department of University Hospital in Monastir , over a period of 25 years (from 1995 to 2020). A review of clinical, paraclinical, pathological and evolutionary data was performed in all cases.
Results: These were 4 female and 2 male, with an average age of 40 months. The average diagnosis time was 2.35 months. The main clinical presentation was abdominal mass. Four cases were limited to the kidney and two had pulmonary metastasis. The treatment was multidisciplinary combining pre-operative CT, surgery and post-operative CT according to SIOP. The pathological examination showed two tumours classified as stage I, one as stage II, one as stage IV and two as stage V. Three cases were classified as intermediate risk, one as high risk and two cases associated intermediate and high risk. The evolution of patients was favourable in 5 cases. One patient was dead.
Conclusion: Nephroblastomatosis is defined by the presence of multiple or diffuse nephrogenic remains, regarded as precursor's nephroblastoma It is a rare disease with a diagnosis based on histological examination. This entity is caracterized by a high recurrence frequency. Long-term follow up is needed. However, the prognostic of nephroblastoma associated with nephroblastomatosis is still favourable.

E-PS-20-002
Multifocal Epstein-Barr virus-associated smooth muscle tumour in an immunosuppressed child with a transplanted liver
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Background & objectives: Epstein-Barr virus (EBV) is widely known to be associated with lymphoproliferative diseases in the setting of post-transplant immunosuppression. Rarely, EBV can also promote smooth muscle proliferation, resulting in an EBV-associated smooth muscle tumour (SMT), a rare and under-recognised clinicopathological entity.
Methods: A 2-year-old girl from Brunei with a history of liver transplant for biliary atresia, presented with stridor, dyspnoea, and subsequent partial focal seizures. Computed tomography showed a 3.9 cm right paratracheal mass with occlusion of the right main bronchus, bilateral lung masses and a 7.9 cm brain mass occupying both cerebrum. The brain and right paratracheal masses were biopsied.
Results: The biopsies showed spindle cell lesions arranged in intersecting long fascicles and a focal sheet-like area of primitive round cells. The spindle cells contained cigar-shaped nuclei with dense eosinophilic cytoplasm while the primitive round cells had high nuclear-to-cytoplasmic ratio, round hyperchromatic nuclei and scant cytoplasm. The nuclear atypia was mild and there was nuclear monomorphism. A staghorn-like vascular pattern was seen. This was initially diagnosed as a synovial sarcoma at the primary institution's laboratory. However, further work up showed the spindle cells (not round cells) were positive for desmin and

h-caldesmon. EBER-ISH was positive in both components and EBV-SMT was diagnosed. Immunosuppressants were withdrawn and the masses were surgically debulked.
Conclusion: EBV-SMT is rare in children with solid organ transplant. The differential diagnoses were spindle cell rhabdomyosarcoma, synovial sarcoma and solitary fibrous tumour. The myoid nature of the spindle cells, the second population of primitive round cells and the clinical history were helpful to prompt investigations for EBV. It can be diagnostically challenging if only the primitive round cell component is sampled, and it should be considered in the work up for small round blue cell tumours in immunosuppressed children.

E-PS-20-003
Tuberous sclerosis complex: case report and literature review
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Background & objectives: Tuberous Sclerosis Complex (TSC) is a rare autosomal dominant, multisystem disorder that is characterized by cellular and tissue dysplasia in several organs. The clinical manifestations are result of a mutation of one of two suppressor genes TSC1 and TSC2.
Methods: We present a 34 weeks foetus with multiples cardiac rhabdomyomas found in the 33rd week ultrasound routine. Consequently, a foetal nuclear magnetic resonance was conducted, showing brain surface, subependymal nodules in thalamus-striated sulcus, cortical tubers and linear lesions in deep white matter. The case met three major criteria for sclerosis tuberous and concluded with the pregnancy's termination.
Results: The autopsy results revealed subependymal lesions composed of vacuolated cells with abundant eosinophilic cytoplasm, and few binucleated and dyscrete atypia. Moreover, pseudonodular agrupations of dysmorphic neuronal cells were found in the subcortical cortex. The heart presented small tumour nodules in both ventricles, formed histologically of large polygonal cells with glycogen vacuoles, central nucleus and cross striations of cytoplasm radiating from the nucleus to the cell membrane. These findings led to diagnosing subependymal giant cell neoplasia, cortical tubers, cardiac rhabdomyoma and multiple renal cysts, compatible with the clinical diagnosis of tuberous sclerosis. In consequence, a genetic study was performed and detected a TSC2 mutation, c22251 C>T, p- Arg751*.
Conclusion: TSC is an uncommon syndrome characterized by formation of hamartomas in multiple organs, which incidence has been estimated in 1/6000-1/10000 newborns annually. It presents a wide range of clinical and phenotypic manifestations with varying severity. The brain, heart and kidney are commonly involved in this syndrome. Most of cases, are caused by a de novo mutation or are the effect of parental gonadal mosaicism. A thorough clinical evaluation should be followed by genetic testing for confirmation of TSC and prognostication.

E-PS-20-004
Clinical and morphological correlations during pregnancy in conditions of circulatory hypoxia
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Background & objectives: Congenital heart disease (CHD) during pregnancy in women leads to severe hemodynamic disorders. We aimed to study the clinical and morphological correlations between maternal hemodynamics during 30-34 weeks and structural remodelling of chorionic villi in placentas in women with CHD
Methods: Thirty-five medical records of pregnancies were analysed with emphasis on the mother's heart rate (HR),blood pressure (BP); systolic and minute blood volumes (respectively: SBV and MBV). Respective placentas studied included 20 cases of CHD and 15 controls (non-complicated pregnancies). H&E slides, were studied microscopically and by point count computer morphometry.The differences between groups' data were elucidated by non-parametric Mann-Whitney test.
Results: The results of the study showed a decrease in maternal hemodynamic parameters: HR, BP, SBV and MBV in the period of 30-34 weeks of gestation during pregnancy with CHD compared with the control ($p<0.05$). Microscopic examination, in the contrast to physiological pregnancy, revealed an increase in syncytiocapillary membranes (SCM) and their thickening compared to the control. The analysis of correlations between the thickness of the SCM and the SBV and the MBV of maternal hemodynamics established the presence of negative linear connections during 30-34 weeks of gestation in the central parts of the placenta (respectively: $r= -0.6635$ and $r= -0.6400$).
Conclusion: Deficiency of maternal hemodynamics during 30-34 weeks of gestation is accompanied by increased sclerotic processes in the placenta in women with CHD. As a result, the permeability of the SCM decreases, the metabolic processes between mother and foetus worsen. Remodeling of the SCM structure is considered in the aspect of adaptation of the placenta to circulatory hypoxia due to hemodynamic disorders in women with CHD.

E-PS-20-005
Neonatal kidney as a rare site of extramedullary haematopoiesis
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Background & objectives: Extramedullary haematopoiesis (EMH) presents development of hematopoietic tissue outside the red bone marrow. During foetal and early neonatal life, the major sites of EMH are liver and spleen. If needed, EMH appears in other organs like adrenals, and perirenal fatt.
Methods: Histological and immunohistochemical analysis of EMH focuses in postmortem samples of neonatal kidneys.
Results: We present an autopsy case of a twin, preterm, hypotrophic male neonate who was born in 32. gestational week and died 2 days after the labor due to neonatal respiratory distress syndrome. During pregnancy, a twin-to-twin transfusion syndrome was diagnosed, while after the labor marked congenital anaemia was detected. The major gross findings were: pailor, anaemia of internal organs, bilateral calcified cysts of periventricular white matter, hydropericardium, neonatal ARDS. An interesting histopathological findings in kidney samples were patchy interstitial infiltrates of uniform cells, with increased N/C ratio, which immunohistochemically correspond to erythroblasts (CD71+), while immunoexpresion of other markers was absent (CD34, CD117, TdT, Pax5, CD19, Lysosim, CD38, CD10, CD20, CD61).
Conclusion: Foetal and neonatal hypoxia, caused by numerous aetiologies, induce EMH in other various internal organs. Unlike in adults, kidney in foetuses and neonates is an extremely rare site of EMH, especially in isolated one-lineage hyperplasia. This finding could help further research in the field of potential sites of EMH.

E-PS-20-006
Foetal arthrogryposis in twin gestation: case report and literature review

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Background & objectives: The term arthrogryposis is used to denote contractures involving at least two joints in different body regions. The most prevalent type is amyoplasia, which may have a higher prevalence in monozygotic twins; however, it usually only impacts one of them.
Methods: We present a case of a primiparous woman without any antecedents, with a bicorial and biamniotic gestation in her 31st week. In a routine ultrasound study, discordance between both foetuses, raised nuchal fold and claw hand was observed in one of them. It concluded with a feticide and request for an autopsy after the birth of the second twin.
Results: A male foetus with a multiarticular flexion position, with skin shortening in the neck (pseudoterigium) was received in our service. Accompanying the joint contractures, marked generalized muscle atrophy (amyoplasia) was identified due to the lack of intrauterine mobility because of these contractures. In addition, he had clawed hands and macroglossia. The complementary studies of chromosomopathies and genetics for neuromuscular diseases did not identify any alterations that justified the origin of the foetal pathology detected. The prenatal ultrasound and autopsy findings in our case were characteristic of arthrogryposis.
Conclusion: The incidence of arthrogryposis is approximately 1/3000 live births; however, the prenatal incidence indicates a high intrauterine mortality. More than 400 specific disorders presenting with arthrogryposis have been identified. Its aetiology is highly heterogeneous with a background of genetic disorders with variable prognosis and inheritance. The most prevalent form is amyoplasia. Current ultrasound identifies approximately 25% of cases before 24 weeks in general obstetrics care population.

E-PS-20-007
The attitude and general knowledge concerning perinatal autopsy in midwivery bachelor students and hospital midwives in internet querend
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Background & objectives: We tried to assess knowledge about perinatal autopsy among bachelor students and midwives. Unanonimous students' request to see one during seminars attracted our attention. We decided to assess attitude and knowledge of this procedure through online querend in other universities.
Methods: Getting positive feedback after presenting recorded autopsies to the students we decided to assess the general knowledge of this procedure, attitude, experience, benefits coming from autopsy among wider spectrum of students and university hospital midwives. Online querend was divided into standard sections describing respondents, medical background, experience, knowledge, the attitude, opinions about the possible benefits coming from such autopsies.
Results: More than 300 students answered the querend, and about 190 midwives so far. The final results will be presented during the Congress as we still gather the data. The results are quite astonishing because overwhelming majority fully understands the need of the perinatal autopsy, with will to attend it if possible (0 to 1 seen so far). The experience is based mainly on written or internet sources. Majority of respondents sees the benefits of postmortem examination for future family counselling (inherited disorders), future perinatal care, correlations with prenatal ultrasound diagnostics. Almost all respondents consider information from autopsy vital for future professional work.
Conclusion: Perinatal autopsy has not yet suffered from dramatic decline as others. After this querend we learn that knowledge from this procedure (so far limited to physicians) is noticed and acknowledged by other medical professionals. Due to obvious obstacles personal attendance is mostly impossible, but in era of digitalisation, remote presence, post factum analysis is available for every medical interested in extra practical knowledge. Discussing results might be an enormous source of information for every part, especially in rare cases.

E-PS-20-008
Placental incidental finding in a context of a giant congenital melanocytic nevus – a case report
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Background & objectives: Melanocyte aggregates within the placenta raise a differential diagnosis between benign nevus and a metastasis of a maternal or foetal melanoma. The association with congenital melanocytic nevi of the newborn is a rare, but already described condition.
Methods: After an uncomplicated pregnancy, a healthy woman gave birth at term. The female infant showed a giant congenital melanocytic nevus in the left lower extremity, with multiple satellite lesions and a thoracic infantile haemangioma. The placenta was sent for pathological examination. Multiple skin resections of the lesions were also performed.
Results: The macroscopic aspect of the placenta was normal. The microscopic examination showed well-delineated incidental cell aggregates within the chorionic villi. These cells were focally pigmented and did not exhibit any cytological atypia. They were absent in the intervillous space. No mitoses could be found. The cells were positive for MelanA red and S100 immunohistochemical stains. HMB45 antibody expression was positive. The microscopic and immunohistochemical examinations of the infant's main melanocytic lesion and the satellite lesions showed features consistent with congenital nevi, without any malignant transformation. Close clinical follow-up of the infant is still ongoing.
Conclusion: Incidental ectopic tissue in the placenta (such as adrenocortical, liver parenchyma) is rare. On the other hand, the differential diagnosis comprises malignant entities, such as metastatic tumour from maternal or foetal origin. The current case report illustrates a rare placental finding (melanocytic nevi cells) in a context of a giant congenital melanocytic nevus of the infant with no signs of malignant transformation at the moment of reporting.

E-PS-20-009
Spinal neurenteric cyst: a case report
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Background & objectives: The neurenteric cyst is a rare congenital deformity, It has a predilection for the lower cervical and upper dorsal region. We present a case of intradural intramedullary spinal neurenteric cyst and discuss its clinicopathological features.
Methods: We report a case of spinal neuroenteric cyst i a 11 year-old child.
Results: An 11-year old child presented with neck pain and gait problems evolving for six months. Magnetic resonance imaging (MRI) was performed and showed intradural and intramedullary cystic formation at the level of C5-C6, isointense to cerebrospinal

fluid(CSF) with non-enhanced wall. The mass was removed surgically.
Histological examination showed a very thin cystic wall with a columnar ciliated coating with numeral mucin-producing cells. The epithelial cells had monomorphic nuclei without atypia.
Reactive gliosis was noted in the adjacent glial parenchyma.
These findings were consistent with a spinal neurenteric cyst.
Conclusion: The neurenteric cyst is a rare congenital anomaly of the medullary canal. There are no specific clinical signs. The size of the cyst and the associated malformations affect the onset of symptoms.
The diagnosis is suggested by MRI and confirmed by an anatomopathological study of the cyst wall. Surgery is intended to be as radical as possible to avoid relapse.

E-PS-20-011
Oral carcinoma cuniculatum in childhood: a rare entity
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Background & objectives: Carcinoma cuniculatum is a rare variant of squamous cell carcinoma (SCC). Only 66 cases affecting oral cavity have been reported to date, three in childhood. We present a case of an 11-year-old girl with oral carcinoma cuniculatum (OCC).
Methods: We reviewed the case of a healthy 11-year-old girl presenting an indurated excrescent lesion on the right hemi-tongue with a diagnosis of OCC.
Results: The biopsy showed a proliferation of well-differentiated squamous cells forming crypts with keratin microabscesses inside, reminiscent of rabbit burrows. A diagnosis of SCC suggestive of OCC was established. A subtotal glossectomy with bilateral cervical lymph node removal was performed. A large tumour size OCC (5 cm) was found with an invasion depth of 24 mm (pT4a), without lymph node involvement (N0) or metastases (M0).
The main causes of SCC in children are congenital syndromes (Li-Fraumeni and Fanconi anaemia), immunodeficiency, Epstein-Barr Virus infection and dyskeratosis congenita. However, our patient did not have any of these conditions.
Conclusion: OCC is a rare entity that, although it can occur at any age, typically affects people in their seventh or eighth decade. The aetiology and risk factors associated with OCC remain unknown. OCC is locally aggressive but non-metastasizing, with an excellent prognosis after complete resection.
The differential diagnosis should be made with benign entities such as osteomyelitis, abscesses, odontogenic or epidermal inclusion cysts, depending on their location. Knowing about this entity is essential to avoid delays and/or erroneous diagnosis.

E-PS-20-012
Exencephaly in 23-week-old foetus with placental anomaly
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Background & objectives: Neural tube defects are the most frequent form of congenital central nervous system abnormalities that can lead to several malformations of the nervous system. Incidence varies widely between populations from 1 to 10 per 10,000 births.
Methods: There is still much to learn regarding the underlying mechanisms of neural tube defects and understanding them could help prevent countless cases. In our case report, we discussed a primigravid woman, whose unborn child was lost due to a neural tube defect.
Results: A 20-year-old primigravid woman appealed to our emergency room after her clinical examination in an external clinic showed there was no foetal heartbeat. She was 23 weeks pregnant and she said that her water broke a month ago.
In the examination, foetus was observed as male. The face of the foetus had some abnormal features that may be linked to a diagnosis: flat nasal bridge, low-set ears, micrognathia and long philtrum. Anal opening was observed to be normal. Pathological findings were developmental retardation, encephalocele, exencephaly, hypertelorism, empty sella, and grade III maceration. Two vascular structures (one artery and one vein) were observed in the umbilical cord. Retroplacental hematoma was observed.
Conclusion: The woman in our case is young and primigravid. There is a great deal of genetic contribution in the development of neural tube defects. The recurrence of neural tube defects after an index case being diagnosed is about %2-5. Routine genetic testing and counselling at least to the women who experience such termination in their first pregnancies would be useful for both understanding the genetic basis of neural tube defects and preventing later abortions with couples who have genetic predispositions.

E-PS-20-013
Evaluation of the recurrency risk of basal plate myometrial fibres
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Background & objectives: In May 2020 an expert panel proposed guidelines for classification and reporting of placenta accreta spectrum (PAS) disorders. The basal plate myometrial fibres (BPMF) category is defined for delivered placentas and portend a risk for PAS in a subsequence pregnancy.
Methods: Between 2007 and 2022, 8 cases of placentas with BPMF that had a subsequent pregnancy were found. The slides were reviewed and reclassified. Data regarding maternal age, parity, prior caesarean delivery, and gestational age was collected. The subsequent delivery history was analysed regarding complications that may relate to BPMF recurrence and, when available, the slides were review and reclassified.
Results: At BPMF first occurrence the mean maternal age was 31 years (range: 22-38). Three were primiparous and four had a prior caesarean. Six were term placentas and two were preterm (28 and 33 gestational weeks). BPMF were equally distributed as stage 1 and 2 with a mean foci number of 3 (range: 1-7) and a mean linear extension of 4,4mm (range: 0,4-6,9mm).
The subsequent pregnancy outcomes showed 5 placentas with pathological evaluation, of which 2 had BPMF recurrences, corresponding to index cases stage 2. They were stage 1 and 2, with 1 and 5 foci, the largest with 2,3mm and 7,7mm, respectively. The 3 remaining deliveries had no complications.
Conclusion: In our series the only clinical factor possibly associated with the development of BMPF was a prior caesarean delivery history. The risk of recurrent BPMF in a subsequent pregnancy seems relevant and associated with a prior stage 2 BPMF. More data is needed in order to develop recommendations regarding clinical management of pregnancies with a prior BPMF and the risk of future PAS.

E-PS-20-014

Hamartoma of mature cardiac myocytes: a case report

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Background & objectives: Hamartoma of mature cardiac myocytes is a rare and benign overgrowth of the mature cardiac myocytes and classified in the benign tumour-like lesions of the heart in the 2021 World Health Organization (WHO) Classification.
Methods: We present a 6-year-old child who was found to have a pansystolic murmur during routine controls. On echocardiography, an ill-defined lesion involving the right ventricle and the interventricular septum (IVS) was described. Cardiac MRI revealed a 68x54 mm sized, contrast enhanced solid mass, with hyperdense foci due to increased vascularity. An incisional biopsy was taken from the IVS.
Results: On histopathological assessment of the formalin-fixed paraffin-embedded specimen, myocyte hypertrophy and disorganization were noted. Nuclei of the myocytes were enlarged, hyperchromatic and significantly bizarre. Sarcoplasmic vacuolization was present in some of the myocytes. Minimal fibrosis, chronic inflammation composed of lymphocytes, a prominent vascular proliferation and dilatation in venules were observed in the interstitial regions. Vascular proliferation was enhanced by using CD31 immunohistochemical stain. These findings suggested the diagnosis of hamartoma of mature cardiac myocytes and excision of the lesion was suggested.
Conclusion: There are less than 30 patients in the literature with hamartoma of mature cardiac myocytes. There is no age predilection, but it tends to occur in children and younger adults. Most are asymptomatic and found incidentally. When symptomatic, patients describe chest pain and palpitations. Although these lesions are morphologically benign, they can have fatal results like arrythmias and functional hemodynamic obstruction. Fortunately, surgical excision is very effective, even when it is incomplete, in preventing these consequences.

E-PS-20-015

VACTERL association: report of a case with additional congenital malformations

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Background & objectives: The association of vertebral anomalies, anal atresia, cardiovascular malformations, tracheoesophageal fistula, and renal and limb anomalies is known by the acronym VACTERL. We will describe the autopsy finding of a VACTERL case with associated features not included in the definition.
Methods: We report the autopsy findings of a foetus with VACTERL association, defined as the presence of at least three of the cardinal features. The autopsy followed medical abortion because of multiple malformations detected on routine first-trimester ultrasound.
Results: The 18 weeks-old male foetus was the first pregnancy of healthy non-consanguineous parents. VACTERL diagnosis was based on the collective findings of scoliosis with lumbar hemivertebra, anal atresia, cardiac defects (subaortic CIV and absence of the left pulmonary artery), tracheoesophageal fistula with esophageal atresia, and left renal agenesis.
Besides the diagnostic findings, we also identified other congenital malformations, such as left lung agenesis, intestinal malrotation, and a single umbilical artery.
Craniofacial alterations such as upward slanting palpebral fissures, micrognathia, and low set ears were also present.
Conclusion: When initially described, VACTERL did not include all cardinal features that now integrate the association. Reporting cases is therefore helpful to clarify the prevalence of other associated malformations. Additionally, cases like ours reflect VACTERL´s clinical heterogeneity and could contribute to understanding its pathogenesis.
This case highlights the necessity of having specialized staff for the foetal autopsy capable of identifying and correlating the findings. Also, it shows the crucial role of Pathology in multidisciplinary teams responsible for managing prenatally diagnosed conditions.

E-PS-20-016

The case of congenital ependymoma in a stillborn

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Background & objectives: Ependymomas are a group of neuroectodermal tumours that arise from a heterogeneous population of radial glial cells (RGCs) during embryonic brain development.
Purpose of the study: to demonstrate a rare case of congenital anaplastic ependymoma in a stillborn.
Methods: For histological examination, the walls of the lateral ventricles (the area of the anterior, middle and posterior horn) and the area of the bottom of the 4th ventricle of the brain were taken. The micropreparation was made according to the hematoxylin and eosin, van Gieson method. Additionally, an immunohistochemical method was used with staining for neural markers .
Results: Histologically, a brain tumour was detected, represented by elongated unipolar cells with monomorphic nuclei of a round-oval shape, with a clear pattern of chromatin in the form of small grains. Mitoses occurred in small numbers. The distribution of cells in the tumour tissue was uneven with the formation of characteristic perivascular rosettes (tumour cells were located At a distance from the vessels, there were parallel and chaotically located tumour cells, small cavities and tubules lined with ependymal tumour cells ("epithelial rosettes") along the vessels of the microvasculature.
Conclusion: Tumour of the central nervous system with localization in the IV and lateral ventricles of the brain (ICD/O - 9392/3: anaplastic ependymoma, grade - GIII. IHC study of tumour cells revealed a positive reaction to GFAP, S100 Protein, vimentin, part cells expressed pancytokeratin, and the reaction with EMA on tumour cells is weakly positive. The proliferative activity marker Ki-67 was expressed on 8-10% of tumour cells. Morphological verification of such tumours requires IHC studies to identify the neural immunophenotype and molecular genetics.

E-PS-20-017

Autopsic case of infantile arterial generalized (IAC) calcification in a newborn

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Background & objectives: We present an observation of an autopsy case of IAC caused by a genetic mutation. In a retrospective study of 1000 protocols of pathoanatomical examination of a child's profile, we identified 3 cases of generalized infantile arterial calcification.

Methods: In a retrospective study of 1000 protocols of pathoanatomical examination of a child's profile, we identified 3 cases of generalized infantile arterial calcification: 2 in newborns, 1 - first detected at the age of 1.5 years.
Histological examination of the internal organs of the child after additional decalcification was performed by staining for hematoxylin-eosin, according to Van Gieson and Kason.
Results: A widespread mediacalcinosis of the internal elastic membrane and the muscular layer of the arteries of the elastic and muscular-elastic type was revealed, with the outcome in stenosing atherosclerosis of the vessels of the heart, kidneys, lungs, spleen, adrenal glands, pancreas, intestines, mesentery, thymus, extremities, calcification of the aorta and pulmonary trunk. In the myocardium, a picture of focal hypertrophy and fragmentation of contractile cardiomyocytes of both ventricles of the heart, diffuse small-focal transmural and subendocardial cardiosclerosis with damage to the rhythmogenic zones of the heart and vegetative ganglia of the heart with their hypoganglionism was found; transmural and subendocardial infarcts in the heart of various degrees of prescription.
Conclusion: Molecular genetic study revealed a mutation c.1298A>T in the homozygous state in the ENPP1 gene. The combination of generalized infantile arterial calcification with early manifestations of atherosclerosis of the aorta and large vessels is an extremely unfavourable prognosis for patients, and in 85% of cases ends in death.

E-PS-20-018
The rare case of pathomorphological study of the acardiac monster from monozygotic twins
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Background & objectives: Reverse arterial perfusion syndrome (ROAP, TRAP) or acardial twinning occurs in 0.3–1% of monozygotic twins and in about 1 in 35,000 births. Acardiac twins or a double reverse arterial perfusion (TRAP) sequence is rare but serious.
Methods: 26,783 protocols of pathomorphological examination of placentas for the period from 2015 to 2020 from women who gave birth in the Chuvash Republic were retrospectively evaluated. A case of own pathoanatomical study of an acardiac monster is described, including the stage of autopsy with an assessment of organometric parameters, histological and immunohistochemical examination of its internal organs.
Results: During the study period, there was an increase in multiple pregnancies, of which the number of monochorionic pregnancies increased from 11 cases to 24 cases, bichorionic - from 42 (in 2016) to 77 (in 2020) cases. The number of artery-vein, vein-vein vascular anastomoses in the monochorionic placental disc increased - 3 cases (in 2016), 4 cases (in 2017), 8 cases (in 2018) and 10 cases (in 2020).). The frequency of occurrence of foetus amorphous acardious was 1:6779 (in 2016) and 1:6759 (in 2020), in the remaining years the SMAP syndrome was not detected.
Conclusion: Based on the anamnesis, the results of a pathoanatomical examination of the placenta and an abnormal product of conception, a pathoanatomical diagnosis was formulated: Acardia monster (acardius amorphus) - acardia, anencephaly, anophthalmia, atresia of the oral fissure, aprosopia (facial bones are missing), aplasia of the ribs, bones of the upper limbs, sternum, aplasia of the pelvic bones, failed I period of intestinal rotation, atresia of the large intestine, and anal canal ; absence of pancreas, liver; aplasia of the trachea, lungs.

E-PS-20-020
A rare lysosomal storage disease: galactosialidosis
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Background & objectives: Galactosialidosis is an autosomal recessive disease caused by a defect in protective protein/cathepsin A (PPCA) that results in a deficiency of the lysosomal enzymes beta-galactosidase and alpha-neuraminidase. PPCA is an intralysosomal protein which protects these enzymes from premature proteolytic processing.
Methods: We herein present the case of a female new-born and her 20-year-old mother. At the 24th week of gestation, on a routine second trimester ultrasound, hydrops fetalis was detected. The mother was hospitalized to further study the cause of the hydrops and was submitted to an amniocentesis. At the 30th week of gestation, the new-born was delivered by elective C-section.
Results: The baby was born with an Apgar score of 6/7/8 and 1700 grams. We received a large and heavy placenta with a weight of 505 grams (above the 95th percentile) and measuring 17,5 x 14 x 4 cm, showing only a green discoloration of the foetal surface and membranes. Histologic examination showed enlarged pale villi with striking cytoplasm vacuolization of the syncytiotrophoblast and of the villous stromal cells. PAS, PASd and Alcian Blue stains were all negative in the vacuoles. Immune and infectious causes for the hydrops were excluded and an array comparative genomic hybridization of the amniotic fluid revealed a homozygous mutation in the cathepsin A (CTSA) gene.
Conclusion: The early infantile phenotype of Galactosialidosis usually presents prenatally or within the first 3 months of life with hydrops fetalis, cherry red spots, visceromegaly, psychomotor delay, coarse facies, skeletal dysplasia, and early death in the first few years of life. Although the placenta is often enlarged or hydropic, vacuolisation or inclusions are not always evident. A thorough examination of the placenta is therefore warranted. The now infant is still alive although with many complications of the disease.

E-PS-20-021
An integrated approach to the diagnosis of pancreatic islet cell hyperplasia in a newborn (sectional case)
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Background & objectives: Purpose of the study: to describe a rare case of pancreatic lesions in a newborn and to demonstrate a multistage approach in making a pathoanatomical diagnosis.
Methods: A sectional case of pathoanatomical autopsy of a newborn with congenital pancreatic pathology was studied, including the stage of autopsy with an assessment of organometric and morphometric parameters, microscopic and histochemical, immunohistochemical studies of internal organs and placenta with additional staining of PAS-reaction. A post-mortem biochemical study of the child's blood for the content of glycohemoglobin, acetone and glucose was carried out.
Results: A pathoanatomical examination of the corpse of a newborn girl at the age of 16 days, born at 39-40 weeks. Histologically, there are 8 to 14 islets of Langerhans in each pancreas lobule; hyperplasia of PAS-positive cells, mitoses were not found in them; periductal interstitial inflammation; transformation of the ductal epithelium into pancreatic β-cells. When staining the pancreas using chromogranin A, a pronounced expression of the glycoprotein in neuroendocrine cells is revealed. In the biochemical study of cadaveric blood samples by the columnless ion-exchange method, the content of glycosylated hemoglobin was 1.1%; determination

of glucose in whole blood by enzymatic colorimetric method with deproteinization - the result is negative.
Conclusion: Taking into account the anamnestic and autopsy findings, the child was diagnosed with a congenital pathology of the pancreas - hyperplasia of the islets of Langerhans (nesidioblastosis) with severe metabolic disorders in the form of uncorrectable hypoglycemia, decompensated metabolic acidosis and multiple organ failure. In the genesis of this pathology, one cannot underestimate the role of a generalized intrauterine infection with damage to vital organs, including the pancreas. A post-mortem comprehensive approach to clarify this pathology is necessary.

E-PS-20-022
Congenital interruption of aortic arch (IAA) – a foetal autopsy findings with literature review
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Background & objectives: Interruption of the aortic arch (IAA) is a rare and severe congenital heart disease, characterized by complete anatomic discontinuity between two adjacent segments of the aortic arch. It's associated with other major intracardiac and noncardiac malformations.
Methods: We present two foetal autopsies:
A 33 week old male foetus that died in utero. The mother was 26 years old, without relevant medical history. An echocardiography revealed several heart defects.
A 36-week-old female foetus that also died in utero, the mother was 33 years old, without relevant medical background, the CHD was only diagnose during the autopsy.
Results: The first foetus had anthropometrical parameters compatible with 33-week-old gestation, without external malformations. The heart dissection revealed an interventricular communication and a complete interruption of aorta. Without other malformations. The second foetus had anthropometrical parameters compatible with 36-week-old gestation also without external malformations. The heart dissection revealed an interventricular communication, a third superior ostium in the posterior wall of the pulmonary artery that communicated with the aortic arch. The aorta emerged and branched as usually till the emerging of the left subclavian artery, where, it became atretic and communicate with the pulmonary artery, which turned out to be a systemic vessel into the remaining thorax and abdomen.
Conclusion: Congenital aortic arch interruption is associated with coexisting intracardiac malformations, chromosomal anomalies and is the most common cardiac defect occurring in DiGeorge syndrome.
We presented two cases of congenital interrupted aortic arch with other coexisting congenital heart defects but without association with a noncardiac malformations.

E-PS-20-023
Foetal thrombotic vasculopathy: a case report
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Background & objectives: Foetal thrombotic vasculopathy (FTV) is a rare entity, defined by thrombosis of foetal vessels leading to fibrosis avascular downstream villi. These lesions occur at the end of the second and third trimester with a prevalence around 1%.
Methods: A 28-year-old G2P1A0 pregnant women without any medical disease history. The pregnancy was normal without incident. The patient presented a decrease in active foetal movements. On examination and abdominal ultrasonography, foetal death at 24 weeks was diagnosed. Foetal extraction was done. The foetus and placenta were referred to pathological diagnosis. There is no history of thrombophilia.
Results: Macroscopically, foetal necropsy showed a macerated male foetus weighed 126 g, of an anatomical age of 18 weeks without any external or visceral malformations. The placenta had an oval shape, weighed 62 g, and measured 11,5cm x 8,5cm. The chorioamniotic membrane was translucent. The umbilical cord was hypercoiled with central insertion measuring 45cm. On section, the placental parenchyma had no macroscopically identifiable lesion, and no thrombi of chorionic vessels were visible.
Histological examination of the placenta showed several endoluminal chorionic vessel fibrosis with fibrosis villi and the presence of groups of avascular villi. No visceral thrombi in necropsy specimens were found. These changes were deemed to be consistent with FTV.
Conclusion: FTV diagnosis is histologic, with foetal thrombotic lesions: chorionic vessel thrombi, and avascular fibrosis villi. These changes are similar to those seen in intrauterine foetal demise but are focal rather than diffuse. The underlying aetiology of FTV is unknown though hypercoagulability(thrombophilia) and circulatory stasis implying chorioamnionitis and cord anomalies were reported in the literature.
FTV may be related to adverse perinatal outcomes including foetal death. However, much studies about pathogenesis and criteria diagnosis are desirable to change the unfavourable outcome.

E-PS-21 | E-Posters Pulmonary Pathology

E-PS-21-001
Pseudoprogression mimicking hyperprogressive disease after pembrolizumab treatment in a patient with lung cancer – histopathological diagnostic clues
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Background & objectives: Pseudoprogression after anti-programmed death-1 (PD-1) antibody therapy is a rare phenomenon in patients with non-small cell carcinoma. There is limited information about the pathological mechanism of pseudoprogression, especially regarding the relationship between intratumoral lymphocytes and exacerbation of pulmonary infiltrative shadow.
Methods: The patient, a 51-year-old woman, with a history of smoking was referred to our hospital for abnormal shadow in chest radiograph and shortness of breath. Diagnostic bronchoscopy revealed pulmonary adenocarcinoma with cT4N3M1c, and programmed death-ligand 1 (PD-L1) was expressed in 75 % of the patient's tumour specimen without any driver mutation. Therefore, only pembrolizumab was administered as the first-line treatment.
Results: On the third day after pembrolizumab treatment, there was a sudden appearance of cough and sputum. Chest radiography showed extensive infiltrative shadow in the right lung field. On the eleventh day, the infiltrative shadow exhibited progressive exacerbation with severe symptoms, and

she expectorated massive sputum which keeps the dendritic shape like a bronchus. The histological examination of the sputum demonstrated adenocarcinoma cell clusters with fibrin formation. Immunohistochemically, CD4- or CD8-positive, tumour-infiltrating lymphocytes (TILs) were observed in the clusters of cancer cells as well as around them. The pulmonary adenocarcinoma cells showed immuno-expressions of PD-L1 and TTF-1. After one cycle of pembrolizumab, the symptoms improved, and chest radiography showed remarkable remission.
Conclusion: To our knowledge, this is the first report eliciting the presence of intratumoral lymphocytes within the pulmonary tissues at the maximal timing of pseudoprogression. Notably, it was hard to distinguish pseudoprogression from hyper-progression because of the huge infiltrative shadow and exacerbating respiratory symptoms. Our current case suggested that progressive exacerbation within 4 weeks from the initiation of anti-PD-1 antibody displays the possibility of pseudoprogression, and the radiographic entity of pulmonary exacerbation could be explained by the presence of TILs.
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E-PS-21-002
Uncommon primary pleural mesenchymal tumours: study of seven cases
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Background & objectives: Primary pleural tumours are uncommon but there is a wide variety of them, both benign and malignant, whose accurate diagnosis is very important. This study aimed to review the cases of mesenchymal pleural tumours in two Spanish institutions.
Methods: We searched in two major hospitals for cases of uncommon primary pleural mesenchymal neoplasms over a period of 10 years (2012-2022). Seven cases (3 male and 4 female) were found, with a mean age of 57 years: two benign (schwannoma) and five malignant tumours (4 synovial sarcomas and 1 angiomatoid fibrous histiocytoma). We analysed clinical, histopathological, immunophenotypic and molecular features.
Results: Schwannomas were incidental findings and malignant tumours symptomology were chest pain and dyspnea. Imaging studies of schwannomas and angiomatoid fibrous histiocytoma showed pleural confined tumours, whereas two out of four synovial sarcomas were poorly defined pleuropulmonary pseudocyst masses. Grossly, the latter, were lesions with cystic change, calcification and necrosis. Histologically, benign morphology and S100 positive helped schwannomas diagnoses. On the other hand, synovial sarcomas consisted of dense fascicles of monomorphic spindle cell without epithelial component, all of them positive for CD99, two of them partially for EMA and Bcl2 and 1 positive for TLE-1. FISH studies showed SS78-SSX fusion in synovial sarcomas and EWSR1 gene rearrangement in angiomatoid fibrous histiocytoma.
Conclusion: Primary pleural mesenchymal neoplasms are uncommon. It is important to recognize, as long as its prognosis and therapy could be different from the one of the most common neoplasms of the pleura, metastatic cancers and diffuse malignant mesothelioma. A pleural spindle cell neoplasm has a broad differential diagnosis, and although immunostaining and molecular advances are helpful, the knowledge of these rare lesions and its morphology together with clinical correlation, continue to be the key issue.

E-PS-21-003
Thymomas sub-classification – WHO 5th classification application
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Background & objectives: Thymomas are indolent neoplasias with an incidence of 1.7 cases/million in Europe and surgery is the gold standard for resectable disease.
WHO 5th edition corroborates wide tumoral sampling for searching patterns, as well as surgical margins invasion evaluation.
Methods: We present a Portuguese case series of resectable thymomas concerning surgical biopsies/resections between 2016 and 2020, reviewed and updated according to WHO 5th edition classification. All cases were staged according to current recommendations. Statistical analysis was performed to examine contingency tables and compare medians between groups.
Results: Our sample comprises 48 thymomas corresponding to 25 women and 23 men; patients' median age at diagnosis was 65-years-old.
In this series, 33 thymomas were in stage I by AJCC, 10 of which showed transcapsular microscopic invasion (Masaoka stage II); 45 cases (93.8%) were staged pT1a, and 3 patients presented lung invasion (pT3).
AB thymoma was the most prevalent histopathologic subtype, accounting for 31.3% of all cases, followed by predominantly B1 thymomas (27.1%).
Commonly it was possible to recognize at least two patterns in each tumour, even observed in the same slide, depending on the tumoral sampling.
Conclusion: Surgical resection status was the most important predictor of outcome, achieved in 45 cases (93,8%); 2 cases were R1 and one specimen could not be evaluated due to extensive fragmentation.
Median age of 65-years-old was observed, higher than 58-years-old reported in literature.
All subtypes frequencies were within published data ranges.
Masaoka staging is still the most widely accepted system for clinicians, requiring further studies to establish prognosis impact. Surgical margins status registries were the most important prognostic feature.

E-PS-21-004
Idiopathic lymphoid interstitial pneumonia misdiagnosed as lung tuberculosis. Case report.
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Background & objectives: Idiopathic lymphoid interstitial pneumonia is an interstitial lung disease not associated with autoimmune diseases (Sjogren's syndrome, rheumatoid arthritis) or infections (HIV) unlike typical LIP. We present a case of ILIP, misdiagnosed as tuberculosis, in a young woman, 23 years old.
Methods: A case of ILIP is presented in a 23-year-old female patient who was initially diagnosed with pulmonary tuberculosis. CT showed chronic cavity formation in the first and second segments of the left lung. Resection of the corresponding segments of the lung was performed, followed by grossing and microscopic examinations.

Results: Gross examination showed a fragment of the lung 4x3x0.8 cm. The resection mergin and pleura have no pathological changes. The lung tissue is brown. On a single area of the lung, a subpleural whitish focus with a yellowish centre with the formation of a small cavity is visible. The size of the focus is 0.6x0.5x0.3 cm.
Microscopic examination revealed foci of pneumosclerosis with numerous confluent epithelioid cell granulomas with multinucleated giant cells, without caseous necrosis. There is a microcavity in the centre of granulomatous inflammation. There is also a weak lymphocytic infiltration along the edge of microcavity. The rest of the lung tissue with moderate peribronchial and perivascular fibrosis.
Conclusion: Thus, we correctly diagnosed ILIP, despite the complexities of clinical diagnosis. ILIP is a rare interstitial lung disease affecting more and more people every year. Although the causes of ILIP are still a mystery, it is still possible to diagnose the disease with the help of competent specialists. This case expands our understanding of this disease and gives hope for further adequate diagnosis and treatment.

E-PS-21-006
Monophasic synovial sarcoma involving the lung
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Background & objectives: Synovial Sarcoma (SS) is an entity of deep soft tissue usually. This tumour generally occurs in the extremities and near the knee joint and mostly in young patients, but in elderly individual, too. Rarely, can involve the trunk, mediastinum and various viscera.
Methods: A 62-year old male presented to our hospital with progressive dyspnea and persistent cough. CT scan revealed a lobulated mass nodule with distinct borders in the upper lobe of the right lung, measuring 7X6,4X3 cm in dimensions. The mass was extending to the thoracic wall and invading two ribs, the 3rd and the 4th ribs. The patient underwent surgery.
Results: Microscopic examination of the mass, revealed a mesenchymal tumour, consisted of uniform blue spindle cells or sheets of spindle cells often arranged in kind of fascicles. Sometimes the fascicles were more swirly or they intersected at sharp angles and had a herring-bone appearance, Dilated branching vessels or hemangiopericytic pattern of vessels were seen. Poorly differentiated areas with rounded or spindled cells showing severe nuclear atypia, high mitotic activity, extensive areas of necrosis and some haemorrhages were also present. Immunohistochemistry was performed: EMA focal (+), Pankeratin (-),TLE-1 (+), CD34 (-), STAT6 (-), S-100 patchy (+). The differential diagnosis was between Synovial Sarcoma and Solitary Fibrous Tumour or Malignant Peripreral Nerve Sheath Tumour.
Conclusion: Synovial Sarcoma, Solitary Fibrous Tumour and Malignant Peripreral Nerve Sheath Tumour can all stain with TLE-1.Synovial Sarcoma is a translocation-associated sarcoma, characterized by a translocation t(X;18)(p11;q11) between chomosome 18 that leads to a formation of a SS18-SSX fusion gene. The genes involved are the SS18 gene (Synovial Sarcoma 18) that fuses with a partner gene called SSX. There are three different SSX genes: SSX1 and SSX2 being the most common genes and rarely SSX4. Molecular testing confirmed the above diagnosis.

E-PS-21-007
Pulmonary benign metastasizing leiomyomatosis presented by severe dyspnea; report of a case
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Background & objectives: Pulmonary benign metastasizing leiomyomatosis (PBML) is a rare entity with unclear pathogenesis, characterized by pulmonary metastases of benign leiomyoma with history of surgical intervention for uterine leiomyoma. We report a case of PBML referred to our centre presenting with dyspnea.
Methods: A 32-year-old woman, presented with severe dyspnea. A chest computed tomography revealed bilateral innumerable cannon ball lung nodules, the largest was 11.8 cm, raising the suspicion of metastatic disease. There was a past surgical history of myomectomy for a uterine leiomyoma at the age of 28. Ultrasound-guided biopsy was taken from the largest nodule.
Results: Radiologically the nodules were variable-sized and sometimes amalgamated, varying in distribution between being pleural-based, parenchymal, and hilar-based. The largest was seen encasing the right lower lobar branch of the pulmonary artery. Histopathologically, the pulmonary nodule consisted of intersecting fascicles, made by bland smooth muscle cells demonstrating sparse mitosis and absence of necrosis. Immunohistochemical staining for smooth muscle actin (SMA), Caldesmon and Desmin were strongly positive. CD117 and HMB45 were negative. Positive immunoreactivity for oestrogen receptor (ER) and progesterone receptor (PR) were identified. Another ultrasound-guided biopsy from a nodule in the contralateral lung revealed the same findings. The final diagnosis was PBML.
Conclusion: Pulmonary Benign Metastasizing Leiomyomatosis is a very rare condition, clonally derived from uterine leiomyomas. Despite the metastatic designation, PBMLs usually follow an indolent course with progression reported in few cases. PBML should be however considered in symptomatic women of reproductive age with a history of uterine leiomyoma who present with multiple pulmonary nodules and respiratory symptoms. The patient received chemotherapy and luteinizing hormone-releasing hormone analog with notale clinical improvement.

E-PS-21-008
The expression of DNA methyltransferases in non-small cell lung cancer
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Background & objectives: DNA methylation, mediated by DNA methyltransferases (DNMTs), regulates gene transcription and genome stability. DNMT inhibitors have shown efficacy in solid tumours. The aim of this study was to analyse the expression of DNMTs in non-small cell lung cancer (NSCLC).
Methods: Tissue blocks from the lobectomy specimens of 115 patients with NSCLC (50 with squamous cell carcinoma-SqCC and 65 with adenocarcinoma-AdCa) were retrieved from the University Hospital of Patras. The expression of DNMT1, DNMT3A, DNMT3B and DNMT3L was studied using immunohistochemistry. Nuclear (nu) and cytoplasmic (cyt) staining in neoplastic and non-neoplastic (bronchial) cells was evaluated. Results were correlated with pathologic parameters.
Results: DNMT1_nu+cyt, DNMT3A_nu and DNMT3L_nu expression was higher in neoplastic cells, whereas DNMT3A_cyt expression was higher in non-neoplastic cells. DNMT3A_cyt and DNMT3L_nu expression was higher in AdCa compared to SqCC, whereas nuclear DNMT3A and DNMT3B expression was higher in SqCC. DNMT1_cyt expression was increased in poorly compared

to highly/moderately differentiated SqCC (p=0.020) and was decreased in N1 compared to N0 SqCC. In AdCa, DNMT3L_nu expression was higher in N0 compared to N1 carcinomas. No difference in DNMTs expression was seen in correlation with the predominant pattern of AdCas (solid vs. acinar vs. lepidic vs. papillary).
Conclusion: Increased nuclear expression of DNMTs in neoplastic cells may account for DNA hypermethylation in various tumour suppressor genes seen in NSCLC. A heterogenous role for the different DNMTs is depicted in the different histologic types of NSCLC. Our results highlight a potential role for DNMT1 in SqCC and DNMT3L in AdCa. Further studies are needed to validate these results and analyse the functional role of DNMTs in the development and progression of NSCLC, in light of their potential therapeutic targeting.

E-PS-21-009
Pulmonary metastasis of extraskeletal myxoid chondrosarcoma as a first sign of a disease
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Background & objectives: Extraskeletal myxoid chondrosarcoma (EMC) is an ultra-rare sarcoma subtype arised in the deep soft tissue. EMC demonstrate a strong tendency for local recurrence (37 - 48%) and metastatic disease (50%), usually pulmonary.
Methods: A 59-year-old patient was hospitalized to clarify the aetiology of an 2,5 cm infiltrative lesion of the right lung discovered on on the thorax CT scan. The patient was operated when video-assisted thoracoscopy with atypical resection of the lower right lobe was performed.
Results: Rapid on site evaluation imprint cytology, as well as frozen section pathohistological finding indicated a soft tissue tumour. FFPE section analysis revealed tumour tissue with multinodular architecture with increased tumour cellularity at the periphery of the lobules. Stroma consisted of abundant myxoid and chondromyxoid matrix into which tumour cells were immersed. Tumour cells were uniform, oval to round nuclei, eosinophilic and vacuolated cytoplasm, organized into bands and small clusters. Nucleoli were small, but conspicuous. Occasional mitotic figures were identified. Foci of intralesional haemorrhages were frequently seen in various proportions. Immunohistochemical analysis showed tumour positivity for S-100 and neuron specific enolase (NSE) markers.
Conclusion: Based on the histological findings and the results of immunohistochemical analysis, final diagnosis correspond to EMC, when the existence of a primary soft tissue tumour of other site was suspected. A detailed examination of the patient revealed a 4 cm tumour in the gluteal region that pathohistologically and immunohistochemically corresponded to EMC. Follow-up showed asymptomatic patient with no recurrence or new metastatic disease.

E-PS-21-010
Epithelioid malignant mesothelioma with signet ring cells of the pleura - a case report
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Background & objectives: Malignant mesothelioma (MM) is an uncommon and very aggressive tumour arising from the mesothelial cells lining serous cavities. Signet ring cell epithelioid MM is an extremely rare subtype. Morphological subtypes of epithelioid mesothelioma seem to have an impact on outcome.
Methods: A 64-year-old male patient admitted to our hospital for chest pain. A CT scan was performed and a lesion of the right pleural membranes was found.
The patient underwent a right thoracoscopy for pleural biopsies.
Results: Multiple fragments of tumour tissue measuring 3X2X0,3cm were sent to the pathology department. The histopathologic examination revealed pleural infiltration by epithelioid cells with signet ring morphology and adenomatoid features in a solid and nested pattern. The neoplastic cells had eosinophilic cytoplasm with cytoplasmic vacuoles, marked nuclear atypia, increased mitotic activity with 12mitoses /2mm2. No necrosis was observed.
The immunohistochemical examination demonstrated the mesothelial origin of the neoplastic cells, with positivity for WT1, calretinin, D2-40 and CK7. Negative immunoreactivity was observed for TTF1, CDX2, CK20, GATA-3 and PSAP.
The diagnosis of high-grade diffuse epithelioid MM with signet-ring cell features, was made.
Conclusion: Although epithelioid malignant mesothelioma is found in up to 80% of patients with MM, signet ring cell epithelioid MM is extremely rare, Architectural pattern, cytological features and nuclear grading have prognostic and diagnostic value.
Median overall survival for this subtype is 15 months and the major diagnostic challenge is ruling out metastasis from other tumours featuring signet-ring cell morphology.

E-PS-21-011
Foetal Adenocarcinoma of the lung - a case report
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Background & objectives: Foetal adenocarcinoma of the lung (FLAC) is a rare tumour, representing only 0.1%–0.5% of all pulmonary neoplasms.
Approximately 25%–40% of patients are asymptomatic at presentation, most of them with incidental findings.
Methods: Male 54-years-old patient presented to our hospital for productive cough. On imaging a tumour was detected in the right lung, 2.5cm in diameter, as well multiple lesions in other regions of the right lung, up to 1cm in great diameter, without lymph node invasion. Right pneumonectomy was performed. One mediastinal lymph node and one subcarinal lymph node were also removed.
Results: Histolopathological examination revealed a tumour featuring a high-grade conventional adenocarcinoma (positive for CK7, TTF-1, Napsin A, AFP, Glypican-3) with a >50% component showing morphology of an adenocarcinoma with clear cytoplasm, large vesicular nuclei, severe nuclear atypia, prominent nucleoli, supranuclear/ subnuclear vacuoles and frequent mitoses (positive only for CK7). Histochemical stains PAS and PAS-D showed glycogen production in the vacuoles.
A diagnosis of high-grade foetal adenocarcinoma with negative lymph nodes was made.
The neoplasm penetrated beyond the external elastic layer of the visceral pleura (PL1).
One lesion from other pulmonary regions was an hamartoma with a small focus of foetal carcinoma, while the rest of them represented fibrous lesions with calcifications.
Conclusion: Based on histopathological features and clinical course FLAC has been categorized into low-grade (L-FLAC) and high-grade (H-FLAC) subtypes. L-FLAC shows low nuclear atypia,

prominent morule formation and has a pure pattern. H-FLAC typically presents ≥50% foetal morphology and is often associated with other conventional types of lung adenocarcinoma. These tumours have different molecular profile from conventional lung adenocarcinomas, with very low frequency of KRAS and EGFR mutations.

E-PS-21-012

A complex case of pulmonary tuberculosis with superimposed chronic cavitary pulmonary aspergillosis: clinical, cytopathological, and genetic contributions

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Background & objectives: We aim to present the clinical, cytopathological, and genetic evaluation of a 52-year-old female patient with a history of treated post-primary tuberculosis (TB), cavitary pulmonary aspergillosis, and bronchiectasis that presents with unexpected hemoptysis, fever, and weight loss.
Methods: Chest high-resolution computed tomography (HRCT), and respiratory evaluations with additional bronchoscopy procedure for bronchial aspiration (BA), and bronchoalveolar lavage (BAL) were performed. Complete cytological evaluation with May–Grünwald–Giemsa (MGG) stain and special fungal stains were done on cytology smears from the BAL fluid. The pathological examination led to a genetics centre referral, in order to understand the precise diagnosis.
Results: HRCT showed a massive cavitary lesion with an intracavitary mass in the RUL extending to the superior segment of the RLL, suggestive of a mycetoma. BA microbiological analysis on GeneXpert MTB/RIF was negative for TB. BAL cytology was remarkable for neutrophil granulocytosis and MGG stained thin fungal hyphae, with septation, and acute-angle (45°), or dichotomous branching, confirmed with Periodic acid–Schiff (PAS) and Grocott stain. Serologically, A. fumigatus IgG antibodies were positive. NGS on whole blood for suspicion of Common Variable Immunodeficiency (CVID) or Granulomatous disease showed 2 variants of uncertain significance (VUS) in the CFTR gene, that could be associated with cystic fibrosis, or a predisposition for bronchiectasis.
Conclusion: We present the complex case of respiratory disease, treated post-primary TB with reactivation, with initially complicated pulmonary aspergilloma, that presently showed an active superimposed chronic cavitary pulmonary aspergillosis (CCPA). Genetic evaluation for a patient with recurrent and unexplained pulmonary infections could be helpful in the differential diagnosis. Underlying genetic causes in adults could predispose them to chronic infections and pulmonary disease entities. Finally, complex cases should include a multidisciplinary approach for the ultimate benefit of the patient.

E-PS-21-015

Sclerosing pulmonary pneumocytoma (SSP) (sclerosing haemangioma)

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Background & objectives: SSP is a generally benign entity, although it has been associated with metastasis to the regional nodes. This is a case seen mostly in adult female patients. Usually, is being detected as a small, solitary nodule on the chest x-ray film.
Methods: A 67 year-old female patient was referred to our hospital with a history of cough and breathlessness. Chest x-ray showed a peripheral, well circumscribed, unique, pulmonary nodule, measuring 1,8 cm in diameter. Wedge biopsy was performed.
Results: Grossly, the nodule was solid, tan or yellowish with occasionally cystic areas. Histologically, two cell types were distinguished among very sclerotic stroma. Hobnail looking cuboidal cells, resembling type II pneumocytes and arranging in a papillary and/or solid pattern with foci of haemorrhages [TTF(+), EMA (+), CK7(+), SpBpr (+)] and a second component, which is more prominent, that is round - oval, small stroma cells, that they grow in sheet like pattern, with fine chromatin nucleoli and sparse nuclear grooving [TTF-1(+), CK7 focally (+),CD34(-), S-100(-), CD1a(-), Langherin (-)] .The double cell population and the absence of atypia helps us in the differential diagnosis with malignant entities as a papillary adenocarcinoma
Conclusion: Sclerosing pulmonary pneumocytoma (SSP) is a rare benign lession, usually seen in females. Based on double cell population and the hyalinized stroma, the pathologists should always keep in mind this entity especially in frozen sections or on a small biopsy , since a benign diagnosis of SSP can make a great difference to the patient and to the surgent, and avoid a lobectomy.

E-PS-21-016

Rare cases of coexistence of non-hodgkin lymphomas with lung carcinomas

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Background & objectives: During long term follow-up 1.2% of oncological patients may experience new unexpected primary malignant neoplasms. Synchronous occurrence of lung carcinoma and lymphoma is very rare, less than 1%.
We present two cases of non-Hodgkin B lymphomas coexisting with lung carcinomas.
Methods: A Case: A 68-year-old male with a past medical history of splenic marginal zone lymphoma (MZL), presented with right lung tumour and right thoracic wall lesion. He underwent right pneumonectomy and partial thoracic wall resection.
B case: A 77-year-old male with a medical history of MZL presented with left lung tumour. The patient underwent left pneumonectomy.
Results: A case: Microscopically, the lung tumour was lung adenocarcinoma, intermediate grade. The thoracic wall lesion was a lymphocytic proliferation consisting of medium size cells with abundant immunoblasts. Immunohistochemical examination revealed a CD20(+), BSAP(+), BCL2(+), BCL6(+), κ- light chain (+), phenotype. A diagnosis of a diffuse large B cell lymphoma (DLBCL), probably a transformation of the splenic MZL, coexisting with a primary lung adenocarcinoma was suggested.
B case: Microscopically, the tumour was a non-keratinizing squamous cell carcinoma, high grade with a coexisting small cell atypical lymphocytic proliferation. Immunohistochemical examination revealed a CD20(+), BSAP(+), BCL2(+), CD3(-), BCL6(-), cyc-d1(-) phenotype. A diagnosis of non-keratinizing squamous cell lung carcinoma coexisting with MZL was suggested.
Conclusion: Coexistence of lung carcinomas and lymphomas is very rare. Such co-occurrence has been documented on rare occasions and includes Hodgkin and non-Hodgkin lymphomas (mainly B- cell origin lymphomas: DLBCL, MCL, MALT) in combination with different

types of lung carcinomas. It is probably caused by genetic predilection, immunosuppression, infectious agents such as EBV and radiotherapy/chemotherapy given for the treatment of the first neoplasm. The therapeutic management of such a combination requires separate consideration of the different coexisting neoplasms.

E-PS-21-017

Adenosquamous carcinoma of the lung - biopsy: MET exon 14 skipping mutation

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Background & objectives: MET exon14 skipping mutation (METex14) occurs in 3% in NSCLCs and coexists rarely with other oncogenic drivers. METex14/MET amplifications indicate poor prognosis.
Recent approvals of capmatinib and tepotinib for metastatic NSCL METex14 depend on this biomarker in metastatic NSCLC.
Methods: A 85-years-old woman - adenosquamous carcinoma of the lung (CK5.6/TTF1/ CK7 expression).
NGS and Idylla techniques - FFPE macrodissected tumoral tissue with 40% representation of tumoral cells from biopsy.
Oncomine Precision Assay (Thermo Fisher Scientific, Waltham, MA, USA) was performed according to manufacturer's instruction by Next Generation Sequencing (NGS) in Genexus. Idylla™ Gene Fusion Assay performed according to manufacturer's instruction.
Results: METex14 was detected by both techniques, Idylla and NGS.
NGS made it possible to identify C.3082G>C;p.(Asp1028His) mutation with 35% allelic frequency.
The two most clinically relevant MET alterations are METex14 mutations as the primary oncogenic driver and MET amplification as acquired resistance to tyrosine kinase inhibitors (TKI).
Conclusion: MET-TKIs, capmatinib and tepotinib, for NSCLCs with METex14 marked a new step of MET-targeted therapy.
METex14 alterations - point mutations/deletions/insertions/complex mutations lead to MET receptor decreased degradation, followed by MET signalling and tumourigenesis. The evaluation methods for METex14 include differential MET exon expression, quantitative reverse transcription polymerase chain reaction (qRT-PCR) or direct RNA sequencing.
METex14 are the most commonly reported oncogenic MET mutations. MET mutations should be tested in the context of targeted therapy together with other molecular markers.

E-PS-21-018

Swyer James MacLeod Syndrome: an uncommon phenomenon

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Background & objectives: Swyer James MacLeod syndrome is an uncommon lung condition characterized by pulmonary vascular reduction and alveolar hyperdistention, with or without bronchiectasis. The radiographic appearance of a single pulmonary lobe or the entire lung is characteristic of this rare lung ailment.
Methods: We present the case of a 43-year-old man who presented himself to the ER for: low fever and chills, dyspnea, wheezes, pleuritic chest pain and cough.
The patient was examined in the ER with EKG, blood tests, a chest radiograph, and a CT scan. The patient's respiratory function was then assessed using spirometry in the internal medicine department.
Results: Chest radiograph: right apico-axillary-laterothoracic hypertransparency that causes passive collapse of the underlying parenchyma - pneumothorax. Cord enlarged by lengthening and accentuating the convexity of the lower left arch. Left pulmonary hilum with increased density and projection area; accentuation of peribronchovascular and basal interstitial pattern.
CT scan: multiple bubbles of emphysema, some with thick walls, at the level of both lung fields, predominantly on the right, the largest of about 9 / 8.5 cm. Right pulmonary sequestration of 9/4 cm. Moderately enlarged heart. Without pleural or pericardial effusions. Nonspecific mediastinal infracentimetric lymphadenopathy. Without changes in bone structure with oncological visa at the level of the scanned segment.
Conclusion: The cause of Swyer James MacLeod syndrome is not completely understood. It seems that the initial abnormality occurs in the distal bronchi after an infection during early childhood.
The clinic and the totality of the investigations carried out plead for the following diagnoses: Swyer James MacLeod syndrome (right pulmonary artery hypoplasia, bilateral diffuse pulmonary emphysema, bilateral bronchiectasis), moderate pulmonary hypertension. Treatment is conservative and preventative, focused primarily on controlling pulmonary infections. Inhaled corticosteroids may have a limited role in treatment.

E-PS-21-019

A contemporary view at the pulmonary collapse

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Background & objectives: Atelectasis or pulmonary collapse is a common complication after upper body radiation therapy and may be clinically noticeable in up to 30% of cases. However, early morphological changes in the lung tissue are not well clear.
Methods: We researched early phases of pulmonary collapse in rats through radiation exposure in a dose of 12Gy on their chest. We took samples of lung tissue and bronchoalveolar washing (BAL) on the various days after exposure. We used electron microscopy (Zeiss-EVO-LS1), routine histology technique, morphometric analysis (Aperio AT2 and NIH ImageJ), and detected the surfactant level in BAL in our study.
Results: We detected initial signs of lung tissue damage by electron microscopy in 24 hours after exposure. Type-II pneumocytes appeared swelling and lamellar bodies looked damaged. Then we observed the significant decline of surfactant level on day-3. We identified atelectasis by light microscopy on the seventh day after the beginning the experiment. In most cases areas of pulmonary collapse were localized in the subpleural regions. Atelectatic area had been doubled in two weeks by adding intrapulmonary regions. By statistical analysis we revealed that changes of thickness of alveolar wall, square, and smooth muscle shortening of the airway had no significant role in the pulmonary collapse on day-7 but dominated on day-14.
Conclusion: In this research we found out that destruction of type II pneumocytes and following reducing the total amount of surfactant level played a key role in pulmonary collapse on day 7. However, the morphometric changes in lung tissue such as

thickness of alveolar wall and smooth muscle shortening of airway contributed in the subsequent enlargement of atelectatic areas.

E-PS-21-020

The relevance of ACE2, TMPRSS2, and androgen receptor expression in male vulnerability to COVID-19 infection

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Background & objectives: A sex-disparity in the outcome of patients with severe SARS-CoV-2 infection was observed during the pandemic's first wave. We analyse these differences by evaluating the immunohistochemical expressions of ACE2, TMPRSS2 and Androgen Receptor(AR) within three groups: autoptic, asymptomatic and control.
Methods: Patients have been divided as follows:
- autoptic, died of SARS-CoV-2 infection,
- asymptomatic, secondarily testing positive for SARS-CoV-2
- control, detected pre-pandemic.

Each lung sample underwent histological and immunohistochemical evaluation for AR, TMPRSS2, ERG, and ACE2. SARS-CoV-2 detection was performed through PCR and ISH. All clinical data were extracted from the patients' medical records.
Results: ACE2 immunohistochemical expression resulted strong and membranous in the autoptic group. In both asymptomatic and control groups, the overall expression of ACE2, TMPRSS2 and AR was low or absent regardless of the gender or the PCR positivity for SARS-CoV-2. Immunohistochemical staining of TMPRSS2 was negative in all patients of all three groups, but interestingly the only 3 positive cases with an high expression also showed high levels of immunoreactivity for ACE2, confirming its role in the cleavage of ACE2.
AR expression in autoptic patients was difficult to assess, due to the postmortem lytic process. In addition to that, TMPRSS2:ERG gene fusion was not detected through immunohistochemical analysis in all samples.
Conclusion: This study confirms the critical function of ACE2 in the viral pathogenicity of human tissues. A higher expression of ACE2 receptor, regardless of gender, was showed in the patients who died of SARS-CoV-2 complicated infection. Three autoptic patients showed also a stronger immunoreactivity for TMPRSS2 associated to a stronger expression of ACE2, confirming its role in the cleavage and activation of ACE2.

E-PS-21-021

Prognostic impact of PD-L1 and PD-L2 expression in malignant pleural mesothelioma

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Background & objectives: Malignant pleural mesothelioma(MPM) is an aggressive malignant neoplasm associated with poor prognosis. Programmed cell death ligand 1,2 (PD-L1,PD-L2) are important immune checkpoints that can inhibit T cell activation. Here we investigated the prognostic value of PD-L1 and PD-L2 in MPM.
Methods: 91 patients who had a histological diagnosis of MPM made on pleural resection or biopsy at Baskent University between 2006 and 2022 were included in the study. Clinical and histopathological data were collected from medical records. Tumour samples were analysed by immunohistochemistry for percentage of PD-L1 and PD-L2. The results were correlated with clinical parameters and outcome.
Results: The mean age at diagnosis was 62±12.1 (range 35-87). The majority of patients were male (58, 63.7%). Most common histological type was epithelioid (77,84.6%), followed by sarcomatoid (10, 11%) and biphasic type (4, 4.4%). Among 91 patients, 36 (39.6%) had positive PD-L1 expression and 55 (60.4%) had negative. On the other hand, forty-seven (51,6%) patients were PD-L2 positive and 44 (48,4%) were PD-L2 negative. The positive rate of PD-L1 and PD-L2 in epithelioid MPM was 33,7% and 50.6%, while the rates were 71,4% and 85,7 respectively in sarcomatoid and biphasic MPM ($p<0.05$). The median survival time of PD-L1 negative patients were 2,2 times longer than PD-L1 positive ones.
Conclusion: The positive rate of PD-L1 and PD-L2 were found to be significantly higher in sarcomatoid and biphasic types MPM, compared to epithelioid type. Also positive PD-L1 expression was found to be associated with lower median survival, while no significant association was found between PD-L2 and patient survival. Therefore, PD-L1 expression levels can be used to determine the prognosis of MPM patients, which may lead to treatment options for PD-L1.

E-PS-21-022

Performance of AmoyDx HER2 mutation detection kit and AmoyDx Pan Lung Cancer PCR Panel for detection of common HER2 and/or EGFR mutations

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Background & objectives: HER2/ERBB2 mutations occur in 2-4% of NSCLC patients and clinical trials are assessing the efficacy of anti-HER2-antibody drug conjugate (ADC) therapeutics in NSCLC patients with HER2 mutations. We assessed the performance of two PCR assays for detection of HER2 mutations.
Methods: Formalin-fixed paraffin-embedded (FFPE) cell blocks containing HER2 indel A775_G776insYVMA or single nucleotide variant V777L were generated at allele frequencies of 0%, 1%, 5% or 50%. Performance of AmoyDx HER2 Mutation Detection Kit was assessed for both mutations (n=3). AmoyDx Pan Lung Cancer PCR Panel was assessed for A775_G776insYVMA in cell blocks (n=3) and EGFR exon19 deletions/L858R in 4 NSCLC samples.
Results: AmoyDx HER2 Mutation Detection Kit demonstrated a 100% pass rate at the recommended 10ng input DNA for HER2 A775_G776insYVMA and V777L at allele frequency ≥1%, with no false positives. The AmoyDx Pan Lung Cancer PCR Panel does not cover the V777L mutation but showed similar accuracy and sensitivity to the HER2 Mutation Detection Kit for the A775_G776insYVMA indel, providing the correct amount of input DNA was used. The panel also correctly identified EGFR exon19 deletions and L858R mutations in the four clinical samples tested.
Conclusion: Detection of rare mutations require sensitive and specific diagnostic assays. AmoyDx HER2 Mutation Detection Kit demonstrated robust performance in detecting representative HER2 indel and single nucleotide variant mutations at low frequencies. The AmoyDx Pan Lung Cancer PCR assay showed similarly robust and sensitive detection of the common HER2 A775_G776insYVMA indel in addition to detecting clinically relevant EGFR mutations.
Funding: This study is funded by AstraZeneca Pharmaceuticals. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

E-PS-21-023

Granulomatous lymphocytic interstitial lung disease (GLILD) in CTLA-4 deficiency: case report

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Background & objectives: CTLA-4 deficiency was first described in 2014, currently categorized as immune dysregulation, with autoimmunity, immunodeficiency and lymphoid destruction (IDAIL). One of the main clinical manifestations is granulomatous interstitial lymphocytic lung disease (GLILD).
Methods: We report a case of 20 year old woman with history of multiple lymphadenopathies, ITP, hemophagocytic syndrome, and recurrent infections. A CT scan was performed due to fever and poor condition, showing bilateral pulmonary nodules, suggestive of lymphomatoid granulomatosis, deciding to perform lung biopsies.
Results: Histologic examination revealed the presence of lymphoid infiltrates with peribronchiolar distribution, forming nodular lymphoid hyperplasic aggregates (in pseudotumor pattern lesions). Abundant histiocytes and multinucleated giant cells without granulomas nor Masson bodies were found. Immunohistochemical stains confirm mixed lymphoid cellularity B (CD20+) and T (CD3), predominantly CD4+ T-cells. EBER was negative. Microbiological elements were not identified with histochemical techniques and the study of IGH and TCR-gene rearrangements was polyclonal. Given the clinical suspicion of immunodeficiency, Sanger sequencing was completed, detecting a heterozygous mutation in the germ line of the CTLA4 gene. Final diagnosis was granulomatous lymphocytic interstitial lung disease (GLILD).
Conclusion: GLILD is characterized by the presence of noncaseating granulomas and recurrent lymphoid. However, there is no consensus regarding diagnostic and therapeutic criteria, with a wide spectrum of histological patterns with or without the presence of granuloma being described in the literature, including diffuse and nodular lymphoid hyperplasia, non-follicular lymphoid aggregates, follicular bronchiolitis and organizing pneumonia, like the ones we can observe in our case. As it is a non-specific entity with low reproducibility, the term of GLILD is not recommended.

E-PS-21-024

Correlation of programmed Death Ligand-1 (PD-L1) expression with clinicopathological features in lung carcinoma in a Macedonian population

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Background & objectives: : Programmed death ligand 1(PD-L1) expression is a predictive biomarker of the success of immunotherapy for lung cancer(LC) patients, yet its prognostic significance remains unclear. This study aims to determine the relationship between PD-L1 expression and clinicopathological features in LCpatients.
Methods: The expression of PD-L1 protein in 63 surgically resected LC was evaluated by immunohistochemistry using clone 22C3 (Agilent, DAKO). The PD-L1 expression was determined by the Tumour Proportion Score (TPS) and classified as negative (TPS<1%), low-expression (TPS=1-49%) and high-expression (TPS≥50%). The statistical significance of the correlation between the clinicopathological features and PD-L1 expression was determined by chi-square test.
Results: Our study group comprised 52 male and 11 female patients, with a median age of 64 (range,33-77). 33(52.4%) of the patients exhibited PD-L1 immuno-positivity, with 23(36%) of them having a low-expression and 10(16.6%) having a high-expression of PD-L1. PD-L1 immunopositivity was significantly higher in squamous cell carcinomas (18/25;72%) compared to adenocarcinomas (10/25;40%)(p=0.023). PD-L1 expression was associated with the smoking status (p=0.0086) for the patients smoking more than 10 cigarettes per day, as well as with a higher level (>30%) of stromal tumour infiltrate lymphocytes (TILs) (p=0.049). No correlation was found between PD-L1 expression and other parameters such as patients' age, gender, stage, tumour status, grade, lymph nodal status and lymphovascular invasion.
Conclusion: This is the first local study to describe PD-L1 expression and its association with clinicopathological features in LC patients. Our preliminary results indicate that the PD-L1 protein expression in LC is associated with some clinicopathological characteristics, such as smoking status, histological type (higher expression in squamous cell carcinomas) and higher level of TILs. Further research should be performed to clarify the clinical relevance and prognostic significance of PD-L1 in LC patients.

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E-PS-22-001

Infantile fibrosarcoma with EGFR rearrangement

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Background & objectives: Infantile fibrosarcoma is a malignant fibroblastic tumour of infants. It is a rapidly growing, locally aggressive tumour characterized by t(12;15)(p13;q25), resulting ETV6-NTRK3 fusion gene. Rare fusion partners of NTRK3 or NTRK1 fusions were also reported in infantile fibrosarcoma.
Methods: RNA was isolated from 50-µm formalin fixed paraffin embedded tissues for Archer™ FusionPlex Sarcoma v2 targeted sequencing assay (ArcherDX, USA). This assay targeted fusions / mutations in 63 genes. A prepared library was sequenced using Illumina (NextSeq 500 Illumina Inc.) Next-Generation Sequencer (NGS). Produced libraries were analysed for presence of relevant fusion with the Archer analysis software version 6.2.7.
Results: A three-month-old female patient presented with a mass in the right axillary region. CT examination revealed a soft tissue mass in axillary lodge, with invasion to ribs. Gross examination revealed a firm, tumour with the largest diameter of 5,4 cm. Microscopic examination revealed a hypercellular tumour composed of fascicles of relatively uniform spindle cells with mild atypia with frequent mitotic figures. Focal herringbone pattern was present. NGS showed no mutations in NTRK gene while rearrangement was observed in EGFR gene (fusion between exon 18 and exon 25). The case was reported as infantile sarcoma with EGFR mutation. This mutation has been reported only in four patients of infantile fibrosarcoma previously.
Conclusion: Infantile fibrosarcoma is a tumour classically known to be characterized by ETV6-NTRK3 gene fusion, may have other genetic mutations including EGFR gene rearrangement. Prognostic significance of this new mutation is yet unknown.

E-PS-22-002

Extraskeletal myxoid chondrosarcoma with novel NR4A3-PRRC1 fusion

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Background & objectives: Extraskeletal myxoid chondrosarcoma is a malignant mesenchymal tumour of uncertain differentiation. These tumours are characterized by frequent fusion of the NR4A3 gene with the EWSR1. Extraskeletal chondrosarcoma involving NR4A3-PRRC1 fusion has not been reported before in the literature.
Methods: Following routine formaline fixation and tissue processing, parafin embedded tissues were used for immunohistochemical analysis and next generation sequencing. RNA based "Archer® FusionPlex Sarcoma v2" (ArcherDX, Inc) was used to analyse fusions and point mutations in 63 different genes, including NR4A3, in next generation analysis.
Results: A 35 years-old female patient presented with weakness in the right leg. On physical examination, a swelling of 8x6cm was detected in the right gluteal region. MRI scan revealed a 156x136mm mass surrounding the right iliac crest and an additional 38x35mm mass at the T12 vertebra level extending into the dural distance. Trucut biopsy revealed a myxoid chondrosarcoma. After 5 cycles of chemotherapy, the patient underwent a right hemipelvectomy. Microscopic examination of the resected specimen revealed cords-formed by uniform cells in a myxoid background. NSE and CD117 focally positive in immunohistochemical study. NGS showed fusion of PRRC1 gene with NR4A3 gene. The case was reported as extraskeletal myxoid chondrosarcoma.
Conclusion: Along with the previously reported frequent EWSR1 and other rare fusion partners, PRRC1 can also be a fusion partner of NR4A3 in extraskeletal myxoid chondrosarcoma.

E-PS-22-003
Two separate metastatic tumours synchronized in the lung: alveolar soft part sarcoma and leiomyosarcoma
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Background & objectives: The lung is a site of widespread metastatic disease, one of the common sites of soft tissue sarcomas. We presented our case because the presence of simultaneous alveolar soft part sarcoma and leimyosarcoma metastases in the lung is rare in the literature.
Methods: A 34-year-old female patient was admitted to the pulmonary medicine outpatient clinic due to hemoptysis. Multiple lesions were observed in the lower lobes of both lungs in thorax computed tomography. A total of 4 tumoral foci with two different morphologies were observed in the resection.
Results: Microscopically, two of these tumours were spindle cell and the other two were epithelioid with clear/granular cytoplasm. An epithelioid-like tumoral infiltrate with nodules, alveolar pattern, some clear and some pink granular cytoplasm was observed in the parenchyma. In the immunohistochemical and histochemical examination, the epithelioid tumour was positive for TFE-3, and cytoplasmic granular material was positive with PAS and D-PAS. In patient's history he had been diagnosed with alveolar soft part sarcoma in the left thigh 12 years ago and leimyosarcoma 2 years ago nearthe first lesion. Examination of morphological and IHC profile, it was reported as leiomyosarcoma and alveolar soft part sarcoma metastasis.
Conclusion: In the presence of multiple tumours in the lung, it should be kept in mind that there may be different primary tumours or tumour metastases, and all foci should be evaluated.

E-PS-22-004
Atypical spindle cell lipomatous tumour: a rare case report
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Background & objectives: Atypical Spindle Cell / Pleomorphic Lipomatous Tumour (ASCLT) are recently described neoplasms, characterized by lipoma-like appearance but with atypical and spindle cell histological features. They resemble pleomorphic lipoma, but are larger in size and with a broader anatomic distribution.
Methods: We present a 34-year-old woman with a 10 x 8 x 3 cm mass in the right knee. A biopsy reported a lipomatous lesion and a resection was performed. Microscopy showed a lipomatous neoplasm with predominantly well-differentiated adipocytic component, and a smaller proportion of lipoblasts and pleomorphic cells in a fibrous matrix. No necrosis and mitosis were identified.
Results: Tumour cells were positive for CD34 and S100, and negative for MDM2 and CDK4. The case was sent for consultation to Dr Christopher Fletcher, supporting the diagnosis of ASCLT. No recurrence has been reported so far.
ASCLT mostly occur in middle-aged adults with a slight male preference and a variable size (up to 28 cm). They have an indolent behaviour with no or very low rate of local recurrence, and no risk for dedifferentiation or metastasis.
Conclusion: It is crucial to differentiate ASCLT from other lipomatous lesions such as atypical lipomatous tumour/well-differentiated liposarcoma, pleomorphic liposarcoma and low-grade dedifferentiated liposarcoma, due to their frequent recurrence and capacity to metastasize. Immunohistochemistry helps in this situation, since even though weak and focal expression of MDM2 and CDK4 may be seen, they do not occur in combination. Also, loss of Rb expression is frequently seen (79%).

E-PS-22-005
Development of epithelioid angiosarcoma as a rare and new complication of retained surgical gauze
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Background & objectives: Epithelioid angiosarcoma (EA) is a rare endothelial cell malignancy. The aetiology is unknown and association with implanted foreign bodies is very rare. We present a case of a 47 year-old woman with EA developed on a long-standing retained surgical gauze.
Methods: A 47 year old woman with history of surgery for an ovarian cyst 19 years ago, presented with abdominal pain and constipation for at least 4 days. Clinical examination revealed diffuse tenderness and pain in the lower abdomen and peritoneal signs. Computed tomography (CT) showed a pelvic mass with necrosis and fecaloid content, multiple liver masses and extensive abdominal lymphadenopathy.
Results: Gross examination of the surgical specimen revealed 40 cm bowel loops with extensive adhesions, centred by a solid mass of a 10x8 cm tumour with a central cystic cavity containing surprisingly a macerated surgical gauze. A fragment of greater omentum with multiple nodules and a mesenteric lymph node were also received.
Histologic examination revealed extensive necrosis with a proliferation of pleomorphic epithelioid cells in a storiform pattern and irregular sheets, focally forming anastomosing channels containing few red blood cells. The gauze fibres were also observed. At immunohistochemical examination, the tumour cells showed diffuse expression of CD31, ERG and D2-40. The omentum and the mesenteric lymph node presented also metastatic deposits.

Conclusion: Although the presence of implanted foreign materials such as: Dacron and plastic grafts, steel plate and bone wax, retained for prolonged periods is known to be very rarely in association with the development of angiosarcomas, there are no cases reported in the literature regarding the association with retained surgical gauzes. Like all the abdominal textilomas, a highly aggressive cancer arising around a retained surgical gauze is a serious medico-legal problem leading to a poor prognosis and a high mortality rate.

E-PS-22-006

Malignant solitary fibrous tumour of the mandibula: a case report

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Background & objectives: Solitary fibrous tumour (SFT) is a rare neoplasm arising most commonly in the thoracic cavity. Those occurring in the head and neck represent 10% of all cases. We report a case of malignant SFT of the mandibula with literature review.
Methods: We report a case of a 73-year-old man, presented with a history of swelling in his lower jaw for the past six months. On examination, the mass was painless, nodular, measuring 1,5cm in great dimension and expanding to the soft palate. The computed tomography scan revealed a destructive soft tissue mass. The patient underwent a surgical resection.
Results: Macroscopically, the mass was firm, lobulated and gray-white in colour with haemorrhage. Microscopically, the tumour consisted of spindle cells arranged in long, interlacing fascicles and whorls. The cells showed moderate atypia. The mitotic range was 6 mitoses / 10 high power fields. The cells grew around dilated, branched thin walled vessels. The surgical margins were positive. Immunohistochemically, tumour cells stained positive for CD34 and STAT6. They were negative for PS-100, β-catenin, Erg, smooth-muscle actin and desmin. Based on these histological and immunopathological findings, the diagnosis of malignant solitary fibrous tumour of the mandibula was made.
Conclusion: The diagnosis of malignant solitary fibrous tumour of the mandibula might be challenging for pathologists. Awareness of it's occurrence in this atypical site is crucial in order to prevent confusion with other spindle cells neoplasms.

E-PS-22-007

Osteosarcoma of the bone in patient with primary hyperparathyroidism

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Background & objectives: The association between osteosarcoma and hyperparathyroidism is very rare, only 10 cases have been reported in the literature to our knowledge. Herein we report an uncommon case of osteosarcoma in women with primary hyperparathyroidism.
Methods: A 39-year-old female presented to our hospital for a subtrochanteric femoral fracture through a lytic lesion. She underwent resection of the bone lesion and the fracture was immobilised. The surgical specimen was analysed in the department of pathology.
Results: The pathological examination showed an undifferentiated tumour composed of pleomorphic, epithelioid and spindle cells producing osteoid matrix in a lace-like arrangement. The diagnosis of high-grade osteoblastic osteosarcoma was made. Afterwards, she was referred to an oncologist for chemotherapy. In the meantime, she experienced a remarkable remission of left hip pain. A computed tomography scan was performed and showed osteolytic lesions of left hip and L5 vertebra.
Therefore, the patient was managed by an endocrinologist who discovered primary hyperparathyroidism with an elevated serum calcium and parathyroid hormone.
Conclusion: The patient in the present report provides one more clinicopathological example of an osteosarcoma in association with hyperparathyroidism.
In light of the increased use of parathormone for treating osteoporosis, we should be aware of possible coexistence between these two conditions.

E-PS-22-009

Anastomosing haemangioma: report of 3 cases with molecular and immunohistochemical studies

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Background & objectives: Anastomosing haemangioma (AH) is a newly described distinct vascular neoplasm that, histologically, may confuse with well-differentiated angiosarcoma (AS) for those who are unfamiliar with this rare entity.
Methods: We aimed to identify the molecular genetic differences between AHs and ASs by carrying out immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS) analysis from three AHs and three ASs
Results: Immunohistochemically, all six cases showed positivity for cyclin D1 and pERK. The three AH case results were weakly positive for p53 and MIB-1, whereas the IHCs for HIF-1α were negative in all three cases. Those three cases of angiosarcoma revealed strong, diffuse positivity for p53, 50-70% for MIB-1, and multifocal, moderate-to-strong HIF-1α expression. To further clarify the difference of p53 expression, we carried out a FISH which revealed polysomy in all three AS cases; genetic aberration was absent in the AH group. In one AH case, the GNA11 c.627G>T; p.Q209H nucleotide variant was detected.
Conclusion: We demonstrated three cases of anastomosing haemangiomas with one case harbouring a GNA11 mutation which, besides conforming to its clonal nature, also serves as an important molecular signature to distinguish AHs from well-differentiated ASs. We also addressed the potential molecular differences between these two entities. Nevertheless, due to the small sample size and its rarity, a larger scale study is needed to elucidate this issue. Clinical information and histology features still serve as the gold standard for the correct diagnosis.

E-PS-22-010

MKL2 rearranged chondroid lipoma - a pitfall in frozen section interpretation

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Background & objectives: Chondroid lipomas are rare benign adipocytic tumours that can be mistaken for more aggressive

mesenchymal tumours including liposarcoma, extraskeletal myxoid chondroscarcoma and myoepithelial tumours. Understanding its pseudosarcomatous histological features and appropriate clinico-radiological correlation is key to avoiding this diagnostic pitfall.
Methods: We describe the morphological features of a rare, extensively cystic chondroid lipoma occurring in the trunk of an adult female on frozen and paraffin sections. In addition, we performed molecular analysis using anchored multiplex PCR assay (Archer FusionPlex® Sarcoma Panel) for gene fusion detection.
Results: Incisional biopsy submitted for frozen section interpretation showed sheets and cords of large, round to epithelioid tumour cells with vacuolated cytoplasm and nuclear atypia, initially worrisome for an aggressive tumour. The presence of lipoblasts, myxohyaline matrix and mature adipocytes were better appreciated on subsequent paraffin sections. Gene fusion analysis revealed the presence of a C11orf95 (exon 5) – MKL2 (exon 12) gene rearrangement, further supporting the diagnosis of a chondroid lipoma.
Conclusion: Frozen section evaluation of chondroid lipomas present diagnostic challenges. Detection of MKL2 gene fusion is helpful in distinguishing this rare pseudosarcomatous entity from its morphologic differentials and in guiding appropriate patient management.

E-PS-22-011
Post-denosumab morphological and immunohistochemical findings in giant cell tumour of bone – is there a risk for malignancy?
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Background & objectives: Giant cell tumour of bone (GCT) is an intermediate and locally aggressive neoplasm. This study aims to emphasize the morphological and immunohistochemical features in a GCT treated with denosumab for 12 months and to assess the risk of malignant transformation.
Methods: We present the case of a 22-year-old female, admitted to "Foisor" Orthopedics Hospital for pain in the left knee. Imaging examination revealed a lytic lesion with benign features expanding the proximal epiphysis of the left fibula and a biopsy was taken. The histopathologic aspects were those of a giant cell tumour of bone associated with a secondary aneurysmal bone component.
Results: Covid-19 restrictions in the hospital led to prolonged neoadjuvant treatment with denosumab (15 doses). After one year of therapy, en-bloc resection of the proximal fibula was performed. Grossly, the tumour was well-defined and measured 6.5/4/2.5 cm. Extensive microscopic examination of the surgical specimen showed complete disappearance of the osteoclastic component, new bone formation, and a densely cellular stromal-like proliferation of spindle cells with osteoid deposition. The tumour was completely circumscribed by new bone formation. The neoplastic stromal-like cells were positive for MDM2 immunohistochemical stain. The correlation between the histopathologic features and immunohistochemical results made us conclude that a low-grade osteosarcoma has developed under the long-term treatment with denosumab.
Conclusion: Malignant transformation occurring in denosumab-treated GCT of bone has rarely been reported. In our case, the osteosarcoma-like features observed on the surgical specimen and the MDM2 immunohistochemical positivity confirmed the malignancy. Therefore, close follow-up was recommended. This case report is consistent with observations made by other authors who have definitively found malignant transformation after long-term treatment with denosumab in GCT.

E-PS-22-012
Hemosiderotic fibrolipomatous tumour - a potential diagnostic pitfall
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Background & objectives: Hemosiderotic fibrolipomatous tumour is an locally aggressive uncommon soft tissue neoplasm which commonly occurs in the ankle and foot. Morphologic data suggests that hemosiderotic fibrolipomatous tumour is related to yet another rare, locally aggressive tumour: pleomorphic hyalinizing angiectatic tumour.
Methods: A 61-year-old man was referred to the Department of Orthopaedics and Traumatology of the University Emergency Hospital in Bucharest for a volumetric increase of a left foot mass which in recent months had begun to cause functional discomfort. After thorough investigation it was decided to opt for surgical option. The surgical sample was sent the Pathology Department for histopathological assessment.
Results: Microscopically, the lesion was composted of clusters of variably sized, thick walled blood vessels surrounded by a thick rim hyalin. The tumour cells were arranged in poorly defined fascicles with abudent brown pigment (hemosiderin), and nuclear pseudo inclusions. At the periphery, the lesion showed a pseudo infiltrative pattern of growth. There were not cytological atypia and mitotic figures but bizarre-looking tumour cells and rare multinucleated cells have been observed. From the immunohistochemical point of view, we found that the lesion was strongly and diffusely positive for CD34, while it was negative for SOX10, Calretinin and S-100. Few tumour cells were calponin positive. The proliferation index (evalued by KI67) was <3%.
Conclusion: To conclude, though rare, it is important for the histopathologists to be aware and recognize this unusual entity and distinguish it from other pigmented spindle cell lesions. Long term follow-up is recommended as rare cases of malignant transformations were reported.

E-PS-22-013
Cervico-thoracic lipoblastoma of the adult: a case report of a rare entity
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Background & objectives: Lipoblastoma is a rare benign neoplasm predominantly diagnosed during infancy. It can remain asymptomatic for years and be a casual finding in the adult, causing diagnostic pitfalls. We present a case of an adult lipoblastoma with an unusual presentation.
Methods: A 34 year-old male presented with a neck and upper thorax mass. Ultrasound examination revealed a solid heterogeneous tumour. The specimen was a well-defined encapsulated nodule. Cut surface was solid, lobulated, yellow-white and myxoid. Tumour consisted of adipocytes in different stages of maturation, with atypia, lipoblasts and branching vessels. Stroma was myxoid. Neoplastic cells were CD34+, p16+ and MDM2-.
Results: Lipoblastoma is a benign neoplasm of embryonal white fat predominantly localized in the trunk and the extremities. In

our case, lipoblastoma was found in the anterior neck and into the upper thorax.
Grossly, cut surface is soft, lobulated, yellow-white and can show myxoid areas, cystic spaces or well-delimited fat nodules. Histologically, lipoblastoma consists of lobules of adipocytes in various stages of maturation. Adipocytes are positive for CD34 and S100 whereas mesenchymal cells stain for desmin. These cells are separated by fibrous septa and plexiform vessels. Several genetic alterations have been described. Molecular analysis didn't demonstrate PLAG gene rearrangement, but this is not mandatory for the diagnosis of lipoblastoma.
Conclusion: Lipoblastoma is a benign neoplasm of embryonal white fat of which rare cases have been reported in adults. Lipoblastoma can cause diagnostic pitfalls with other adipocytic neoplasms (particulary myxoid liposarcoma), requiring molecular studies for diagnostic confirmation. Detection of molecular alterations such as PLAG gene rearrangement are desirable but not mandatory. Prognosis after excision is excellent, with no risk of metastasization and low rates of recurrence after complete excision.

E-PS-22-014
Epithelioid Hemangioendothelioma: a case series of a rare vascular neoplasm
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Background & objectives: Epithelioid Hemangioendothelioma (EHE) is an extremely rare malignant proliferation, accounting for <1% of all the vascular tumours. It's locally-aggressive, affecting one or multiple organs (such as soft tissues, lung, liver and bones). Herein, we aim to describe its clinico-pathological features.
Methods: All cases of EHE diagnosed during a 24 year-period (1997-2021) and compiled by the Cancer Registry of the Center of Tunisia, which provided clinical data and pathological reports. 4 cases were included in our study.
Results: Three patients were male and one was a female. Patients' age ranged from 38 to 67 years (mean age 47). The female patient had Von Recklinghausen disease. Two tumours , identified by imaging studies , developed in the vertebral bones, one in the lung and one in soft tissue of the thumb. Histologically, they displayed strands, cords and solid nests of epithelioid cells with vacuolated cytoplasm and mild nuclear atypia, set in a myxo-hyaline stroma . In 2 cases, nuclei showed promiment nucleoli, marked atypia and high mitotic-rate. The lung EHE displayed micro-calcifications and focal necrosis. In Immunochemistry, tumour cells expressed CD34 in all cases and ERG in one case.
Conclusion: EHE is a rare aggressive tumour, with unknown pathogenesis, that is often misdiagnosed because of its atypical presentation and morphological similarities with other epithelioid vascular neoplasms, such as haemangiomas and angiosarcomas. When available, the molecular profile of these tumours should be explored as almost all EHEs harbour WWTR1-CAMTA1 or YAP1-TFE3 fusions; and identifying these alterations may, in the future, benefit the patients with immunotherapy and selective inhibitors treatments.

E-PS-22-015
Giant cell tumour of the bone under treatment with Denosumab
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Background & objectives: Giant cell tumour (GCT) of the bone is a locally aggressive and rarely metastasizing neoplasm. Some cases may be treated with denosumab and may exhibit important histological changes. Our goal was to characterize the histology of GCT after denosumab treatment.
Methods: A retrospective study included 5 patients submitted to neoadjuvant treatment with denosumab between 2019 and 2022 and subsequent surgical resection.
Clinical and pathological parameters, including the duration of treatment, gender, age at diagnosis, location, histologic description and percentage of tumour response were recorded.
Results: According to location, tumour developed in the radius (in two), fibula (1), vertebral column (1) and acetabulum (1). The median duration of the treatment was 7 months (4-9 months). Tumour response was complete in four, and in one, up to 40% of tumour was viable. After a median follow-up of 5 months (1-22 months) one patient relapsed, 7 months after surgery.
Histologically, there was replacement of the tumour by woven bone and fibrous tissue was found between the trabeculae. There was a general decrease in the number of giant cells, which were absent in four patients. In one the histological appearance mimetized an osteosarcoma.
Conclusion: Denosumab inhibits RANKL and thus reduces bone lysis, which helps control the disease.
This drug induces morphological changes in bone histology that ought to be recognized in order to make the differential diagnosis with its mimics, which include malignant lesions.

E-PS-22-016
Lipoma arborescens of the knee: report of a rare case
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Background & objectives: Lipoma arborescens (LA) is a relatively unusual benign intra-articular lesion, with only few cases reported in the literature. The knee is the most commonly involved joint. The aim of the study is to discuss clinicopathological features of this rare disease.
Methods: An 80-year-old Women was presented to the department of orthopaedic surgery with gradually increasing pain and swelling in the left knee.
Results: On examination, there was a diffuse swelling of the left knee, which was doughy in consistency with limited range of movements. There was no history of trauma. An arthrotomy was performed with a total synovectomy and resection of hypertrophic multilobulated synovial tissue. The histological examination revealed hypertrophic villous projections of fat lined by synovial cells with variable scattered inflammatory cells. The postoperative period was uneventful and the patient had good range of movements over left knee without recurrence in 3 months of follow up period.
Conclusion: LA is a lipomatous proliferation of subsynovial connective tissue often associated with chronic joint disease. It affects typically adults aged in fourth and fifth decades of life. It commonly involves the knee. The aetiology remains unclear. Recent work has shown that this adipocytic proliferation lacks HMGA2 overexpression. Recurrence is uncommon. LA should always be considered

in the spectrum of differential diagnosis when clinicians deal with chronic swelling of a joint. MRI findings are characteristic. Early synovectomy offers best functional outcome.

E-PS-22-017

The cytotoxic properties of graphene derivatives and 2-metoxyestradiol / graphene compound on human melanoma (A375) and osteosarcoma (143B) cell lines

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Background & objectives: The objective was to assess and confirm cytotoxic properties of graphene derivatives (graphene oxide and reduced graphene oxide) and compound of 17-beta-estradiol metabolite with graphene on selected malignant cell lines with safety for the nonmalignant cells (fibroblasts).
Methods: Human melanoma (A375), osteosarcoma (143B) and fibroblast (HDF) cell lines were incubated with 2-metoxyestradiol, graphene oxide and reduced graphene oxide solutions for 24 hours. Cytotoxicity as well as cell viability and proliferation potential was later assessed through MTT test and under microscope with additional immunostaining. Oxidative stress was analysed by Elisa assay.
Results: Our in vitro studies confirm the stronger cytotoxic activity of 2-methoxyestradiol-graphene complexes compared to 2-methoxyestradiol sole activity against melanoma and osteosarcoma cells in analysed samples.
The results are promising as we observe a selective cytotoxic effect on tumour cells, in contrast to normotypic fibroblast cells which remain intact. These results also show that there is no toxic effect in relation to healthy tissues, and that it is toxic in relation to neoplastic tissues, which is the goal of all oncological therapies. The mechanism of action of 2-metoxyestradiol/ graphene oxide is related to the induction of oxidative stress in malignant cells.
Conclusion: Researchers are looking for substances efficient against malignancies and safe for the nonmalignant tissue. Cytotoxic properties of 2-methoxyestradiol and graphene derivatives were confirmed in separate in vitro tests against various malignancies. Graphene may be used as a carrier for other antineoplasmatic drugs, improves bioavailability, but its nanocomposite tags are also suitable for bioimaging and confirmation of drug delivery to the affected tissue as well. It all gives opportunity to use this type of materials in bio-nanotechnology and personalized therapy.

E-PS-22-018

Spindle cell lipoma with ossification mimicking atypical lipomatous tumour/well-differentiated liposarcoma

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Background & objectives: Spindle cell lipoma (SCL) is a subtype of lipoma, but the characteristics of SCL are observed in both lipomatous and non-lipomatous tumours. In this article, we present a case of SCL with ossification mimicking atypical lipomatous tumours/well-differentiated liposarcomas (ALTs/WDLs).
Methods: A 56-year-old man presented with a mass on the lateral side of the right distal thigh. Plain radiography showed a soft tissue mass with a high fat density and ossification. MRI revealed high and diffuse low signals on a T1-weighted sagittal image, heterogeneous low signal on T2 short tau inversion recovery images, and diffuse enhancement on gadolinium-enhanced T1-weighted axial image.
Results: Needle biopsy findings suggested lipoma or ALT/WDL. Marginal resection with tumour capsule intact was performed. Macroscopically, the tumour was 8x5.5x2 cm in size, and the edge of the tumour was white owing to ossification. Histologically, the tumour consisted of ropey collagen bundles containing mature adipocytes and spindle cells without atypia. There was no fat necrosis in the tumour or malignant osteoid tissue in the ossified region. Immunohistochemistry showed positive staining for CD34, heterogeneous deficiency in spindle cell, and positive staining in ossified region for RB1, and negative staining for MDM2 and CDK4. Fluorescence in-situ hybridization showed no amplification of MDM2. One year after surgery, the patient remains free of recurrence.
Conclusion: We described an atypical case of SCL with ossification. SCLs are pathologically classified as classic, fibrous, myxoid, low-fat, pseudoangiomatous or fat-rich, and all 6 classes have various signals on MRI. Furthermore, differentiating between ALT/WDL and SCL is challenging and clinically important. Consideration of all aspects of SCLs, including their clinical, imaging, histopathological, and especially immunochemical features, is the most comprehensive means of ensuring an accurate diagnosis. (Int J Surg Pathol, in press)
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E-PS-22-019

A unique presentation of IgG4 related disease mimicking soft tissue tumour

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Background & objectives: Although IgG4 related disease (IgG4-RD) was originally reported in sclerosing pancreatitis associated with increased serum IgG4, IgG4-RD was recognized as systemic disease because of involvement of multiple organs. Soft tissue involvement is rare and diagnostically challenging.
Methods: A 60-year-old male noticed a mass in the abdomen one year ago and visited our hospital. The mass was 6 cm and located subcutaneously in the lower abdomen. The mass did not change in size for a year, but surgical resection of the tumour was performed for definitive diagnosis. He had no medical history including autoimmune disease and abdominal surgery.
Results: Magnetic resonance imaging study revealed intermediate intensity on T1WI, heterogeneously high to intermediate intensity on T2WI without fat component. Macroscopically, the tumour was well-demarcated, and the inside of tumour was yellow with heterogenous myxoid change. Histologically, the mass was fibromyxoid tumour with mild lymphocytic and plasmacytic infiltrate with focal aggregates of lymphocytes. Most of the sparsely infiltrated cells were plasma cells, which were positive for IgG and IgG4, and IgG4/IgG ratio exceeded 80%. No light chain restriction was identified by kappa/lambda stains. The patient is free of recurrence or metastasis after the surgery at least for two years.
Conclusion: Because of the rare location of IgG4-RD and absence of systemic symptoms, the diagnosis is challenging clinically and histologically. Especially soft tissue sarcoma and haematological malignancy must be carefully ruled out to reach IgG4-RD. Our case shows a unique clinical presentation and histopathological

diagnosis is crucial in the definitive diagnosis. The present case will expand our knowledge and spectrum of IgG4 related disease.
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E-PS-22-020

Extraskeletal osteosarcoma with preceding myositis ossificans

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Background & objectives: Extraskeletal osteosarcoma (EO) is an unusual soft tissue sarcoma characterized by production of bone matrix by neoplastic cells and is diagnosed by pathological identification of osteogenic differentiation. Benign osteoid in EO, which is rarely encountered, may pose a diagnostic problem.
Methods: A 21-year-old man had swelling of left knee. Magnetic resonance imaging showed a 39 mm mass in the posterolateral side of the left tibia, and it had peripheral mineralization and uneven enhancement with cystic change. The tumour was located outside of the bone. Because myositis ossificans (MO) or hematoma with malignancy potential was clinically suspected, wide resection was performed.
Results: Macroscopically, the mass was 4.5 x 4 x 2.5 cm in size and greyish to brown in colour. Cut section showed multiple cystic lesions with solid components. Histopathologically, the solid components demonstrated diffuse proliferation of pleomorphic tumour cells with frequent mitoses, and abundant osteoclast-like giant cells were admixed. Tumour cells focally formed osteoid without other specific differentiation. Cystic lesions showed aneurysmal bone cyst-like change. In the periphery was mature bone tissue with bland osteocytes and focally non-malignant woven bone and fibroblasts, compatible with zonation. Immunohistochemically MDM2, CDK4, and H3.3 G34W were all negative. Fluorescence in situ hybridization demonstrated split signals of the *USP6* gene.
Conclusion: EO with preceding MO was collectively diagnosed by pathological findings. The patient had no local recurrence and metastasis, 16 months after surgery. To the best of our knowledge, this is the first case cytogenetically confirmed as well as the second case with distinct zonation of MO. Although the exact pathogenesis is to be elucidated, *USP6* rearrangement might promote the understanding of the aetiology as well as the diagnosis of EO with preceding MO.
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E-PS-22-021

Indolent multinodular synovial sarcoma of foot with peripheral nerve extension

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Background & objectives: Synovial sarcoma is a malignant spindle cell sarcoma which could involve virtually any location. Its clinical presentation and/or course is diverse and could mimic other tumours. Herein we report a unique case of multinodular synovial sarcoma with nerve extension.
Methods: A 33-year-old female had a painful nodule in the dorsum of her left foot four years ago. She came to our hospital three years ago, but was followed up because her symptom was mild, and the tumour was suspected of Schwannoma. However, her pain was gradually increased and excisional biopsy with wide resection was performed. She had no medical history.
Results: Magnetic resonance imaging revealed heterogenous high to intermediate intensity on T2WI, intermediate intensity on T1WI. Continuous beaded masses showed heterogenous enhancement. Biopsy was taken from the clinically recognized two different lesions, both of which showed similar histology; diffuse proliferation of spindle cells and cellularity differed between the nodules. Immunohistochemically, CD34 (-), Desmin (-), SOX10 weak (+), S100 (-), H3K27me3 (+, retained), STAT6 (-), SMA (-), beta catenin (-). Fluorescence in situ hybridization (FISH) demonstrated split signals of the *SS18* gene. Additional wide resection specimen included peripheral nerve involvement. The patient had no recurrence and metastasis after the surgery at least for one year.
Conclusion: Diagnosis of synovial sarcoma is rather straightforward, but the atypical presentation is characteristic masquerading benign tumours such as Schwannoma. Our case is considered to be multinodular synovial sarcoma with peripheral nerve extension due to intranerve involvement. It might also be histologically diagnosed as malignant peripheral nerve sheath tumour when FISH is not available or differential diagnosis of synovial sarcoma is not in mind. The present case will expand the clinical diversity of synovial sarcoma.
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E-PS-22-022

RREB1–MKL2 fusion in a mesenchymal spindle cell tumour of the heart: ectomesenchymal chondromyxoid tumour in an atypical location or new entity?

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Background & objectives: Primary cardiac tumours are rare. Approximately 90% are benign (mostly myxomas). We report the first case of a spindle cell mesenchymal tumour harbouring a fusion of RREB1-MKL2 located in the right atrium.
Methods: A 58 year-old woman with dyspnea on exertion since 3 months and history of frequent travels was found to have a 9 cm cystic mass in the right atrium on chest CT-scan. An hydatid cyst was clinically suspected and the lesion was resected. The case was referred to our centre for second opinion.
Results: Microscopic examination of the fragmented specimen showed a proliferation of monotonous spindle cells with pale eosinophilic cytoplasm, indistinct borders, ovoid nuclei with open chromatin and variable cellularity. Hypercellular areas were storiform with a fibrous background and thick collagen bands. Hypocellular areas showed haphazardly arranged cells in a loose myxoid matrix. The mitotic activity was low (< 1 mitose/10 high-power fields). Immunohistochemically, the cells were diffusely positive for S100 protein and INSM1, weakly positive for panTRK, while negative for AE1/AE3, EMA, SMA, SOX10, desmin, CD34, oestrogen receptors, HMB45, GFAP, MDM2 and CD56. Targeted RNA sequencing identified a fusion between RREB1 (exon 8) and MKL2 (exon 11).

Conclusion: Fusion of RREB1-MKL2 has been recently described in 90% of ectomesenchymal chondromyxoid tumour (ECMT), all located in the tongue, in a biphenotypic « oropharyngeal » sarcoma, a biphenotypic sinonasal sarcoma and two mesenchymal tumours involving the superior mediastinum. Our unusual case broadened the spectrum of mesenchymal tumours associated with RREB1-MKL2 fusion. Despite sharing some similarities with the phenotype of ECMT, whether our case represents extra-glossal ECMT remains uncertain.

E-PS-22-023

Immature teratoma of the thigh (mixed germ cell tumour). A case report

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Background & objectives: Immature teratomas (I.T.), also known as mixed germ cell tumours, are mainly found in gonadal sites, e.g., testis. Extragonadal location site is rare (2-5%) and mostly found to arise in the sacrococcygeal location (50-70%), or the gonads (30-40%).
Methods: A 67-year-old male patient, admitted to our hospital with a progressively enlarging painless mid right thigh mass, with no other reported complaints. Examination revealed a compact firm elastic tumour measuring 4X4 cm, without erythema or tenderness. On imaging, a regular heterogeneous mass was noted, and it was decided to be excised, with wide surgical borders.
Results: Macroscopically, we received a wide excised skin specimen with a whitish brownish in hue and of elastic firm in consistency neoplasm. Histologically, the tumour was mainly composed of immature neuroepithelial elements, with immature cartilage and other immature elements of ecto- and endodermic lineage. Immunohistochemical studies were performed with the following antibodies: S100, which highlighted the neural elements, CK 8/18, which revealed the epithelial elements, WT1 was negative, a-fetoprotein and OCT4, were found to be focally reactive, chromogranine and synaptophysin were also found to be focal, desmin was reported as negative and the mitotic index ki67 varied 20-50%. The tumour was totally excised and had pushing borders.
Conclusion: I.T. in the soft tissue of the thigh is extremely rare with only a few similar cases reported, in this very unlikely location, which one can only explain as a disturbed migration of the primordial germ cells along the urogenital ridge, and hence undergoing a microenvironment related transformation. In our patient we suggested metastasis from a germ cell tumour of the testis, but further imaging examination (testicular US) didn't reveal any gonadal association, or any other lesions elsewhere

E-PS-22-024

Immunohistochemical marker VEGF in the diagnosis of periodontal diseases

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Background & objectives: The purpose of the study was to determine the effect of a chronic inflammatory-destructive process in periodontal tissues on the expression of vascular endothelial growth factor (VEGF), on the process of angiogenesis in the connective tissue structures of the gums.
Methods: The study group - 20 patients (age 20-36 years) burdened with chronic generalized periodontitis of mild/moderate severity. Biopsy material (pieces of gum) was obtained during closed curettage after tooth extraction for orthopaedic and orthodontic reasons. VEGF was detected by an indirect immunohistochemical method. Polyclonal rabit anti-VEGF antibodies (ThermoScientific, USA) were used as the first antibodies.
Results: In patients with chronic generalized periodontitis, VEGF-immunopositive vessels were found in the lamina propria with strong and moderate reactions to VEGF. In the own plate of patients in the control group (patients with intact periodontium who applied for planned dental care), most of the studied pieces of gum contained vessels that were not stained when reacting to VEGF.
Conclusion: Expression of the VEGF protein reaches lower levels in healthy connective tissue areas of the gums and increases in periodontitis. VEGF is involved in the initiation and progression of inflammation from gingivitis to periodontitis. This is due to the ability to stimulate vasodilation and angiogenesis in an inflammatory response. Vascular endothelial growth factor (VEGF) has mitogenic activity, regulates endothelial cell migration, vascular permeability, and induces the expression of anti-apoptotic proteins in these cells.

E-PS-22-025

Pseudoanaplastic/symplastic giant cell tumour of bone: case report and review of the literature

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Background & objectives: Giant cell tumour of bone (GCTB) is a locally aggressive primary bone neoplasm. Unusually, conventional GCTB displays marked nuclear atypia designated as pseudoanaplastic change mimicking primary sarcoma or sarcomatous transformation. We aim to analyse clinico-pathological aspects of this entity.
Methods: We present a case of pseudoanaplastic GCTB in a 14-year old girl, without significant pathological history. This case was diagnosed in our institution in 2022.
Results: Patient presented with a mass of the upper extremity of the humerus. Magnetic resonance imaging showed infiltrating haemorrhagic lesion measuring 16x12x11cm, suggesting a telangiectatic osteosarcoma. There were no distant localisations on computed-tomographic scan. Grossly, the specimen consisted of numerous loose haemorrhagic fragments of soft tissue and bone. Histological examination revealed areas of typical GCTB composed of uniformly distributed giant cells interspersed with mononuclear cells exhibiting moderate atypia. Other areas demonstrated scattered foci of cells displaying marked nuclear pleomorphism. Mitotic figures were numerous. Prominent haemorrhage and necrosis were seen in these areas. Positivity for H3G34 made the diagnosis of pseudoanaplastic GCTB.
Patient was treated using curettage.
Conclusion: Pseudoanaplastic GCTB is an uncommon variant of a conventional GCTB which can mimic primary sarcoma or sarcomatous transformation. Distinction from a sarcomatous lesion is made by a careful analysis of all factors suggestive of malignancy.

E-PS-22-026

An unusual presacral mass: case report

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Background & objectives: Myelolipoma is a rare disease and benign mesenchymal tumour, usually found in the adrenal region. Extra adrenal sites of this entity are uncommon. Patient are usually asymptomatic. We aim to analyse clinical and pathological aspects of a presacral myelolipoma.
Methods: We report a case of presacral myelolipoma in a 62 year-old woman which was initially misdiagnosed as a liposarcoma. This case was diagnosed in our institution in 2022.
Results: The Patient presented with atypical coccygeal pain evolving for five years. Patient's comorbidities consisted of hypertension. Physical examination revealed an abdominal tenderness in the right iliac foss. Magnetic resonance imaging of the pelvis showed a presacral mass measuring 5x3.5x2 cm with fatty and solid components, suggestive of a liposarcoma. Thus, patient underwent surgical resection of the mass. Histological examination of the resected mass revealed mature adipose tissue with prominent cellular stroma that was consisted of all three hematopoietic cell lineages ; myeloid, erythroid, and megakaryocytic forming cell lines without any evidence of dysplasia. Therefore, the diagnosis of myelolipoma was made.
Conclusion: Presacral myelolipoma is an uncommon disease consisting of adipose tissue and hematopoietic cells, easily confused with both primary and secondary malignant retroperitoneal tumours. In fact, it still remains a diagnosis challenge for clinicians to make the distinction between liposarcoma and myelolipoma based only on imaging features.

E-PS-22-027
An old calcifying aponeurotic fibroma
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Background & objectives: Calcifying aponeurotic fibroma is a rare, benign fibroblastic tumour more frequent in male children usually in hands and feet. We report a case of a 9 years-old female with a calcifying aponeurotic fibroma with 8 years of evolution.
Methods: At the age of 3 years the patient was referenced to the paediatric orthopaedic consultation for a mass in plantar surface of the second finger of the right foot with 2 years of evolution, the patient lost follow up and returned at the age of 7 with a size increase, complain of discomfort walking barefoot and tenderness with palpation.
Results: Sequential evaluation at 7 and 8 years old of the foot magnetic resonance imaging showed densification in the plantar, medial, and lateral aspects of the second finger at the proximal phalange of the right foot level. The tendons and the bone were unaffected. The lesion increased in size between the two exams.
An excisional biopsy was performed and revealed an infiltrative proliferation through the adipose tissue of ovoid to spindle fibroblasts in a storiform to fascicular pattern. It also forms a palisade around the nodular areas of chondroid and calcified metaplasia The stroma is collagenous with slit like vascular spaces. Rare osteoclast-type giant cells are present.
Conclusion: The diagnosis of calcifying aponeurotic fibroma was made. This is a benign entity, its infiltrative pattern could mimic malignancy, and although it has a high rate of recurrence, aggressive treatments should be avoided. Conservative surgery with preservation of function, is recommended.

E-PS-22-028
Collagen orientation probed by polarized Raman spectra on 5µm-thick FFPET sections can be readably used for grading meniscal degeneration
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Background & objectives: To analyse normal and degenerated menisci with Raman methodology on 5µm-thick FFPET sections and correlate Raman findings with histiopathological grade of meniscus degeneration. 27 degenerated and 6 healthy menisci from human knee joints after total knee replacement/meniscectomy were tested.
Methods: H&E analysis on FFPE sections to determine the grade of meniscal degeneration. Raman polarization to evaluate collagen fibrils orientation in different levels of the same sections, used for histopathology. Raman spectra were collected in two different polarization geometries, v-HH and v-VV. We calculated mean value of the v-HH/v-VV intensity ratio of two Raman bands, sensitive/non-sensitive to the molecular orientation.
Results: Collagen specific amide I band at 1665 cm−1, has the higher sensitivity dependence on Raman polarization. Mean values of ratio v-HH/v-VV of the 1665cm−1 peak intensity was significantly higher in healthy, mean ± SD:2.56±0.46, compared to degenerated menisci, mean ± SD:1.85±0.42 ($p=0.0014$). Mean values of v-HH/v-VV intensity ratio were 2.18 and 1.50 for low and high degenerated menisci, respectively ($p<0.0001$). The difference of peak intensities in the two laser polarizations is decreased in the degenerated menisci; this difference is diminishing as the degeneration increases. The v-HH/v-VV ratio was also significantly different in low, compared to control/high grade lesions ($p=0.036$ and $p<0.0001$, respectively) mirroring their biology and function.
Conclusion:
Raman analysis can be reliably applied on FFPET sections and thus can be applied on archival tissues on a variety of pathologies, including cancer.
Raman analysis on FFPET can serve as an additional, reliable tool for accurate discrimination between normal/degenerated menisci and between menisci with low- and high-grade degeneration.
Technically advanced, preferably portable Raman instruments combined with intra-operative histological analyses could provide faster, real-time and reliable data, adding to the decision making algorithm for management of meniscal and other pathologies

E-PS-22-029
Intracranial sclerosing epithelioid fibrosarcoma - a rare neoplasm in an unusual location
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Background & objectives: Sclerosing epithelioid fibrosarcoma (SEF) is an uncommon malignant mesenchymal neoplasm, composed of epithelioid fibroblasts in a dense sclerotic stroma. Most cases occur in the extremities and limb girdles of adults. Intracranial location and occurrence in paediatric age are rarely reported.
Methods: We herein report a case of a 16 year-old male, admitted due to left hemiparesis. MRI revealed a 42mm extra-axial intracranial mass in the falx cerebri. He underwent surgical resection and neoadjuvant chemo-radiotherapy. Eleven years later, following surgical reconstruction of the scalp defect, he presented with new onset dyspnea, left pleural effusion and subpleural lung nodules, the greatest measuring 43mm.
Results: Histology of the intracranial mass resection revealed epithelioid tumour cells disposed in nests and cords within a dense sclerotic hyalinized stroma. Neoplastic cells showed strong and diffuse MUC4 and vimentin immunoreactivity and were

negative for EMA, SSTR2a, CD34 and STAT6. The biopsy of the lung nodules showed the same morphological and immunohistochemical profile, leading to the diagnosis of intracranial SEF and metastatic relapse of disease. Molecular study by RNA sequencing was inconclusive due to poor RNA quality. Break-apart FISH for EWSR1 fusions was negative. Literature review showed only three intracranial sclerosing epithelioid fibrosarcomas. Metastasis of SEF occur in up to 50% of cases, most commonly to the lung.
Conclusion: Diagnosis of extra-axial intracranial tumours can be quite challenging. Meningioma is the most common neoplasm but it may display a wide variety of patterns, making mesenchymal neoplasms, besides solitary fibrous tumour, an important differential diagnosis in selected cases. SEF usually harbours EWSR1/FUS-CREB gene fusions, nonetheless cases without this molecular alteration have been reported. Furthermore, an alternative YAP1-KMT2A gene fusion has recently been identified. Accurate diagnosis is of utmost importance given its aggressive behaviour with frequent recurrences and late metastasis.

E-PS-22-030
A case report of retiform hemangioendothelioma as pleural tumour with rib infiltration
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Background & objectives: Retiform hemangioendothelioma is an extremely rare vascular tumour of intermediate biological behaviour which is prone to local recurrence but rarely shows distant metastases. It predominantly arises in the skin and subcutaneous adipose tissue of the distal extremities.
Methods: 39-year-old woman underwent video-assisted thoracoscopic surgery during which a tumour of the left parietal pleura has been resected with partial resection of the seventh rib. The pleural tumour was radiologically detected during workup of an invasive breast cancer, earlier that year. (Neoadjuvant chemotherapy, left-sided mastectomy with axillary dissection and adjuvant chemotherapy were performed).
Results: Histologically, the resected pleural tumour showed retiform arborizing vascular spaces lined by bland endothelial cells with hobnail nuclei, characteristic of retiform hemangioendothelioma. Immunohistochemical markers CD31, CD34 and ERG were positive, while D2-40, synaptophisin and HHV-8 were negative. Features of malignancy or any other type of vascular tumour were not present in this material, but the tumour infiltrated the underlying resected bone superficially and was on the resection margins marked with tissue dye. Given the possible local aggressive behaviour and recurrence (60% of cases), additional resection and regular monitoring of the patient was recommended.
Conclusion: Although retiform hemangioendotelioma predominantly affects skin and subcutis, unusually affected sites (only few cases) are head and neck region, thorax, penis and pleura. Retiform hemangioendothelioma on location other than skin or subcutis may lead to corresponding symptoms or even threatened survival. It is important to completely rule out a possibility of more aggressive vascular tumours (e.g. angiosarcoma), which may harbour areas morphologically similar to retiform hemangioendothelioma. Retiform hemangioendothelioma often recurs many years after diagnosis so extensive local excision is required.

E-PS-22-031
De-differentiated liposarcomas with heterologous and homologous elements: MDM2, CDK4 and DDIT3 testing on several blocks with homologous and heterologous elements is useful for diagnosis
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Background & objectives: Osteosarcoma (OS) heterologous component in dedifferentiated liposarcoma (DDL) is rare but should be considered and MDM2/ CDK-4 testing employed. Myxoid liposarcoma-like (ML) homologous differentiation with simultaneous MDM2 and DDDIT3 amplification is also unusual and needs to be recognized.
Methods: We report three special cases of DDL, two in the retroperitoneum and one in the abdomen: a DDL with OS differentiation, confirmed by MDM2 and CDK4 positive testing, as well as two DDL with homologous ML differentiation confirmed by simultaneous positive MDM2 and DDIT3 testing.
Results: The DDL with heterologous osseous differentiation and very rare WDL foci, which were important to identify in order to exclude the diagnosis of extraosseous OS. Without the rare foci of WDL, the extensive high grade spindled DDL may have been misinterpreted as part of an extraosseous OS. MDM2 and CDK4 testing was needed to guide the diagnosis. The other two cases are DDL with homologous myxoid differentiation; FISH testing for MDM2 and DDIT3 amplification is necessary.
WDL and DDL can contain ML component, a diagnostic challenge when confronted with a small biopsy. Such tumours have been shown to contain co-amplifications of MDM2 and DDIT3, further adding to a diagnostic dilemma.
Conclusion: The presence of pleomorphic cells or lipoblasts in WDL or DDL, as seen in our two cases, should prompt considering MDM2 FISH testing in conjunction with DDIT3, rather than DDIT3 alone. Furthermore, the first case illustrates the utility of MDM2 and CDK4 testing in ruling out other high-grade sarcomas when a DDL diagnosis is uncertain due to absent WDL or presence of heterologous component, particularly high grade OS.

E-PS-22-032
Multiple enchondromatosis of the upper limb in combination with multiple haemangiomas in a 20-year-old patient with Maffuci syndrome
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Background & objectives: Maffucci syndrome (MS) is a rare congenital disease caused by mutations in the IDH1 or IDH2 genes, manifested by a combination of soft tissue haemangiomas with multiple enchondromes as well with other malignant soft tissue and bones tumours.
Methods: We present a case of MS in a 20-year-old female with enchondromatosis of the upper extremities in combination with multiple haemangiomas of the face and oropharynx.
The patient was operated on for the thumb of the right hand. MSCT showed solid septated mass with low echogenicity. Methods of histologic examination and IHC studies were applied.
Results: Microscopy shows fragments of cartilage tissue in its own capsule, which has the structure of an enchondroma, with areas of myxoid degeneration of cartilage and severe necrobiotic changes; fragments of bone tissue with sclerotic changes, foci of axillary bone resorption and the growth of fibroreticular tissue in the intervertebral spaces. Against this background, there are multiple, merging foci of haemorrhages, as well as signs of pathological regeneration in the form of an excessive number of small, thin-walled blood vessels of the microcirculatory bed (mimicking capillary haemangioma).

Conclusion: MS is rare disease with a sporadic character, benign, but gradually disabling course. Affects both sexes. The first manifestations occur in childhood. True venous malformations and hemangioendotheliomas appear on the skin. The second most important clinical sign is the bone deforming enchondroma. MS represent a medical and social problem, which implies the importance of the task of choosing the tactics of treatment of patients with such a disease.

E-PS-22-033

Poorly differentiated chordoma, a rare type of chordoma, in a 2.5-year-old girl

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Background & objectives: Chordoma is a relatively rare locally invasive and potentially malignant tumour of foetal notochord. Poorly differentiated chordoma (PDC) is a rare type of chordoma. In the most cases with PDC, cytogenetic studies identified deletions in SMARCB1, a tumour suppressor gene.
Methods: We report an exceptional case of a late local failure of a PDC of the cranio-cervical junction in a 2.5-year-old girl. The patient was admitted to the hospital with complaints of tenderness and limitation of movement in her neck. MRI and PET/CT revealed a tumour infiltrating C1 vertebra, compressing spinal cord and conglomerated metastatic lymphadenopathy in the left supraclavicular area.
Results: On histological examination, tumour was composed of multinodular sheets of cells in mostly epithelioid and scattered sarcomatoid morphology with eosinophilic cytoplasm and prominent pleomorphism. The nuclei were round to ovoid, with vesicular chromatin and mitotic activity was increased. Necrosis was present. The physaliphorous cells typical of chordoma with classic features were absent. Immunohistochemistry staining revealed that the cells were reactive for panck, brachyury; nonreactive for s100, myogenin, myod1, desmin, CD99, CD34 and SMARCB1(INI1) expression was found to be lost. Loss of SMARCB1 protein expression has recently been identified in a variety of tumour types such as PDC and malignant rhabdoid tumours (MRT) including atypical teratoid/rhabdoid tumour.
Conclusion: Although the histological and clinical features of PDC resemble MRT, brachyury and cytokeratin immuno-expressivity may help to distinguish PDC from those. PDC is a newly recognized entity in the recent World Health Organization classification of tumours of soft tissue and bone. Treatment consists of a combination of surgery and chemo-radiotherapy. Fewer than 60 cases have yet been reported in the English literature and this rare-type of chordoma, PDC, is associated with poor prognosis that worse than conventional chordoma.

E-PS-22-034

Whole exome sequencing analysis of dedifferentiated chondrosarcoma

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Background & objectives: Dedifferentiated chondrosarcoma (DDCS) is a biphasic malignant mesenchymal tumour with a low malignant component equal to chondrosarcoma grade 1 and a highly malignant component resembling pleomorphic sarcoma. Studies comparing genetic alterations of these components using whole exome sequencing are rare.
Methods: In our study DNA was extracted from formalin-fixed, paraffin-embedded tissue samples. After thorough quality checking, the DNA samples were analysed. For an improved understanding of the molecular genetic differences in DDCS, whole exome sequencing of 5 tumours with 2 samples each, was used to compare the genetic landscape of paired conventional and dedifferentiated tissue components.
Results: In line with recent publications IDH1/2 mutations could be observed in both tissue components of several samples. While alterations in the COL2A1 gene (Collagen Type II Alpha 1 Chain) were found in both components, we also discovered broad alterations of different collagen type genes. Mutations in the TP53 and TP53BP1 gene could be found in both portions. Interestingly alterations within the CD4/CD6 pathway were found predominantly in the dedifferentiated tissue. Moreover Wnt/β-catenin and hedgehog pathway mutations as well as TERT promoter mutations were observed along with a broad spectrum of alterations in APOB, ATRX, BRCA, GLI1/2, SOX9 and chromatin regulatory genes.
Conclusion: Our results confirm the detection of IDH1 and IDH2 mutations in both tissue components. This points to a monoclonal origin of DDCS. Furthermore, our findings confirm an established pattern of particular mutations in important driver genes, like CDKN2A, BRCA, KIT. Exploring extensive mutations in the CD4/CD6, Wnt/β-catenin and hedgehog pathways could lead to advances in possible targeted therapies.

E-PS-22-035

Pseudomyogenic Hemangioendothelioma in the thumb – report of a rare case

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Background & objectives: Pseudomyogenic hemangioendothelioma is a rare soft tissue tumour, mostly indolent and infrequently metastasizing. It usually presents with multiple cutaneous nodules in extremities, mainly affecting young adults. Due to its relative uncommonness and unusual presentation, this tumour can be diagnostically challenging.
Methods: We report a multifocal PMHE in the left thumb of a 41-year-old man. The patient described painful lesions, and three tumours were confirmed by MRI, located in the thenar eminence, proximal phalanx and subungual area. He was submitted to a distal amputation through the interphalangeal joint and a separated resection of the proximal tumour, resulting in symptomatic relief.
Results: Histopathological examination of the resected specimens revealed multiple foci of a mesenchymal neoplasm of high cellularity, consisting of short fascicles of spindled and epithelioid cells with low pleomorphism, with ample and eosinophilic cytoplasm, vesicular nucleus and evident nucleolus. The neoplasm had no necrosis, had low mitotic index and was permeated by neutrophils. The growth pattern was infiltrative, with skeletal muscle tissue and bone invasion. Immunohistochemistry was performed in sections of both soft tissue component and bone-infiltrating component (with decalcifying procedure). The tumour cells were immunoreactive for CD31, ERG, AE1/3, CAM5.2 (focal) and INI1 (preserved). In the decalcified sample, however, the nuclear staining of INI1 and ERG were equivocally weak.
Conclusion: With the described findings, the diagnosis of pseudomyogenic hemangioendothelioma was made. The decalcification procedure, however, can cause misinterpretation

of the INI1 and ERG stains as negative, which can lead to misdiagnose it as an epithelioid sarcoma, its most important differential diagnosis, with a very different prognosis. Therefore, whenever possible, it is essential to reserve a sample without bone, in which to perform the ancillary studies. The patient is disease-free since the surgery, with a follow-up time of 5 months.

E-PS-22-036

Differential diagnosis of spleen sarcoma: cytokeratin-positive interstitial reticulum cell (CIRC) sarcoma - a rare extranodal presentation

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Background & objectives: CIRC sarcoma (or tumour) is an exceptional neoplasm originating from mesenchymal stem cells, which differentiate into fibroblastic reticulum cells of lymphoid organs. Cytokeratin expression in that malignancy is a diagnostic pitfall and falsely leads to the metastatic carcinoma histopathological diagnosis.
Methods: A 44-year-old female was admitted for consultation after splenectomy, which was performed outside our centre. Initially, tumour with the greatest dimension of 14cm was well-circumscribed and confined to the spleen. Histopathological, immunohistochemical and molecular testing (next-generation sequencing with extended sarcoma panel) were done. Concurrently, the updated clinical and radiological examination revealed multifocal recurrences within the peritoneal cavity.
Results: Microscopically, a pleomorphic tumour, with mitotic activity up to 11 mitoses /10HPF, with necrosis <10% was found. Neoplastic cells with high cytological atypia, with prominent, partially lobed nuclei and nucleoli (Reed-Sternberg or "viriocyte-like" cell morphology) were identified; stroma was abundant and contained numerous macrophages/histiocytes, neutrophils, eosinophils ("inflammatory" background). Immunohistochemically cells were: Vimentin(+), CAM5,2(+), CKAE1/AE3(+/-), SMA(-), Desmin(-), CK5/6(-), EA(-), EMA(-), p40(-), CDX2(-), PAX8(-), TTF1(-), GATA3(-), CD1a(-), S100(-), CD163(-/+), CD68PG-M1(-/+), SOX10(-), HMB45(-), BRAF(-), CD21(-), CD23(-), CD35(-); CD31(-), CD34(-), ERG(-), CD30(-), PAX5(-), CD43(-), TdT(-); WT1(-), Calretynin(-), ALK1(-), ER(-), CD4(-), CD8(-), EBER(-), Ki67(+) 30%. NGS testing did not reveal any specific molecular signature. The final diagnosis CIRC sarcoma was established.
Conclusion: The major directions in the differential diagnosis of CIRC sarcoma include not only metastatic carcinoma but also follicular dendritic cell tumour/sarcoma, interdigitating reticulum cell tumour, histiocytic sarcoma, and inflammatory pseudotumour-like follicular/fibroblastic dendritic cell sarcoma. CIRC tumours (only 14 presented cases) are positive for epithelial markers and vimentin with variable expression of other markers (variable Desmin, SMA, S100, CD68 positivity). A wide spectrum of clinical behaviour (mostly inferior) and combined treatment (surgical resection, chemotherapy, and radiotherapy) are described.

E-PS-22-037

The conundrum of primary Rosai-Dorfman disease of the bone - a very rare lesion

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Background & objectives: Rosai-Dorfman Disease, or sinus histiocytosis with massive lymphadenopathy, is a rare benign histiocytic neoplasia, mostly affecting young adults. Extranodal involvement can occur in up to 40% of the patients. Less than 10% develop bone lesions and these are usually multifocal.
Methods: We report the case of a 42 year-old woman who presented with pain and regional deformity in the distal third of her right calf. CT scans revealed an osteolytic lesion with thinning and disruption of the bone cortex, extraosseous expansion and periosteal reaction, without other affected sites. An excisional biopsy was performed, followed by extensive histopathological and immunohistochemical analysis.
Results: Microscopic examination showed a diffuse infiltrate of small lymphocytes, plasma cells and frequent foamy histiocytes as well as pigment laden macrophages (siderophages), displayed around small vascular structures with slightly thickened walls. Some histiocytes displayed abundant, pale cytoplasm with phagocytized lymphocytes, suggestive for emperipolesis. This inflammatory infiltrate extended into adjacent bone and soft tissue. Immunohistochemical analysis demonstrated that the foamy histiocytes stain intensely for S100, CD68, CD163 and Cyclin D1, while CD1a reaction was negative. Based on these results, the diagnosis of primary RDD of the bone was established. Subsequently, the patient underwent complete surgical removal of the tumour. Six months later, clinical and radiological exams showed no sings of recurrence.
Conclusion: Solitary RDD of the bone, without nodal disease, is a rare pathology, which can be easily confused clinically, radiologically and on fine needle biopsy analysis with various other entities. As a consequence, surgical removal of the lesion is often warranted in order to diagnose and control the disease. However, patients should be monitored for several years as both local recurrence or development of new lesions have been reported. In such cases, various combinations of systemic therapies may be justified.

E-PS-22-038

Small cell osteosarcoma: a diagnostically challenging tumour arising on the rib

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Background & objectives: Small cell osteosarcoma (SCO) is a very uncommon tumour that rarely affects short bones, especially ribs. We herein present the fourth case of rib SCO described in the literature. The diagnosis and treatment of theses tumours pose several challenges.
Methods: We present the case of an 18-year-old woman who suffered from right basi-thoracic pain and had an appearance of a swelling at the level of the 10thright rib.
Results: Chest CT showed a heterogeneous hyper vascular mass, measuring 106 x 93 x 110 mm. Surgical biopsy was performed. The mass was composed of small round cells with round uniform nuclei and a diffuse membranous CD99 positivity. The diagnosis of Ewing sarcoma was made. The patient received 6 cycles of chemotherapy followed by surgical resection. Pathological examination of the specimen showed a small cell proliferation with foci of lace-like osteoid production. Finally, the diagnosis of a SCO of the rib, with 20% of tumour necrosis was established. Adjuvant chemotherapy with Methotrexate was indicated in association with radiotherapy. The patient recovered well, with no signs of local recurrence.
Conclusion: SCO rarely affects short bones and should be kept in mind in the management of ribs' tumours. Histopathological investigation plays an important role in the diagnosis. In fact, osteoid production is the characteristic pathological feature of SCO, and may easily distinguish it from Ewing sarcoma. However, in small biopsies, osteoid

production can be missing. Thus, immunohistochemistry as well as molecular studies are necessary to make the right diagnosis.

E-PS-22-039

Why does not ossification of posterior longitudinal ligament involve an upper part of the axis?

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Background & objectives: Ossification of posterior longitudinal ligament (OPLL) can involve any parts of the ligament only except an upper part of the axis. To elucidate the reason why this part is not affected we examined 52 cervical spines dissected at autopsy.
Methods: The specimens were dissected from cadavers aged over 50 years old at autopsy performed in Dokkyo Medical University and Koshigaya Hospital. There were 39 men and 13 women with a mean age of 69 years old. The formalin fixed specimens were cut into sagittal slices with 5 mm in thick. Decalcified ones were processed for histology after X-ray examination.
Results: OPLL were observed in 25 cases on X-ray. The most common type was segmental and the largest lesion involved consecutive 3 vertebral bodies (C4-C6). The most common location was C6 in 20 cases followed by C4 and C5 in 13 cases, each, C7 in 12 cases, C3 in 5 cases, and C2 in 2 cases. OPLL was found along the axis but never seen at an upper half part. Seven OPLL lesions at intervertebral disc were found in 6 cases: C3/4 in one case, C4/5 in 3 cases, C5/6 in 2 case, and C6/7 in one case. In addition, a specific anatomical structure was found around the axis.
Conclusion: Pathogenesis of OPLL is unknown, however, ligament ossification requires blood flow. This study demonstrated that the cervical longitudinal ligament except an upper part is directly attached to the posterior aspect of the cervical vertebral bodies and intervertebral discs. The upper part of the ligament is separated from the upper half of the axis because a bursa and the transverse ligament of atlas lay between them. We conclude that this anatomic structure does not lead to ligament ossification.

E-PS-22-040

NTRK-rearranged spindle cell neoplasm: a case report

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Background & objectives: NTRK (neurotrophic tyrosine receptor kinase)-rearranged spindle cell neoplasms, included in the 5th edition of the World Health Organization (WHO) classification of Soft Tissue and Bone Sarcomas, are characterized by morphological and molecular features resembling lipofibromatosis-like neural tumours.
Methods: A 2-year-old boy presented with painless mass that grew as the child got older was observed in the dorsum of the left hand. In the ultrasonographic examination, a vascularized fat-rich lesion measuring 45x16x40 mm was observed in the subcutaneous soft tissue. Excision of the lesion was performed. Prepared slides and blocks were presented to us for consultation.
Results: No macroscopic information was available. Histologically, sections showed cellular spindle cell proliferation altered with adipose tissue, with pigmentation. In cellular areas, spindle cells showed moderate pleomorphism, ovoid-to-elongated nuclei with amphophilic cytoplasm. 7 mitoses/mm2 were counted. No necrosis was observed. Histochemical examination of pigmentation showed a positive reaction with Masson Fontana, compatible with melanin. Immunohistochemically, tumour cells were positive for panTRK, patchy positive for CD34, weak positive in myofibroblastic pattern for SMA, negative for desmin, EMA, HMB45, SOX-10. Ki-67 was 25%. We concluded that, this melanin pigment containing tumour similar to lipofibromatosis, is a NTRK-rearranged spindle cell neoplasm with low-intermediate histological grade. Investigation of NTRK fusion with molecular methods were recommended.
Conclusion: The NTRK mutation is one of the new entities discovered in spindle cell neoplasms with genetic rearrangements. Although there is a wide histological presentation in the literature, it is valuable to evaluate NTRK rearrangement in spindle cell neoplasms, especially when infantile fibrosarcoma, lipofibromatosis and fibrosarcoma-like morphology are observed. Molecular examination can be done, also pan-TRK İHC can be used to support the diagnosis. Demonstrating this genetic rearrangement is clinically important for targeted therapies.

E-PS-22-042

Case report of a primary renal vein leiomyosarcoma

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Background & objectives: We report a rare case of leiomyosarcoma arising from the renal vein. Leiomyosarcomas are rare malignant soft tissue tumours. A minority of these originate from vessel walls, usually from the vena cava with only few arising from other large veins.
Methods: An 82 year old female with a history of malignant melanoma, presented at the hospital with a mass on the upper left abdominal quadrant diagnosed from a routine ultrasound. A CT and MRI were performed and a circumscribed large non-functioning mass at the location of the left adrenal gland and the retroaortic position of the left renal vein were depicted.
Results: Histological examination revealed a tumour that consisted of intersecting fascicles of spindle-shaped cells with smooth muscle differentiation, nuclear pleomorphism and 10-19 mitoses per High Power Field (HPF). The neoplasm originated from the left renal vein, without invading the left kidney while pushing and causing atrophy to the left adrenal gland. Immunohistochemistry showed diffuse positivity for smooth muscle actin (SMA), Desmin, H-Caldesmon and negativity for S-100, Mart-1, HMB-45, SOX-10. Ki-67 was estimated 35%.
Conclusion: These observations confirmed the diagnosis of a leiomyosarcoma of intermediate malignancy Grade 2 according to FNCLCC classification originating from the left renal vein. Primary renal vein leiomyosarcomas are quite rare with only a few cases reported in literature.

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E-PS-23-001

Mediastinal teratoma with 4 different somatic type malignancies: a case report

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Background & objectives: Teratomas are germ cell tumours (GCT) containing cells from the three germ layers. The rise of somatic type malignancy in the context of GCT is rare phenomenon. Herein we describe a case, with 4 different somatic type malignancies.
Methods: A 44-year-old male who presented with a complaint of persistent cough. Physical and systemic examination were unremarkable. A CT scan revealed a mediastinal mass. Fine needle aspiration results were suggestive of teratoma. The patient underwent surgical resection of the tumour.
Results: Histopathologic examination revealed a mass measuring 20 x 13.5 x 11 cm surrounded by a thickened fibrotic capsule of variable thickness with areas of necrosis and cystic like appearance. Microscopically, the tumour was composed of heterologous components, mainly of mesenchymal but also of epithelial origin. Tumour demonstrated 4 different malignant components including: angiosarcoma (CD31+, CD34+, ERG+, Ki67 at 67%), chondroblastic osteosarcoma, primordial cells tumour yolk sac type (PHOX2B+, GFAP+, NF+), well differentiated intestinal adenocarcinoma (CK 8/18+, CK20+, and CDX20+).
The rest of the tumour's area consisted of mature hyaline cartilage, mature neural tissue with neural parenchyma (S100+, GFAP+), respiratory type epithelium with the presence of cilia and stratified squamous epithelium.
Conclusion: The most frequent malignant component associated with GCT are sarcomas. In our case, the rise of 4 different somatic type malignancies is a rare finding, and to our knowledge, very few are reported so far.

E-PS-23-002
Thymic carcinoma: a rare type of cancer. Clinicopathological study of 9 cases
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Background & objectives: Thymic carcinomas are rare malignancies (less than 6/100,000 persons) from thymic epithelial cells in the anterior mediastinum. There are more than 10 subtypes. The presence of an isolated anterior mediastinal mass with no tumour elsewhere should make us suspect it.
Methods: The pathology archives of two University Hospitals were searched for patients originally diagnosed as thymic carcinomas. The cases were reviewed by the authors (histopathology and immunophenotype). Clinical parameters such as age, gender, and follow up were obtained from the existing medical records.
Results: Nine patients were identified: 4 males and 5 females, age ranged from 50 to 89 years (median 66,7 yrs.). The most common symptoms included chest pain and shortness of breath. CT scan showed in all patients large lesions in anterior mediastinum, measuring 2-10,5 cm and an advanced stage at diagnosis in three cases. Histologically the tumours were classified as squamous cell carcinomas (6), neuroendocrine carcinoma (2) and high-grade undifferentiated carcinoma (1). Overall, 2 tumour was classified as moderately differentiated and 6 as poorly differentiated. Immunohistochemically, the tumours were positive for cytokeratin (100%), 4 for c-Kit, and 5 for CD5. None of the tumours showed staining for TTF-1 or napsin.
Conclusion: Thymic carcinomas are a rare type of cancer that can show a variety of histologic types. Squamous cell carcinoma is the most frequent subtype in our series and accounts for 66,6%. Thymic Neuroendocrine carcinoma are exceedingly rare neo-plasms (only 2 cases in our series). Morphology and immunohistochemical markers do not differentiate between carcinomas of different locations, thus making it difficult to establish the exact site of origin in cases of metastatic tumours.

E-PS-23-003
Ectopic mediastinal parathyroid adenoma: report of unusual location and literature review
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Background & objectives: The mediastinal location of ectopic parathyroid adenomasis is unusual and it reported in up to 10% of cases. It is an important cause of refractory and recurrent hyperparathyroidism. The aim: describe the clinicopathological characteristics and discuss the differential diagnosis of this entity.
Methods: We performed a retrospective study of 14 cases of ectopic mediastinal parathyroid adenoma diagnosed at our department between 2004 and 2021.
Results: There were 3 male and 11 female patients, aged between 15 and 71 years with a mean of 57,72 years. All patients presented with manifestations of chronic hypercalcemia. They checked elevated serum calcium levels and parathyroid hormone levels above normal range. Computed tomography of the chest showed an anterior mediastinal mass (n=10) or posterior mass (n=1). All patients underwent a surgical resection. The postoperative pathology test confirmed that the mass was diagnosed as a parathyroid adenoma. The patients had a successful postoperative recovery and then were discharged from the hospital in good condition. Serum calcium and parathyroid hormone levels were normalized immediately.
Conclusion: An unusual location for a parathyroid adenoma is the mediastinum, and it can be a cause of persistent hyperparathyroidism. This study helps bring to light the necessity to consider the diagnosis of an ectopic parathyroid adenoma as an important differential diagnosis in mediastinal tumour with persistent hypercalcaemia, and as a cause of hyperparathyroidism.

E-PS-23-004
Mesothlioma of the pericardium: report of 3 cases of a rare neoplasm
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Background & objectives: Mesothelioma is a rare malignancy that develops from mesothelial cells lining the pleura, pericardium and peritoneum. Pericardial mesotheliomas are exceedingly rare accounting for < 1% of malignant mesotheliomas .We describe the clinico-pathological and immunohistochemical characteristics of primary pericardial mesothelioma (PPM).
Methods: We report 3 cases of PPM collected from the Cancer Registry of the Center of Tunisia during a period of 22 years from 2000 to 2021.
Results: Two patients were male, aged 56 and 65 years, presented chronic pericarditis with recurrent pericardial effusion for, respectively, 3 and 4 months. The latter developed symptoms post COVID-19 infection. One female patient, aged 44 years, developed acute heart failure by pericardial tamponade . Clinico-radiological investigations suspected PPM in 2 cases. The 65-year-old patient underwent pericardial decortication while the others had pericardial biopsies. Microscopically, two mesotheliomas were of the epithelioid-subtype, displayed solid and tubulopapillary patterns, in which tumour cells showed mild nuclear atypia and low mitotic-rate. One case was of sarcomatoid-subtype , showed spindle cells with marked atypia and frequent mitotic figures. All tumours expressed Cytokeratin 5/6, Calretinin, Vimentine, and WT1.

Conclusion: The diagnosis of PPM can be challenging, especially in small samples, due to non-neoplastic mimickers such as reactive pericarditis with mesothelial hyperplasia. A through pathological exam, cemented by a targeted immunohistochemical panel, remains the cornerstone for establishing an accurate diagnosis . PPM carries a bleak prognosis, given its non-specific symptoms that produce an insidious progress, its difficult surgical management and its slight benefit from radiation and chemotherapy.

E-PS-23-005

Intrathymic melanoma: report of two cases with a rare localization

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Background & objectives: Melanoma can have various visceral localizations with or without the presence of a known skin origin. Thymic localization represents an exceptional event with rare cases reported in the literature. Herein we describe two cases of intrathymic melanoma.
Methods: All thymectomy cases performed in our centre over the last 20 years were reviewed and two cases of melanoma were found. Both cases were reviewed by expert pathologists. An extensive immunohistochemical panel and molecular analyses were performed to confirm the diagnosis. Clinical-pathological data of the two patients were collected.
Results: Case 1: A 53-year-old man accessed to the emergency room for dyspnoea and thoracic pain. The CT-scan showed a mass of the anterior mediastinum. A thymectomy was performed. Histological examination showed a neoplasm morphologically and immunohistochemically compatible with melanoma. Molecular examination showed no mutation of BRAF. Dermatological and gastrointestinal examination did not detect neither skin nor visceral melanoma.
Case 2: A 62-year-old man with a history of cutaneous melanoma showed a retrosternal mediastinal mass during radiological follow-up. A thymectomy was performed and a diagnosis of intrathymic metastasis of melanoma was made. The neoplasm harboured the same mutation of the primary cutaneous melanoma (BRAF V600E) and showed a high PD-L1 expression.
Conclusion: Intrathymic localization of melanoma is an exceptionally rare event. When intrathymic localization represents the onset of the disease (as in the case of the patient 1), it raises the question about the existence of the primary melanoma of the thymus or whether it is a metastasis from an occult skin melanoma. In-depth studies based on high throughput molecular investigations are needed to answer these questions.

E-PS-24 | E-Posters Uropathology

E-PS-24-001

Pleomorphic adenoma with PLAG1 fusion presenting as an isolated kidney mass: report of a challenging case

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Background & objectives: Metastasizing pleomorphic adenoma is an infrequent diagnosis (81 cases described). Metastasizing pleomorphic adenoma involving the kidney is rare, with only eight cases disclosed until 2018. Presentation as a single incidental kidney mass is unusual.
Methods: We herein report a case of a pleomorphic adenoma presenting as a kidney mass in a 43-year-old female, and discuss challenges in differential diagnosis with primary renal tumours.
Results: The tumour was low-grade and showed a triphasic pattern, with ductal epithelial cells (strongly staining for CK7 and pan-cytokeratins), myoepithelial cells (proved by co-expression of p63, GFAP, S100, Calponin and SMA) and myxoid/oedematous stroma. Next generation sequencing identified a PLAG1 fusion typical of pleomorphic adenoma (also confirmed by immunohistochemistry), and plasmacytoid features (frequently associated with PLAG fusions) were also present in our case. The diagnosis led to further clinical observation, and the patient referred that she had removed a pleomorphic adenoma of the parotid gland 36 years before, at age 12.
Conclusion: The case highlights the relevance of carefully examining the salivary glands and of exploring past medical history related to salivary gland disease (even decades before) when in the presence of myoepithelial differentiation, and underscores the usefulness of PLAG1 immunohistochemistry and molecular testing for diagnosis.
Funding: H.M. receives a Swiss National Science Foundation grant (No. S-87701-03-01).

E-PS-24-002

Malignant triton tumour of the kidney in a 57-year-old male: a case report

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Background & objectives: Preoperative diagnosis of malignant triton tumour (MTT) remains challenging as no specific imaging characteristics distinguish it from other sarcomas. The aim is to describe a rare case of MTT of the kidney and its diagnostic challenges and patient outcomes.
Methods: Histopathologic examination and immunohistochemical staining with S-100, desmin, and myogenin were performed.
Results: Gross examination showed a 16 x 12.5 x 12.5 cm, cream-white, fleshy mass almost replacing the entire kidney. Cut sections revealed whorled cut surfaces with areas of necrosis. Histologically, the tumour is composed of spindle shaped cells with pleomorphic, hyperchromatic nuclei with prominent nucleoli and pale wavy cytoplasm, reminiscent of their Schwann cell origin. Seen within the tumour are several rhabdomyoblasts having large eccentric nuclei with prominent nucleoli and abundant densely eosinophilic cytoplasm. The tumour cells stained focally positive for S-100, desmin, and myogenin, indicating Schwannian and skeletal muscle differentiation.
Conclusion: MTT of the kidney is an exceptional occurrence and has a highly aggressive behaviour associated with rapid growth and propensity for early recurrence and metastasis. Preoperative diagnosis of this tumour is difficult, thus highlighting the importance of histopathology and immunohistochemistry in the definitive diagnosis. The optimal treatment strategy may depend on tumour characteristics and clinical presentation and should be individualized.

E-PS-24-003

Glomangiomyoma of the kidney-case report of a rare subtype of glomus tumour with unusual location

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Background & objectives: Glomus tumours arising in the kidney represent rare benign lesions, with only a few cases described in the

literature. We report a case of a young female with a kidney mass, highlighting the microscopic characteristics of this tumour.
Methods: A 30-year-old female patient with an incidental tumour mass in her left kidney was admitted for surgical treatment. The abdominal computed tomography and MRI examinations revealed a well-defined heterogeneous enhancing lesion measuring 2.62 × 2.38 cm located in the peripheric medial zone of the left kidney. Radical nephrectomy with locoregional lymphadenectomy was performed and microscopic evaluation was requested.
Results: The paraffin-embedded tissue demonstrated a nodular neoplasm composed of monomorphic round cells with eosinophilic cytoplasm and centrally located nuclei, admixed with delicate-branching vascular spaces and smooth muscle fibres. No evidence of increased mitotic index or necrosis was found. The neoplastic cells were positive for CD34, smooth muscle actin, desmin, calponin, CD117, and collagen IV in a characteristic pericellular pattern. In contrast, tumour cells were negative for Melan A, HMB-45, S100, synaptophysin, cytokeratin AE1/AE3, CD31, and CD57. The Ki-67 staining index was 1%. Periodic acid-Schiff (PAS) staining revealed well-defined cytoplasmatic membranes of the neoplastic cells. The morphological features and the immunohistochemical profile indicated a benign glomus tumour of the kidney, glomangiomyoma-subtype.
Conclusion: Primary glomus tumours of the kidney are rare, and they can mimic other renal neoplasms radiologically. By adding another case to the literature, we emphasize the histological and immunohistochemical features of this entity. A long-term follow-up is recommended despite its benign nature. It would be wise to investigate such rare cases of sporadic glomangiomas arising in young patients for an oncogenic mutation (BRAF and KRAS mutations or NOTCH gene rearrangement), but further research in this field is needed.

E-PS-24-004
Amphicrine carcinoma of the urinary bladder: a case report
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Background & objectives: Amphicrine carcinoma (AC) is a rare neoplasm with hybrid exocrine and neuroendocrine morphological, immunohistochemical and ultrastructural features. We present the case of an 82-year-old man which, to our knowledge, is the first report of an AC of the urinary bladder.
Methods: In May 2018 an 82-year-old man presented with painless gross haematuria at Circolo Hospital, ASST-Sette Laghi, Varese (Italy). Trans-urethral resection of the bladder (TURB) showed endoscopic evidence of a mass involving the posterior vesical wall which was biopsied. The patient also underwent cystoprostatectomy.
Results: TURB specimen revealed a muscolaris-propria-infiltrating neoplasia with tumoral necrosis, cytoplasmatic granularity, extra- and intra-cellular Alcian+ mucins. Immunohistochemical phenotype was as follows: synaptophysin+, chromogranin+, INSM1+, MUC5AC+, MUC2+ (patchy), MUC6-, abnormal (hyper-expressed) p53, Rb1-, p16+. Proliferative index (Ki-67): 90%. The concomitant presence of dense-core neuroendocrine and exocrine mucinous vesicles within the same neoplastic cell was confirmed with the use of transmission electron microscope and with colloidal-gold ultrastructural immunocytochemistry. Final diagnosis was AC of the vesical bladder.
Similar results were present in the cystoprostatectomy specimens which brought to a pT3b pN0 pathologic staging. The patient eventually died after 434 days from bioptical diagnosis of AC for multiple systemic infections.
Conclusion: We present the first reported case of bona fide AC of the urinary bladder. While the differential diagnosis with metastatic adenocarcinoma and urachal carcinoma is of paramount importance, recognizing the hybrid exocrine-neuroendocrine nature of these neoplasms is key with regard to the acquisition of further knowledge on this rare entity.

E-PS-24-006
V600E BRAF mutation in Rosai-Dorfman disease with testis-brain localization
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Background & objectives: Rosai Dorfman disease (RDD) is a rare form of systemic non-Langerhans cell histiocytosis. RDD classical presentation is with lymphadenomegaly, but extranodal sites may be involved. We described the immunohistochemical and molecular profile of an unusual testicular/cerebral RDD.
Methods: A 54-year-old male patient presented at San Raffaele Hospital with an unusual testicular enlargement and neurological alterations characterized by gait disorders, dysarthria, and dysesthesia in the four limbs dating since a year. On MRI, a pontine mass was found, with PET enhancement, detected bilaterally in the testes and at the root of abdominal aortic arterial branches. Monolateral orchiectomy was performed.
Results: On macroscopic examination, the testis appeared to be slightly increased in size with the presence of interspersed miliary-shaped yellowish formations in the parenchyma. Histologically, nodules of large, pale histiocytes (S-100+/CD163+/CD68+/CD207-/CD1a-) with emperipolesis were observed. Diagnosis of Rosai-Dorfman disease, extranodal subtype, was made. Molecular analysis performed on testicular tissue detected V600E BRAF gene mutation; the same mutation was detected in cerebrospinal fluid.
Conclusion: RDD usually has an indolent course, characterized by frequent spontaneous remission. RDD localization to the testicular parenchyma is extremely rare and our case is the first with synchronous presentation to the central nervous system. The V600E BRAF gene mutation is extremely rare in RDD; it has been described till now only in brain RDD localizations. BRAF mutation in our case, besides relevant clinical opportunities, suggests a testis-brain axis for this form of RDD

E-PS-24-007
Basaloid carcinoma of the bladder: is it a new variant with poor prognosis? Case report
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Background & objectives: Basaloid carcinoma is an exceptional variant of squamous cell carcinoma of the bladder.
We aim through this case, the 4th in the literature, to describe the pathological features of this entity and highlight its poor prognosis according to our experience.
Methods: A 51-year-old patient consulted for haematuria with bladder mass on imaging. So, he underwent a cystprostatectomy. Histological study confirmed the diagnosis of basaloid squamous cell carcinoma of the bladder. The patient subsequently benefited from chemotherapy, but died after the third session.

Results: Squamous cell carcinoma of the bladder constitutes 2% to 7% of urothelial cancers. The basaloid variant of squamous cell carcinoma is exceptional in the bladder and only three cases have already been reported in the literature.
Histologically, the morphological appearance of basaloid carcinoma of the bladder is identical to that of basaloid carcinomas in other anatomical sites such as the lung.
The treatment of this tumour is not specific due to the lack of clinical data; it is essentially based on surgery. The importance of adjuvant treatment with radiotherapy or chemotherapy is unclear.
Basaloid carcinoma has a more aggressive clinical course and poorer prognosis than conventional squamous cell carcinoma.
Conclusion: Basaloid squamous cell carcinoma of the bladder is a very rare entity with a poor prognosis. The diagnosis of this rare variant is based on histological study.
The optimal treatment has yet to be defined due to the limited data available.

E-PS-24-008

Expression of glycodelin in the prostate gland in patients with prostate adenocarcinoma

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Background & objectives: Glycodelin (Gd) is expressed in various types of cancer and correlates differently with the diagnosis and prognosis. The aim of the study was to evaluate the immunohistochemical expression of Gd in areas of adenocarcinoma, hyperplasia, and intact prostate tissue.
Methods: The study included 64 men diagnosed with prostate cancer aged 50 to 79 years. By immunohistochemical (IHC) study using monoclonal mouse antibodies to the peptide part of Gd we evaluate localization and intensity of staining (in points (0-3) in cancerous foci, areas of hypertrophy and areas of normal glandular tissue of the prostate.
Results: We have revealed IHC cytoplasmic expression of Gd in prostate tissue, both in normal and pathologically altered areas. The lowest median staining intensity in the cytoplasm of tumour cells was in younger patients aged 50-59 years (0 (0; 1)), in higher degree of cell differentiation ISUP 1 (0 (0; 1)), as well as in the group without metastases (0.5(0; 1.125)). In unchanged areas of the prostate, the lowest median staining intensity was also recorded in groups aged 50-59 years (0.5 (0; 1)) and without metastases (0.5 (0; 1))
Conclusion: In this study, we have shown the expression of Gd in prostate cancer samples for the first time. Low expression of Gd probably characterizes a more favourable course of prostate cancer. This fact can serve as a prerequisite for further research and clarification of the role of Gd in carcinogenesis.
Funding: The study was carried out within the framework of State Assignment No. 122030200534-4

E-PS-24-009

Cystic nephroma in a 40-years old female patient with a history of craniopharyngioma. A case report

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Background & objectives: Cystic nephroma is a rare renal mixed epithelial –stromal tumour. It presents in children, rarely in adults. Herein we present a case of a 40-years-old woman with a history of brain surgery for craniopharyngioma She was also under cortisone therapy.
Methods: we received in two parts, left kidney weighting 306gr and measuring 11X6X4cm. On cutting there was a tumour measuring 11X5X5 cm extending from the upper pole to the middle of the kidney. There was not a clear capsule. The tumour was multicyctic and the cystic component had a smooth surface. The rest of the kidney was macroscopically normal.
Results: Pathological examination revealed a biphasic tumour. The epithelial component was represented by cystic spaces covered by a single (rarelly multiple) layer of flattened or cubical cells without atypia. The epithelial cells were monomorphic, with scant cytoplasm The stromal component was represented by spindles cells arranged in small fascicles without atypia too. There were neither mitotic activity, nor necrosis. The immunohistochemistry showed positivity for KerAE1/AE3 and Ker34βE12, as well as PAX-8. The stromal component was negative for CD34.
Conclusion: The diagnosis was : cystic nephroma (adult type). This tumour is a rarely observed tumour. It has a benign course. Partial nephrectomy is an appropriate treatment. Long term follow up is recommended to avoid malignant transformation, local recurrence, or metastasis. To our knowledge, it is the first such tumour that relates with craniopharyngioma.

E-PS-24-010

Significant variation of tumour stage by size in clear cell renal cell carcinoma from a prospective national database with a sub-analysis for causality

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Background & objectives: The Canadian Kidney Cancer information system (CKCis) is a prospective, fourteen-institution database collaboration of the Kidney Cancer Research Network of Canada. This study assessed tumour stage by size for clear cell renal cell carcinoma (ccRCC) within the CKCis database.
Methods: All ccRCC resections in CKCis database were retrieved and stratified by pathology tumour size (≤4 cm, >4 to ≤7 cm, >7 cm). Each institution's staged by size criteria (SBSC) rates for different tumour size brackets were assessed and compared via funnel plots. A sub-analysis at one institution reviewed the pathology reports and assessed for possible causes of variation.
Results: 4,804 ccRCC resections met inclusion criteria. By size ≤4 cm, >4to≤7 cm and >7 cm were 2,213, 1,418, and 1,172 cases, respectively. For pT1a tumours, the SBSC was 2,030 cases, institutional SBSC rate range was 75-95%, median rate was 90% and there were 3 of 14 outlier institutions outside the 95% confidence interval. For pT1b the numbers were 919, 38-77%, 66% and 4 of 14. For pT2 the numbers were 281, 10-34%, 27% and 3 of 14. The sub-analysis demonstrated insufficient renal sinus sampling and significant provider variation among seven pathologists that each examined >60 ccRCC cases ($p<0.05$); the pT2 rate for >7cm ccRCCs range was 0-41%.
Conclusion: This analysis suggests there is significant variation of the pathologic stage for ccRCC. Literature benchmarks suggest an over-call of pT2. The focused sub-analysis suggests both the grossing and microscopic interpretation can be significant factors in pT2 over-call. pT2 rate for >7 cm ccRCC should be followed

as a quality metric, as recommendations for adjuvant therapy may depend on differentiation between pT2/pT3. Secondary reviews of pT2 ccRCCs by urologic pathologists may assist in optimizing risk stratification and patient management.
Funding: Kidney Cancer Research Network of Canada (https://www.kcrnc.ca/), Canadian Kidney Cancer Information System (CKCis) (https://www.kcrnc.ca/ckcis/)

E-PS-24-011
Clear cell carcinoma of the urinary bladder of Müllerian type - a case report
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Background & objectives: Müllerian neoplasms of the urinary system are rare and are subdivided into Clear Cell Carcinoma (CCC) and Endometrioid Carcinoma. These neoplasms have been associated with endometriosis and Müllerian duct remnants.
Methods: A female 65 years old was referred to our hospital for haematuria. A transurethral resection of bladder tumour (TURBT) was performed. On gross examination the specimen from the urinary bladder had no uncommon aspects.
Results: On histological examination a high grade invasive adenocarcinoma was observed showing a predominant solid growth with rare tubulocystic or papillary patterns. The neoplastic cells displayed abundant clear cytoplasm and hobnail morphology. The carcinoma invaded lamina propria and submucosa while the muscularis propria was free from invasion in our specimen.
The immunohistochemistry was positive for CK7, CA125, AMACR, Napsin A, PAX-8 and negative for ER, PgR, GATA-3, p63, CK20, CDX2, PSAP.
In correlation with the clinical information a diagnosis of CCC of Müllerian type was made.
Conclusion: Müllerian type CCC of the lower urinary tract is rare, it has a higher incidence in elderly females and requires radical treatment with variable outcomes. Prompt diagnosis and multidisciplinary approach are indispensable for management. Due to its rarity and lack of long-term follow-up, the prognosis of this entity remains unclear.

E-PS-24-012
Extramammary Pagets disease: a case report
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Background & objectives: Extramammary Paget's disease (EMPD) is a rare intraepithelial carcinoma arising in areas rich in glands, including the vulva, scrotum, penis, perineum and axilla. EMPD typically presents in older adults (>80) as an erythematous, itchy lesion, often initially diagnosed as eczema.
Methods: We present the case of an 80 year old gentleman presenting with an 18 month history of an erythematous, non-pruritic rash of the penile shaft. Past medical history was significant for diabetes mellitus, ischaemic heart disease and radiotherapy-treated prostate cancer 8 years previous.
Results: An excision biopsy of the rash showed a population of nested atypical cells infiltrating into the epidermis. These cells had pleomorphic nuclei, prominent nucleoli and mitotic activity. Underlying adnexal structures were involved but there was no evidence of dermal invasion. We performed a number of immunohistochemical stains to further characterize this lesion. The cells were positive for AE1/AE3, CK7, EMA, BerEP4, GATA3 and CEA. Focal positivity was noted for CK20 and GCDFF15. PAX8 was weakly positive. The cells were negative for CK5/6, p63, CDX2 and melanocytic markers. This gentleman was diagnosed with a primary extra-mammary Pagets disease of the penis.
Conclusion: EMPD is a rare carcinoma which requires a high index of suspicion, particularly in the elderly and those with failed medical management. The most common area affected are the vulva (65%) and perineum (20%) while the penis and scrotum account for 14% of EMPD cases. Patients are often initially treated with topical steroids and ointments without improvement. A median time to diagnosis of 2 years has been reported. Surgical resection is the treatment of choice for EMPD.

E-PS-24-013
Sarcomatoid carcinoma of the urinary bladder arising from squamous cell carcinoma. A case review
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Background & objectives: Bladder cancer is the 10th most common malignancy worldwide with a male to female ratio of 4:1. The majority (95%) of cases consists of urothelial carcinoma. We present a rare case of sarcomatoid carcinoma of the urinary bladder.
Methods: A 77 year-old male patient was admitted for scheduled radical cystoprostatectomy due to previously diagnosed muscle invasive (T2) squamous cell carcinoma of the urinary bladder on TURBT chips. Gross examination of the bladder specimen revealed a whitish exophytic friable tumour, measuring 9X4cm, along with areas of ulceration.
Results: Histopathological examination revealed two distinct and in close proximity malignant cell populations; a squamous cell carcinoma component mostly regarding the exophytic tumour and a high-grade malignant spindle cell tumour infiltrating large portion of the muscle wall and partially invading the pervesical fat. The latter also showed areas of osseous differentiation. In situ urothelial carcinoma was also present in the superficial epithelium. Prostate, bilateral seminal vesicles, vas deferens, and ureteric margins were free of tumour. On immunohistochemical analysis, spindle cells were positive for Vimentin, SMA and negative for CK5/6, GATA 3, CK7, p40. The aforementioned results established the diagnosis of sarcomatoid carcinoma.
Conclusion: Bladder sarcomatoid carcinoma is a rare malignant type and is estimated to account for 0.1%–0.3% of all bladder tumours. Less than 100 case reports have been published in the literature. It is characterized by the presence of an epithelial urothelial and a sarcomatous population. For most cases the epithelial component is urothelial carcinoma, however, squamous cell and small cell carcinoma components have also frequently been reported. Due to aggressive nature of disease, it is usually diagnosed at advanced stage.

E-PS-24-014
In situ urothelial carcinoma of the urinary bladder with pagetoid extension into prostatic urethra and prostatic duct epithelium - a case report
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Background & objectives: Urothelial cell carcinoma of urinary bladder is characterized by multifocal development throughout the

urinary tract. 4–17% of the cases develop urethral recurrence after cystectomy affecting the prostatic gland either by invasion or by pagetoid extension through the prostatic duct.
Methods: A patient 70-years-old was admitted to our hospital with a previous prostate needle biopsy, which on histopathological examination showed urothelial carcinoma extending into the prostatic ducts. We review the biopsy and proceed to bladder biopsy from different sites. A biopsy of prostatic urethra was made too. After the pathology results a radical cystoprostatectomy was decided.
Results: All urinary bladder biopsies showed in situ urothelial carcinoma. In the specimen of radical cystoprostatectomy, after extensive sampling, the histopathology examination showed in situ urothelial carcinoma which involved prostatic ducts and glands in a pagetoid manner, without invasive component. The same lesions were recognized in both ureters. The seminal vesicles, the prostatic urethra margin and both ureteral margins were negative for in situ or invasive carcinoma. All ten lymph nodes were negative for metastatic carcinoma.
The immunohistochemistry was positive for GATA-3, p63, CK20 and negative for PSAP and PSA. The p63 and CK14 shows presence of myoepithelial cells surrounding prostatic ducts and glands.
Conclusion: Conservatory treatment is an option for in situ urothelial carcinoma extending in the prostatic duct. Radical surgery is the best treatment for extensive intraductal prostatic involvement. The clinicopathologic features associated with an increased risk of urethral recurrence are: involvement of the urinary bladder neck or trigone, diffuse carcinoma in situ, multifocality, synchronous upper urinary tract tumours, involvement of the prostatic urethra or deep prostatic invasion and the positive urethral margins.

E-PS-24-015
Seminoma in a case of ovotesticular disease (true Hermaphrodith)
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Background & objectives: Ovotesticular disorder is defined as the presence of both ovaries and testes in the same person, regardless of karyotype. Patients with ovotesticular disorder have a higher risk of developing gonadal neoplasms such as gonadoblastoma or seminoma than the general population.
Methods: The karyotype analysis of a 32-year-old male patient with phenotype who was examined for bilateral abdominal undescended testis was 46 XY. In his radiological examination, a complex internal genital structure compatible with ovotestis was detected. The patient whose operation material was examined in our unit is presented with histopathological and clinical features.
Results: Macroscopically, the specimen consisted of bilobed gonadal structures and a single cordial structure adjacent to it. In the histopathological examination, in addition to seminoma, tissues including vesicle seminalis, atrophic testis, tuba uterina, endometrium and endocervix component were seen. Most of the structures thought to belong to the female genital tract were not of the usual morphology, possibly due to insufficient hormonal effect. Immunohistochemical markers contributed greatly to the distinction of the organs and diagnosis. The patient, who was diagnosed with ovotestis and Stage I seminoma based on histopathological findings, received a single dose of carboplatin chemotherapy and free of disease at 6th month of follow-up.
Conclusion: Ovostesticular disorder is a very rare sex developmental disorder, with a 10% risk of germ cell tumour development in 46XY and mosaicism cases. As a result, orchiectomy is required in the presence of an undescended testis or development of a tumour. Because male and female genital organs have similar morphological and immunohistochemical features, a multidisciplinary approach is required for pathological examination.

E-PS-24-017
Old markers, new perspective in urothelial carcinoma
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Background & objectives: Bladder cancer is one of most common malignancies of the urinary tract. The present study was conducted to study the immunoexpression of CD10, c-KIT and Her2 protein in urothelial carcinoma and to correlate it with histological grade and pathological stage.
Methods: 41patients were subjected TURBT for non-muscle-invasive and muscle-invasive urothelial carcinoma between 2019-2021 in our hospital.CD10, HER2 and c-KIT membranous/cytoplasmic expressions in cells were the main variables of interest; strong-positive result is defined as strong/moderate immunoreactivity in >50% cells(2+), weak-positive result is defined as mild immunoreactivity of <50% of tumour cells(1+) and cells with faint/no staining will be scored as negative(0).
Results: High-grade T2 tumours showed strong or week expression of all the markers that we used: HER2 staining was graded 2+ in 2/8 high-grade T2 tumours (25%) and 1+ in 3/8 high-grade T2 tumours (37,5%). Strong and week immunoreactivity of c-KIT was noted in 12,5% respectively 25% in this category of tumours. 50% (4/8 high-grade T2 tumours) showed strong membranous staining for CD10. Regarding of Ta and T1 high-grade tumours, week expression of HER2 (4/25 tumours), c-KIT (5/25 tumours) and CD10 (6/25 tumours) was observed. All low-grade Ta and T1 tumours were negative.
Conclusion: Our findings indicate that overexpression of HER2 protein, expression of CD10 and c-KIT is correlated with high-grade tumours and stage, suggesting its possible role in pathogenesis and progression of urothelial carcinoma.

E-PS-24-018
A bone in the bladder – rare case report and review of literature
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Background & objectives: Stromal osseous metaplasia (SOM) is one of the three instances of bone formation within bladder tumours. It is also the least common, with a total of 21 cases reported in the English literature. Here, we report an additional case.
Methods: A 64-year-old man with a history of multiple acute cystitis presented to our hospital with urinary retention. Cystoscopy revealed a 3 cm pedunculated tumour with papillary architecture located on the right lateral bladder wall, removed with transurethral resection.
Results: Pathological examination was performed on pink-tan to grey friable tissue fragments that varied from soft and gelatinous to firm. Microscopy showed papillary projections lined by a thick layer of stratified transitional epithelial cells with central fibrovascular cores, with orderly architecture and mild pleomorphism. Invasion through the basement membrane was not identified.

These findings were consistent with the diagnosis of low grade non-invasive papillary urothelial carcinoma. Rare lamellated or coarse-fibred bone trabeculae separated by loose fibrous connective tissue with osteoid seams were found in the tumour stroma. Numerous cells with blue cytoplasm that correspond to osteoblasts outlined those osteoid and bony structures, without atypia or pleomorphic stromal cells.
Conclusion: Stromal osseous metaplasia is a rare benign condition found in urothelial carcinomas. Its presence has no effect on their therapeutic approach, which is determined by histologic grade and tumour stage. Metaplastic bone, on the other hand, must be distinguished from malignant osteogenous conditions, most notably sarcomatoid carcinoma.

E-PS-24-019
Histoepidemiological study of eosinophilic metaplasia of the prostate gland
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Background & objectives: The current study investigates the relation between prostatic eosinophilic metaplasia (EM) in a large series of cases with the basic prostate pathology in transurethral resection of the prostate (TURP) material. The study is supported by statistical analysis of the results.
Methods: 61 TURP-specimens were reviewed for the presence of EM. Simultaneously BPH, BCH, PCa and National Institutes of Health-category IV prostatitis (so-called histologic prostatitis – HP -acute and chronic) were evaluated.
Results: Prostatic EM was found in 34/61 cases (55.7%). This high frequency of EM in TURP correlated to the HP (p=0.000), BCH (p=0.000), and BPH (p=NA). No difference in patient's age, clinical and laboratory data (PSA was found).
Conclusion: The study presents the first attempt to quantify with statistical analysis the association between prostatic EM in a series of patients in the context of basic pathology in TURP-material. Our results enrich the available information about morphogenesis and relation between EM and other prostatic diseases.
Chronic inflammation (HP), persistent irritation (BPH) and BCH are basis of adult stem cells metaplastic conversion in some organ(prostate). The frequent combination between these processes is in favour of their unified molecular and cellular pathogenesis.

E-PS-24-020
Sarcomatoid spermatocytic tumour: report of a rare case
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Background & objectives: Spermatocytic tumour (ST) accounts for 1% of testicular germ cell tumours. It is an indolent neoplasm with good prognosis. Sarcomatous dedifferentiation may occur, portending an aggressive behaviour and representing a significant diagnostic challenge that can lead to its misdiagnosis.
Methods: Herein, we report the clinicopathological features of a case of sarcomatoid ST, initially misdiagnosed as malignant mixed germ cell tumour (MMGCT), which was referred to our institution with lung metastases exclusively composed of rhabdomyosarcomatous elements.
Results: A 46-year-old man with bilateral lung metastases and a history of right radical orchiectomy for MMGCT (with teratoma, yolk-sac tumour and seminoma components) was referred to our institution for further therapy. Serum markers were all negative, and a lung biopsy was performed, revealing a rhabdomyosarcoma. Slides of the testicular mass were reviewed and showed a high-grade spindle and rhabdmyoblastic sarcoma with focal positivity for desmin, myoD1 and myogenin, and a minor component of spermatocytic tumour with colonization of peritumoral seminiferous tubules. A final diagnosis of sarcomatous ST with rabdhomyosarcomatous lung metastases was rendered. The patient developed brain metastases and underwent chemoradiotherapy and neurosurgery, but died 10 months after orchiectomy.
Conclusion: ST is generally described as having an excellent prognosis. The presence of a sarcomatous component is a well-established event that renders a poor prognosis, despite aggressive systemic therapy and, as in this case, may be misinterpreted as teratoma. In addition, colonization of seminiferous tubules can be mistaken with in-situ germ cell neoplasia. Awareness of this entity and its peculiarities is essential for its recognition and further adequate management of patients.

E-PS-24-021
Incidentally discovered testicular metastatic tumour
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Background & objectives: Testicular metastatic carcinoma is a rare entity, often the primary is a prostatic adenocarcinoma. We report a new case incidentally discovered, to emphasize the importance of the examination of the testicles in the assessment of extension of prostatic cancer.
Methods: An 82 year-old man followed for prostatic adenocarcinoma consulted for clotting and deglobulating haematuria. Physical examination finds a right testicular mass. An endoscopic resection with bilateral orchiectomy was performed for voiding and haemostasis.
Results: The testicular examination showed an invasive carcinomatous proliferation dissociating the seminiferous tubules made of clusters and patches of cells with some glandular structures leaning in cribriform massifs. The tumour cells have a similar appearance to those of the prostatic tumour; large cell with amphophilic cytoplasm and a very atypical and highly mitotic nucleus with a prominent nucleolus. there are many lymphatic emboli. On immunohistochemistry, tumour cells were diffusely positive for CK and PSA. We concluded to the diagnosis of testicular metastasis of prostatic adenocarcinoma.
Conclusion: Testicular metastases are very rare in known patients with prostate cancer. Careful physical examination through specimen sampling and imaging of all the possible sites of metastasis are indispensable in the process of identifying metastasis.

E-PS-24-022
Undifferentiated carcinoma with osteoclast-like giant cells in the renal pelvis: a very rare entity
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Background & objectives: Undifferentiated carcinoma with osteoclast-like giant cells of the urinary tract are rare, with less than 15 cases described involving the renal pelvis. Another case is presented, with the aim of delving the clinicopathologic, immunohistochemical and biological behaviour of this entity.
Methods: A case of a 63-year-old male, with no medical history of interest, who attends the urology office due to haematuria and right flank pain. An ultrasound and a URO-TAC with contrast is requested, where a repletion defect of 3.3 x 2.5 cm in the right upper calicial group was detected. The patient underwent a right nephroureterectomy.
Results: Histological study revealed an eosinophilic biphasic tumour composed of a monotonous population of mononuclear cells with round-oval nuclei and slight nuclear pleomorphism, with prominent nucleoli, as well as numerous intercalated osteoclast-like giant cells. There were areas of necrosis with several mitoses per high magnification field. This lesion was associated with urothelial carcinoma (UC) in situ. The immunohistochemical study was positive for GATA3 and vimentin in the mononuclear component and positive for CD68 in the multinucleated giant cells. On the other hand, it was negative for ß-HCG and pankeratin in both components. The definitive diagnosis was Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC).
Conclusion: UCOGC is diagnosed mainly in elderly patients with male predominance [3:1]. The intimate association of these tumours with UC and their immunohistochemical profile supports an epithelial origin for the mononuclear cells and non-neoplastic reactive histiocytic lineage for the osteoclast-like giant cells. The differential diagnosis is made with sarcomatoid carcinoma of the renal pelvis, UC with anaplastic giant cells and UC with divergent trophoblastic differentiation. It is important to keep this entity in mind because of its dismal prognosis.

E-PS-24-023
Study of TERT mutations in uropathological biopsies. Use of a molecular technique in a daily practice
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Background & objectives: TERT promoter mutations are the most common somatic alteration identified in urinary bladder cancer. We present a review of 34 urinary tract biopsies and resection specimens with benign and malignant results, between 2018 and 2022, diagnosed at a Tertiary Hospital.
Methods: We reviewed 34 specimens of 27 patients, including 26 malignant lesions, 7 benign lesions such as hyperplasia, verrucous squamous hyperplasia, papilloma and 1 papillary neoplasm of low malignant potential. We also included one specimen of transurethral prostatic resection with neuroendocrine carcinoma and one lymph node metastasis of urothelial origin. TERT mutation analysis was performed.
Results: The twenty-seven patients were represented by 5 female and 22 male. The average age was 63 years (range 13-89). Primary site was bladder for 23 specimens (67.64%) and upper urinary tract for 9 specimens (26.47%). One case corresponded to a lymph node metastasis by carcinoma of urothelial origin and one case was a neuroendocrine carcinoma of the prostate.
TERT mutation was positive in 16 malignant lesions (61.53% of all malignant lesions) and in verrucous squamous hyperplasia and was negative 6 benign lesions (85.71% of all benign lesions), 8 malignant lesions (38.47% of all malignant lesions), 1 papillary neoplasm of low malignant potential.
Conclusion: TERT promoter mutations are the most common genetic alteration in urothelial carcinoma. We found TERT mutations occurring in papillary urothelial carcinoma, variant-predominant histology such as nested, neuroendocrine and clear cell carcinoma and sarcomatoid carcinoma of the bladder. The majority of benign lesions were negative. TERT analysis is very useful in small biopsies. It can also be useful in sarcomatoid carcinomas of the bladder and in metastases of unknown origin where the positivity for TERT mutation can support urothelial origin.

E-PS-24-024
Incidental discovery of prostatic adenocarcinoma following ureterectomy
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Background & objectives: Prostate cancer is the second most common cancer in men. It generally metastasizes to the lymph nodes, bone, and liver. Ureteral metastasis from prostate cancer is extremely rare. We present a case of prostatic adenocarcinoma revealed by ureteral metastasis.
Methods: We report a case of a 58-year-old man with metastatic prostatic carcinoma incidentally diagnosed following ureterectomy.
Results: Our patient, who has a history of nephrolithiasis, presented with acute renal failure. Ultrasonography and computed tomography showed right hydroureteronephrosis secondary to obstruction of the pelvic ureter; atrophy of the left kidney and hypertrophy of the prostate. Ureteral urothelial carcinoma was suspected. Because the right kidney was a solitary functioning kidney, our patient underwent segmental ureterectomy with lymph-node excision. Pathologic examination revealed ureteral and lymph-node metastases of prostate adenocarcinoma. Immunohistochemistry confirmed the diagnosis (positivity for PSA, P504s and negativity for GATA3 and p63). Subsequently, serum PSA test was made and its level was 41.14 ng/mL. Prostate MRI found a locally advanced prostatic tumour classified T4N+. The patient started hormone therapy.
Conclusion: Ureteral metastasis from prostatic adenocarcinoma is rare. It can present with obstructive symptoms or as an asymptomatic mass on imaging. Due to the difficulty in making a preoperative diagnosis, it is typically diagnosed after nephroureterectomy. Prostate cancer should be considered in the differential diagnosis of elderly men presenting with ureteral tumour. PSA test should be done on all patients over 50 to exclude the diagnosis of metastatic ureteral tumour from prostate cancer.

E-PS-24-025
Recurrent deep angiomyxoma of the bladder neck presenting as voiding dysfunction: a case report
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Background & objectives: Deep (aggressive) angiomyxoma is a benign, locally infiltrative, myxoid soft tissue tumour that most commonly arises in the deep soft tissues of the pelviperineal region of women. Deep angiomyxoma of the bladder has been extremely rarely reported.
Methods: A 57-year-old male patient presented with recently aggravated voiding difficulty. Twelve years ago, the patient had undergone transurethral resection (TUR) of the prostate and bladder tumour due to voiding symptoms. Computed tomography revealed a 3 cm sized heterogeneously enhancing lesion in the

bladder neck. TUR of the prostate and bladder tumour was performed for the second time.
Results: Histologically, TUR tissue revealed an ill-defined, infiltrative tumour composed of bland spindle cells within an abundant myxoid matrix interspersed with prominent vessels. Immunohistochemically, the spindle cells were positive for progesterone receptor and negative for oestrogen receptor. The histopathology was the same as that of the initial TUR specimen. The diagnosis of recurrent deep angiomyxoma of the bladder neck was confirmed.
Conclusion: Though rare, deep angiomyxoma of the bladder neck should be considered as a cause of obstructive urinary symptoms.

E-PS-24-026
Primary Ewing sarcoma/primitive neuroectodermal tumour of the kidney: a rare case report
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Background & objectives: Ewing sarcoma/Primitive neuroectodermal tumour (ES/PNET) are undifferentiated tumours that originate from neuroectoderm. The occurrence in kidney is extremely rare (<1% of renal tumours), with less than 150 cases reported. We present a case of a young adult with a renal-ES/PNET.
Methods: A 18-year-old woman presented with abdominal pain and haematuria. A computed tomography showed a 20 x 14 x 10 cm mass on the left kidney. A left radical nephrectomy was performed. Histology showed a small round cell malignant tumour with areas of necrosis and frequent mitosis.
Results: Tumour cells were positive for CD99, synaptophysin and Fli-1. TLE-1, S100, AE1/AE3, EMA, CD34, desmin, CD45, GATA-3, WT-1 and PAX-8 were negative. Ki-67 was 20%. Fluorescence in situ hybridization for the translocation EWS-FLI1/t(11;22) was negative. Due to the rarity of this tumour, neoplasms like blastemal-Wilms tumour, neuroblastoma, lymphoma, small cell carcinoma, rhabdoid tumour, desmoplastic small round cell tumour and synovial sarcoma, must to be excluded. Immunohistochemistry is helpful, but there could be immunophenotypic overlap that requires molecular testing.
t(11;22) has been reported in approximately 70% of the kidney ES/PNET, but other members of the ETS genes have less frequently been reported as variants, supporting the diagnosis in this case.
Conclusion: The diagnosis of ES/PNET of the kidney depends on an integrated approach that includes histology, immunohistochemistry and molecular/genetic testing. Accuracy in the diagnosis is critical because compared to other primary renal tumours, ES/PNET have a poor prognosis and an specific multimodal therapy.

E-PS-24-027
Paraganglioma of the urinary bladder: two cases report
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Background & objectives: Paragangliomas are rare, especially in the bladder. They represent 0.05% of bladder tumours and less than 1% of paragangliomas. Due to its rarity and symptomatic variability, preoperative diagnosis is often difficult. We present two cases of bladder paragangliomas in adults.
Methods: 2 women, 54 and 59 years-old, presented with abdominal pain. Laboratory studies were normal. In both cases a cystoscopy revealed lesions less than 5 cm in the bladder wall, and a transurethral resection was performed. Histology showed solid nests and sheets of small granular cells with salt-and-pepper chromatin. Mitotic rate was low, and no necrosis or lymphovascular invasion was identified.
Results: Tumour cells were positive for chromogranin, synaptophysin, CD56 and GATA-3. S100 highlighted the sustentacular cells, and Ki-67 was 2 - 5%. Keratin markers were negative. These findings were consistent with nonfunctional paragangliomas, and no recurrence has been reported so far.
Bladder paragangliomas arise from the chromaffin cells of the bladder, explaining their intramural location. In nonfunctional cases the most important differential diagnosis is urothelial carcinoma. Reactivity for CD56, chromogranin, synaptophysin, and S-100 are helpful in this distinction. Also, lack of reactivity with keratins, specially CK7, helps rule out other neuroendocrine neoplasms.
Conclusion: Bladder paragangliomas may present clinical, radiological and pathological features similar to bladder cancer, with few cases reported in the literature. Early and correct identification is key to avoid misdiagnosis and overtreatment.
Complete surgical removal of the lesion is considered the definitive treatment, either by transurethral resection or partial cystectomy, but long clinical and biological follow-up is warranted, as local recurrence can occur very late after the surgery.

E-PS-24-028
Intermediate-risk solitary fibrous tumour of the prostate presenting as an intravesical prostatic protrusion: a case report
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Background & objectives: Solitary Fibrous Tumour (SFT) of the prostate is rare, with approximately 50 cases reported, 14 confirmed after the discovery of the NAD2-STAT6 fusion. We present a case of a middle-age-adult with a SFT presenting as an Intravesical Prostatic Protrusion (IPP).
Methods: A 42-year-old man with a 5-year history of urinary retention and suprapubic pain, was diagnosed with a benign prostatic hyperplasia, and treated with alpha-blockers. One year later he had persistence of the symptoms and an ultrasound revealed an enlarged prostate with a lesion protruding into the urinary bladder lumen (17 mm). A transurethral resection of the prostate was performed.
Results: Microscopic examination showed a mesenchymal neoplasm with variably cellular patternless pattern, cells were spindled to ovoid with uniform nuclei, branching staghorn vessels, and areas of fibrosis, without necrosis. 7 mitosis per mm2 were identified. Neoplastic cells were diffusely positive for STAT6 and CD34, and Ki-67 rate was 7%. A diagnosis of intermediate-risk SFT was made. Patient is currently being followed up with no evidence of recurrence or metastasis.
Prostate-SFT mean age of presentation is 55 years, and most patients present with obstructive urinary symptoms. Presenting as an IPP is extremely unusual. Morphologic features are similar to extraprostatic SFTs and most of them are positive for STAT6, CD34, Bcl-2 and CD99.
Conclusion: Many metastatic risk models have been developed; the most widely used, also validated in extra thoracic SFTs, includes mitosis, patient age, and tumour size to classify tumours into low, intermediate, and high risk. Recurrence and metastasis are rare.

Complete surgical resection is the treatment of choice and the most important prognostic factor. Chemotherapy and/or radiotherapy should be considered as palliative treatment.

E-PS-24-029

Spontaneous regression of primary renal cell carcinoma: two cases

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Background & objectives: Renal cell carcinoma (RCC) accounts for 2% of all new cancer cases in adults. Although spontaneous regression in primary RCC and metastases is rare, it is a well-known phenomenon.
Methods: We report two cases of spontaneous regression of RCC in an 81-year-old and a 70-year-old male that underwent partial nephrectomy for an incidental kidney mass. The entire lesion was sampled in both cases, and immunohistochemistry studies were performed.
Results: In the first case, a 4.5 cm haemorrhagic and necrotic mass separated from the parenchyma by a smooth thick fibrous capsule was observed macroscopically. No viable tumour cells were observed in H&E sections and immunohistochemistry studies. The case was evaluated as RCC showing spontaneous regression. Subtype couldn't be determined.
In the second case, a 2.5 cm, off-white, hard tumoral mass surrounded by thin parenchyma was observed macroscopically. Tubular structures formed by cells with clear cytoplasm, which can hardly be distinguished between hyalinized and calcified areas, were seen in H&E sections. Cytoplasmic membranous staining with CA-IX was demonstrated by immunohistochemistry. The case was diagnosed as RCC-clear cell type showing spontaneous regression.
Conclusion: Spontaneous regression was reported in partial or complete RCC metastases from time to time. However, spontaneous regression of primary RCC is extremely rare. Only 4 cases have been reported in the literature. Regressed renal cell carcinomas should be considered in the differential diagnosis of solitary renal lesions and the entire lesion should be sampled.

E-PS-24-030

Tubulocystic renal cell carcinoma – a malignant entity with bland features and good prognosis

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Background & objectives: The differential diagnosis for multicystic renal neoplasms includes adult cystic nephroma and the recently described multilocular cystic renal neoplasm of low malignant potential and tubulocystic renal cell carcinoma. The latter is an indolent entity with few reported cases.
Methods: In this case report we present the case of an otherwise healthy 66-year-old male with an incidental finding of a Bosniak IIF-III cystic renal lesion with 2.8 cm. The growing of the mass in subsequent imaging studies prompted a partial left nephrectomy in this asymptomatic patient.
Results: The gross examination showed a well circumscribed and completely excised multilocular cystic lesion with 3x2.6x0.9 cm. Histology revealed multiple cysts lined by a single layer of hobnail cells with conspicuous nucleoli at 100x magnification and eosinophilic cytoplasm. No clear cell type of lining, areas of epithelial proliferation or intracystic structures were present. In the cyst walls there were tubular structures lined by flattened to cuboidal cell with no to little atypia. Immunochemical CD10, CK7, CK19, AMACR stains were positive in neoplastic cells while CD117, carbonic anhydrase IX and oestrogen and progesterone receptors were negative. Ki67 stain was positive in 1% of tumour cells. There was no colloidal iron staining.
Conclusion: While having good prognosis in most cases the exclusion of non-malignant entities is warranted since recurrence and metastasis have been reported. This case underlines the incidental diagnostic aspect of this carcinoma which is assonant with its indolent course. Recent studies have showed the tubulocystic renal cell carcinoma distinct genomic profile, but more is to be done in order to assert the prognosis of pure tubulocystic renal cell carcinoma and when in association to other entities.

E-PS-24-031

Basal cell carcinoma of Prostate with MSMB-NCOA4 fusion and a probable basal cell carcinoma in-situ: case report

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Background & objectives: Basal cell carcinomas of prostate (BCCP) is very rare. Lower urinary tract symptoms, normal PSA & rarity of tumour renders diagnosis difficult. This is an attempt to describe a non-existent Basal cell carcinoma in situ (BCCIS) for first time ever.
Methods: Prostatectomy material from a 74-old man was evaluated histologically, immunohistochemically and molecular studies (Archer FusionPlex Solid Tumour panel, whole genome sequencing & Single Nucleotide Polymorphism Arrays). Needle biopsies of abdominal wall metastasis and prostatic needle biopsy performed in 2005 were also evaluated.
Results: Histology revealed a diffusely infiltrative tumour with solid growth pattern and glandular structures representing BCCIS. Tumour cells were positive for P40/P63/CK5/ & Vimentin. PSA/NKX 3,1/CK7/CK20/GATA3/ & Uroplakin 2 were negative. A diagnosis of BCCP was rendered. Additionally, the glandular structures were seen 2-layered, the adluminal NKX 3,1 & PSA positive single cell layer of normal cubical cells and abluminal broader neoplastic cell layer positive for basal cell markers (Figures 3 and 4). These glands with prominent bilayering, noninfiltrative character, and a stiff basement membrane highlights a probable "Basal carcinoma in situ (BCCIS). Molecular examination detected MSMB-NCOA4 fusion. Patient had metastasis to abdominal wall 8 months later and showed similar features.
Conclusion: BCCP is an aggressive type of prostate cancer challenging to diagnose based on routine protocols. This results in delayed diagnosis & treatment and thus poorer prognosis. Patients with this subtype of prostate cancer need appropriately designed, and maybe a totally different follow-up regimen independent of PSA, as it's of no use in BCCP patients. Finally, diagnosis of BCCIS, if agreed upon, needs to be studied in a larger cohort to justify its existence and its role as a precursor lesion.

E-PS-24-032

Primary urothelial carcinoma of the prostate. Case report and review of literature

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Background & objectives: Primary urothelial carcinoma of the prostate is a very rare tumour accounting < 2 % of prostatic neoplasia. It has a poor prognosis even with in-situ disease only and 20% have distant metastases, commonly to bone, lung, liver.

Methods: Transurethral resection of prostate was done and covnetial biopsy with Hematoxylin Eosin was performed accompanied with immunohistochemistry to make the differential diagnosis.
Review of English literature for the Primary Urothelial Carcinoma of the Prostate.
Results: In this case report we present a 62 years old male, diagnosed with primary urothelial carcinoma of the prostate. The patient was diagnosed with hyperplasia of the prostate before 4 years. The levels of PSA are normal. Symptoms worsened 6 months ago with haematuria, pain, frequent urination. Digital rectal examination revealed that the prostate is enlarged and hard in the left lobe. The transurethral prostatic resection was performed and after the histopathologic examination together with immunohistochemistry the patient was diagnosed with primary urothelial carcinoma of the prostate.
Conclusion: Primary urothelial carcinoma of the prostate is a very rare tumour with a poor prognosis. In this way an early diagnosis and differential diagnosis is very important and should be taken in consideration in cases of worsening symptoms in a patient suffering with dysuria and with a firm prostate.

E-PS-24-033
Papillary renal neoplasm with reverse polarity: an emerging entity
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Background & objectives: Papillary renal cell neoplasm with reverse polarity (PRNRP) is a recently described entity of renal tumour with unique morphological, immunohistochemical and molecular features. The objective is to emphasize on its pathological characteristics.
Methods: We report the case of a 40-year-old woman with an indolent renal nodule which was operated on by right partial nephrectomy. Gross examination revealed a 2 cm well limited tumour.
Results: On microscopy, the tumour show papillary and tubulopapillary architecture. Tumour cells were cubic and had predominantly eosinophilic cytoplasm, round to oval nuclei with stippled to clumped chromatin, minimal nuclear pleomorphism, inconspicuous nucleoli, and very rare mitosis. Tumour cells showed expression of CK7, GATA3 and PAX8. There were no expression of CD10, P504S, CK20, TFE3 and FH. Expression of INI1 and SDHB was retained. New Generation sequencing showed a KRAS c.35G>T, p.Gly12Val mutation. SNParray showed loss of chromosomes 1, 7, 11, 13, 19 and 20. There were also segmental loss in 2p25-q23, 3p12-p11, 5q22-q35, 6q, 9p, 10p15-q21, 17q21-q27, 18p-q12 and segmental gains in 4p13-q35, 6p25-p21 and 15q11-q15.The final diagnosis was PRNRP.
Conclusion: PRNRP is a recently described tumour, by Al-Obaidy et al in 2019, defined by a tubulo-papillary architecture, GATA3 positivity and the presence of KRAS mutations. Approximately, 100 cases of PRNRP have been reported on the literature and they all exhibit an indolent clinical behaviour. Thus, this entity must be more recognized by pathologists for a better clinical guidance.

E-PS-24-034
Well differenciated neuroendocrine tumour of the kidney. Histological, immunohistochemical, molecular and electron microscopy, analysis of a single case in a universitary hospital
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Background & objectives: Well differenciated neuroendocrine tumour of the kidney (WDNETK) not related to urothelial carcinoma is an extremely rare entity with less than 100 reported cases worldwide. It occurs in the renal parenchyma and shows neuroendocrine differentiation based on morphology and immunohistochemistry.
Methods: We reviewed our files from 1970 to April 2022 founding a single case of WDNETK. The diagnosis was achieved by using Hematoxilin-Eosin, immunohistochemical, molecular studies and electron microscopy. From the clinical history we obtained the age at diagnosis, symptomatology and radiological studies.
Results: A 45 year old female with a renal mass first diagnosed in US after an acute renal colic. A radical nephroureterectomy with regional lymphadenectomy was performed. The tumour showed organoid architecture, diffuse positivity for synaptophysin and CD56, focal for chromogranin A. GATA 3, TTF1, p63, PAX 8, CK7, CK 20 and cathepsine K were negative. The proliferation index (Ki 67) was close to 8% in hotspot areas. Necrosis and lymphovascular invasion were identified. TFE3 and TFB were non rearranged by FISH. Following histological, immunohistochemical and molecular analysis the diagnosis of well differenciated neuroendocrine tumour of renal parenchyma was achieved. Four lymph nodes had metastasis.
Conclusion: WDNETK is an exceptionally rare entity and due to its rarity it poses both a diagnostic and therapeutic challenge. Its main prognostic factors are stage and Ki 67 proliferation index and both should be reported. According to WHO 2022 classification the threshold of 3% of Ki67 separates good from poor prognostic although there are no consensus to establish grades like in gastrointestinal well differentiated neuroendocrine tumours.

E-PS-24-036
Changes of nerve density in prostate cancer
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Background & objectives: Innervation and axonogenesis in prostate cancer might be a promising therapeutic target, prognostic marker, and replacement for reporting perineural invasion in small samples. We aimed to detect changes in nerve density in BPH, prostate cancer, and correlation with Gleason score.
Methods: We used patient samples of prostate cancer (n=34), BPH (n=18), and autopsy prostate samples without pathological changes (n=36). For immunohistochemical detection of nerves and nerve proliferation, we used double-staining using antibodies against S100 and PCNA. The nerve area was measured by histomorphometry with colour deconvolution to extract S100 positivity. The proliferation of nerves was analysed quantitatively.
Results: There was a significant decrease of nerve density in prostate cancer compared to normal prostate and BPH. We also found a non-significant decline of nerve density with an increasing Gleason score. There was higher nerve density in BPH than in normal prostate tissue, but the difference wasn't significant.
There were only isolated PCNA-positive cells in nerve fibres, mostly in benign hyperplasia. However, because of the sparse occurrence of these cells, we didn't quantify them.
Conclusion: We found a significant decrease of nerve density in prostate cancer without proof of axonogenesis. These findings are opposite to the results of other authors. However, almost all of the works are experimental, whereas there is a minimal amount of data about changes of the innervation of human

prostate cancer, specifically compared to normal tissue and benign changes. Our findings are important for further research on the innervation of human prostate cancer and its possible applications.
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E-PS-24-037
Undescended testis associated with seminoma and persistent Mullerian duct syndrome
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Background & objectives: Male sex differentiation is driven by testosterone and anti-mullerian hormone (AMH) for the regression of Mullerian ducts in foetuses. Mutations inactivating AMH or its receptor AMHRII lead to rare Persistent Mullerian Duct Syndrome (PMDS) in otherwise normally-virilized 46, XY males.
Methods: A 21-year-old man was referred to a urologist for right cryptorchidism, an early clinical sign of PMDS. Laparoscopy revealed the atrophic testis in the inguinal canal attached to the uterus. Excision of the testis and uterus was done. We received testis (1.5x1.2x1 cm), spermatic cord (3 cm), an attached hypoplastic uterus (2.5x1.2x1 cm), and a fallopian tube (4 cm).
Results: Microscopically, the testis was atrophic with marked loss of germ cells, and with classical seminomatous germ cell tumour measured 1.3 cm. Cut sections of the uterus and fallopian tube showed the classical histology of these organs.
Conclusion: Though rare, every surgeon operating upon inguinal hernia or undescended testes, or cryptorchidism needs to know about the presence of the uterus in a phenotypic male patient at any age. A high degree of suspicion and awareness is needed to diagnose this condition. Patients with PMDS are at higher risk of testicular malignancy than patients with isolated undescended testis. Early treatment is needed to maintain fertility and prevent the occurrence of malignancy in the testis or in remnant Mullerian structures.

E-PS-24-038
Collecting duct carcinoma, a great mimicker - a case report of a rare neoplasia and literature review
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Background & objectives: Collecting duct carcinoma is a high-grade renal neoplasia, presumably arising from the Bellini ducts. It accounts for less than 1% of renal malignancies, yet the clinicopathological overlap with other high-grade malignancies makes the incidence of this lesion difficult to ascertain.
Methods: We report the case of a 69-year-old male without previous history of neoplastic lesions that presented in our institution with a history of gross haematuria. At admission, an imagological evaluation was performed that revealed a cystic lesion with an internal solid component in continuity with the cystic wall. This lesion was classified as Bosniak IV. A tumorectomy was then performed.
Results: The superior pole of the kidney was occupied by a cystic lesion with a smooth surface. In section, a solitary white papillary projection was identified in the interior component of the cyst. The projection had continuity from the parenchyma to the adipose tissue. Histologically, the lesion was adjacent to the renal medulla with a solid and tubo-papilary architecture and an desmoplastic infiltrating component. Composed of cuboidal cells, with eosinophilic cytoplasm and large nuclei with prominent nucleoli. Sarcomatoid differentiation was also present. The cells expressed diffuse positivity for PAX-8 (strong) and GATA3 (weak); negativity for p63, CK5, CK7, CA IX, CD117 e CD10. The diagnosis of collecting duct carcinoma was made.
Conclusion: Other clinicopathological overlapping entities, such as fumarate hydratase-deficient renal cell carcinoma, papillary renal cell carcinoma, mucinous tubular spindle cell carcinoma with high-grade transformation, high-grade unclassified renal cell carcinoma and metastatic carcinoma, must be considered in the differential diagnosis and excluded. At the time of this report, the patient presents no signs of disease progression.

E-PS-24-039
Divergent infiltrating high grade urothelial carcinoma with small cell neuroendocrine carcinoma differentiation
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Background & objectives: Approximately 25-30% of urothelial carcinomas (UC) show divergent differentiation that includes urothelial and non-urothelial (squamous, glandular or neuroendocrine) histological variants. The vast majority of bladder neuroendocrine carcinomas (NECs) are usually admixed with a non-neuroendocrine component, mostly infiltrating UC.
Methods: A 60-year-old man presented with painless gross haematuria and CT and cystoscopy revealed an exophytic mass localized at the dome of the bladder. A transurethral resection of bladder tumour (TURBT) was performed and the surgical specimen was entirely submitted for microscopic examination in the pathology lab.
Results: Histological examination revealed a high-grade muscle-invading UC with tumour cells arranged in nests and sheets. Interestingly, four neoplastic foci had distinct morphological features and the typical appearance of small cell neuroendocrine carcinoma (SmCC). Immunohistochemical analysis revealed that the SmCC component had a proliferation marker Ki-67 labelling index above 90% and expressed CD56 and CD117 but was negative for other neuroendocrine markers (chromogranin, synaptophysin and INSM1) and for TTF1 and LCA. On the contrary, the UC component displayed focal and weak expression of CD117 and was CD56 negative. Moreover, both the SmCC and UC components showed aberrant expression (strong and diffuse) of p53, overexpression of p16 and loss of RB1.
Conclusion: Although the presence of SmCC mixed with other bladder neoplasm should always be reported, it is controversial if the diagnosis should reflect the percentage of the SmCC component. We avoided the term "mixed SmCC-UC", following the definition of mixed neuroendocrine-non neuroendocrine neoplasms (MiNENs). Instead, the term "UC with SmCC differentiation" was used to highlight the focal distribution of the neuroendocrine component. The expression profile of p53 and RB1 classifies this tumour in the neuroendocrine-like molecular subtype of muscle-infiltrative bladder cancer.

E-PS-24-040
Temporal bone metastasis revealing a papillary renal cell carcinoma
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Background & objectives: Papillary renal cell carcinoma (PRCC) is the second most common type of renal carcinoma(RC), representing approximately 18.5% of RC. Metastatic PRCC involving temporal bone is extremely rare.
We aim to analyse the clinico-pathological features of inhabituel metastatic sites of PRCC.
Methods: We present a case of PRCC revealed by a temporal bone metastasis whose clinical and radiological appearances were misleading in a 34 year old woman, without pathological past history. This case was diagnosed in our institution in 2022.
Results: Patient was referred to neurosurgery department for a rapidly evolving mass of the fronto-temporal region. The magnetic resonance imaging concluted to an osteosarcoma. Thus, patient underwent neurosurgery which revealed an haemorrhagic tumour appearing to be of muscular origin.
Grossly, specimen consisted of a whitish fribale lesion measuring 4cm.
Histologically, the tumour was composed of papillae formed by delicate fibrovascular cores, lined by a single layer of tumour cells with abundant eosinophilic cytoplasm and enlarged hyperchromatic nuclei with prominent nucleoli. Tumour cells expressed CD10, P504-S and focally CK7, TTF1 ans CK20 were negative evocating renal metastasis. Abdominal-ultrasound was performed showing a renal mass. Therefore, patient was referred to urologic department.
Conclusion: Lung metastasis and bone metastasis are the most most metastatic sites of PRCC. Metastatic PRCC involving the fronto-temporal bone is a rare condition and misdiagnosis is not uncommon. Clinical history information of the metastasis, morphological characteristics and combined immunohistochemistry are the key to identify the renaal origin of a metastatic PRCC.

E-PS-24-042
Unusual presentation of ureteriris cystica associated with malignancy
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Background & objectives: Ureteritis cystica is a rare urological disease and is usually seen as incidental finding. Its aetiology is not clearly known, but it is associated with chronic urothelial irritation caused by nephrolithiasis and urinary tract infections.
Methods: We present the case of 86-year-old who complained of haematuria. Abdominal ultrasonography revealed a right-sided renal mass with extension into the renal vein and inferior vena cava. Nephroureterectomy and thrombectomy was performed. On the gross examination, two different lesions was observed: a multycistic-yellow polypoid mass protruding into the ureter lumen, and a solid tumour mass in the kidney.
Results: Postoperative histopathological examination revealed clear cell renal carcinoma, G1 according to WHO/ISUP (sized 11,5 cm). The renal vein thrombus was composed of the same carcinoma cell and the perirenal fat and margin of the ureter were negative (pT3N0M0). Microscopic lymphovascular invasion was observed near the right renal hilum.
The ureteral lesion was composed of multiple dilated urothelial cysts, known as van Brunn nests, embedded below their mucosal lining, and filled with macrophages and eosinophilic and amorphous material content. The final diagnosis was polyoid ureteritis cystica (sized: 1,4 cm).
Conclusion: Ureteritis cystica is a benign and indolent lesion characterized by the formation of single or multiple cysts in the ureteral lumen. It is usually associated with inflammation/infectious diseases. Although, in this case, it was is shown as a polypoid mass associated with a renal carcinoma.

E-PS-24-043
Encrusted cystitis and pyelitis: study of 2 cases
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Background & objectives: Encrusted urinary tract infections (EI) are an uncommon disorders characterized by the calcification of the urothelial wall. EI is usually due to Corynebacterium-urealyticum, a Gram-positive-bacillus, which has a major urease activity.
We aim to analyse clinico-pathological aspects of the EI.
Methods: Two cases of encrusted cystitis and pyelitis of 2 males aged 57 and 62 years old, respectively, without pathological past history, were diagnosed between 2014 and 2020 in our institution. The patients were referred to the urology department for a management of urosepsis.
Results: Physical examination showed systemic manifestation including fever and pelvic pain. Urologic symptoms consisted of dysuria in two patients and macroscopic haematuria in one patient. Blood analysis showed a neutrophilic leukocytosis. Urinalysis revealed alkaline urine with pyuria and haematuria. CT-scan showed in all cases a calcified thickening of the urothelial wall and moderate bilateral and unilateral hydronephrosis, respectively. Thus, the diagnosis of urosepsis caused by perforated urinary EI was suspected. Bacterial culture results were positive to Corynebacterium-urealyticum in all cases. Adjusted antibiotherapy was undertaken in all cases. Histological examination showed chronic cystitis comprising calcic deposits. The evolution was fatal in one patient due to septic shock and uneventful in another patient.
Conclusion: Encrusted cystitis and pyelitis is a rare entity characterized by a poor prognosis in case of delayed diagnosis and inappropriate treatment. Bladder perforation and urosepsis are a serious complications that can be fatal as described in our case.

E-PS-24-044
Ductal adenocarcinoma of the prostate presenting as penile metastasis
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Background & objectives: In spite of its rich vascularization, penile metastasis are extremely rare and are commonly from the prostate and bladder. Herein we present a case of ductal adenocarcinoma of the prostate presenting as a penile metastasis in a 83-year old patient.
Methods: A 83-year old patient with a history of chronic urethral catheterization post-urethroplasty and a diagnosis of prostate acinar adenocarcinoma(2019), for which he received combined hormonal-radiation therapy, presented with an exofitic lesion of the glans (13 mm) and general stiffness of the penis. After imagiologic evaluation documenting the presence of

nodular lesions in the penile shaft, the patient underwent radical penectomy.
Results: Macroscopically, the entirety of the corpora cavernosa were occupied by a tumour that infiltrated the glans but spared the urethra. Histologic examination showed it was composed of large and complex glands lined by tall pseudostratified columnar cells; moderate nuclear atypia with proeminent nucleoli was seen. Immunohistochemistry studies showed positivity for NKX3 and negativity for cytokeratins 7 and 20, PSA and GATA3. Given the clinical history and these histologic findings, a diagnosis of metastatic ductal adenocarcinoma of the prostate was made.
Conclusion: The prostate is the most common site of origin of secondary tumours of the penis, presenting ductal features in most cases. Our patient had a previous biopsy diagnosis of acinar adenocarcinoma, which showed foci of intraductal carcinoma; however, he was not submitted to radical prostatectomy hence we are not aware of the extent of the morphological spectrum that composes the primary tumour. Nevertheless, immunohistochemical analysis is essential in these cases to rule out urethral urothelial carcinomas, a histological pitfall.

E-PS-24-045
Lobular breast carcinoma metastasis to the urinary bladder mimicking plasmacytoid variant of urothelial carcinoma
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Background & objectives: Very few cases of breast cancer metastasis to the bladder are reported in the literature. With 13 recognized variants, urothelial carcinoma can be easily mimicked by metastasis, so a high level of suspicion is needed to avoid pitfalls.
Methods: A 67-year-old woman with history of mixed lobular and ductal breast carcinoma, in 2006, with multiples relapses over the years, presented to our institution with haematuria. Diagnostic exams showed, right uretero-hydronephrosis. Cystectomy showed a bladder lesion which was resected.
Results: Multiple fragments of tissue were analysed, which revealed, upon histologic examination, a diffuse infiltration of the submucosa and detrusor muscle of cords, solid sheets, and singly dispersed neoplastic cells, with eccentric hyperchromatic nuclei and dense eosinophilic cytoplasm, sometimes univacuolated. No evidence of urothelial carcinoma-in-situ was found. Immunohistochemistry showed positivity for pan-cytokeratin's AE1/AE3 and CAM5.2, while p40 was negative. GATA-3 was also positive. With the known history of breast cancer, oestrogen and progesterone receptors were performed, which were diffusely positive, thus proving the breast origin of the lesion. Bloodborne metastasis to the bladder are exceedingly rare and breast cancer represents a small minority of those.
Conclusion: This case encompasses an insidious metastasis pattern of lobular breast carcinoma and how it can overlap morphologically and immunohistochemically (GATA3+) with the plasmacytoid variant of urothelial carcinoma. This case-report shows that a high level of suspicion and a careful clinical investigation are essential to avoid misdiagnosis and adds to the few cases reported of breast cancer metastasis to the bladder. The patient recovered from her urinary symptoms but died from advanced metastatic breast cancer one month after this diagnosis.

E-PS-24-046
Morphological findings in paediatric heminephrectomy specimens – the pathological and MRI study
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Background & objectives: The aim of this study was histopathological evaluation of renal dysplasia and other changes in heminephrectomy specimens from the children with malformations or urodynamic disorders, in context of clinical and modern radiological imaging (Hydro-MRI, Urography MRI).
Methods: The material: 24 heminephrectomy cases (16 girls, 8 boys; age 8 months -18 years), operated due to renal duplication, vesicoureteral reflux, ectopic ureter, hydronephrosis or afunctional renal pole. Multiple sections stained H-E and Masson trichrome were examined for the presence and degree of dysplasia, severity of inflammation, fibrosis, areas of cartilage, arteriolosclerosis, and dysmorphic vessels. Uro-MRI own scale analysis.
Results: Pathologically the presence of renal dysplasia was observed in 20 out of 24 cases, while radiological changes- in 17 cases. In four cases dysplasia was classified as segmental and in the remaining 16 as focal. The percentage of area covered by dysplasia varied from 2 to 100%. Small multiple cysts were found in 8 cases. All cases with renal dysplasia showed chronic pyelonephritis with lymphoid follicle formation. The degree of renal parenchymal fibrosis varied from minimal to severe. Areas of increased fibrosis were usually accompanied by intense chronic inflammation, more advanced arteriolosclerosis, and glomerular sclerosis. Cartilage foci were identified in three cases.
Conclusion: Renal dysplasia is a quite common finding in the paediatric chronic kidney disease connected to the urinary tract malformations such as vesicoureteral reflux, ureteral atresia, or duplication of the kidney. The percentage of renal parenchyma affected by dysplasia may be low, especially in kidneys with hydronephrosis, where renal dysplasia can be undetectable radiologically.

E-PS-24-047
Primary prostatic leiomyosarcoma: a rare misleading tumour
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Background & objectives: Primary prostatic leiomysarcoma is an extremely rare malignancy that accounts for only 0.1% of all primary prostatic neoplasms. Clinical presentation is not specific mimicking other prostatic disorders.
We aim to analyse the clinical and pathological aspects of this rare entity.
Methods: We present a case of primary prostatic leiomyosarcoma in a 64 year old man, without pathological past history. This case was diagnosed in our institution in 2019.
Results: Patient presented at the urology consultation with lower urinary tract symptoms related to bladder obstruction. He reported no haematuria or perineal pain. Serum prostate-specific-antigen level was normal.
The diagnosis of benign prostatic hypertrophy was suspected and patient underwent prostatic transurethral resection.
Histological examination showed a large necrotic sarcomatous proliferation composed of spindle-shaped cells, with elongated plump nuclei, nuclear

pleomorphism and brisk bizarre multipolar mitotic activity. Some areas revealed an epithelioid morpholgy. The tumour infiltrates massively the prostatic gland.
Immunohistochemistery showed positive staining for vimentine and smooth muscle actine. Tumour cells were negative for Cytokeratin and CD34.Subsequently, the diagnosis of high grade leiomyosarcoma was made. Meanwhile, the patient had died.
Conclusion: Primary prostatic leiomyosarcoma is a rare aggressive neoplasm with misleading clinical features which may delay the diagnosis. Generally, the overall prognosis is poor. There are no guidelines concerning the therapeutic approach since primary prostatic sarcomas are extremely uncommon.

E-PS-24-048
Fumarate hydratase deficient renal cell carcinoma – a case of hereditary leiomyomatosis and renal cell carcinoma - associated renal cell carcinoma?
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Background & objectives: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an inheritable autosomal dominant syndrome caused by germline mutations in the fumarate hydratase (FH) gene and is characterized by the development of cutaneous and uterine leiomyomas and renal cell carcinoma (RCC).
Methods: We report a case of a 56-year-old man with a renal lesion measuring 10 cm associated with lymph node metastasis and peritoneal carcinomatosis, found incidentally on a CT scan in 2014. After 5 years of chemotherapy, a pancreatic lesion measuring 5 cm was also found on a follow-up CT scan. The patient was submitted to a total nephrectomy and splenopancreatectomy.
Results: We received a total nephrectomy specimen with a solid capsulated neoplasia on the upper pole of the kidney measuring 4,5 cm with a white and firm cut surface that invaded the ipsilateral adrenal gland. The splenopancreatectomy specimen showed a similar appearing neoplasia involving the pancreas, peripancreatic fat and lymph nodes. At histologic examination the neoplasia presented papillary, tubular, and solid architecture, cells with clarified or eosinophilic cytoplasm, prominent nucleoli (grade 3 WHO/ISUP) and perinucleolar halo. Immunohistochemistry revealed multifocal positivity for CAIX, AMACR, CK34βE12, CD10 and Vimentin in the neoplastic cells with negativity for CK7 and TFE3. There was loss of expression of Fumarate Hydratase.
Conclusion: Our patient had no history of cutaneous leiomyomas. As the germline mutation status is often unknown at the time of diagnosis, and not all cases are syndromic, the term FH-deficient RCC is preferred over HLRCC-associated RCC. FH-deficient RCCs demonstrate a variety of architectural patterns and therefore a low threshold for immunohistochemistry is recommended in difficult cases. The estimated lifetime renal cancer risk for FH mutation carriers is estimated to be 15-30%. Our patient is alive 9 months after the surgery.

E-PS-24-049
A recently described entity: biphasic squamoid alveolar papillary renal cell carcinoma
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Background & objectives: Biphasic squamoid alveolar papillary renal cell carcinoma (BSA-PRCC) was first described in 2012 by Petersson et al. who reported two cases of tumours with a distinctly dual-cell population composed of alveolated islands of large squamoid cells surrounded by smaller cells.
Methods: We herein report a case of a 61-year-old woman who was submitted to a renal ultrasound due to a six-month history of sustained weight loss. The ultrasound and subsequent CT scan revealed a renal mass in the lower pole of the kidney measuring 1,5 cm. To remove this lesion, a partial nephrectomy was performed.
Results: We received a partial nephrectomy specimen almost totally occupied by a tumour measuring 1,8 cm with a solid and yellow-tan cut surface. Histologic examination showed a distinctly dual cell population, one of relatively uniform, small neoplastic cells with clarified cytoplasm and round low-grade nuclei forming alveolar-like structures. The other, separated from the former by a slit space, composed of solid nests of larger squamoid cells with eosinophilic voluminous cytoplasm and large nuclei with prominent nucleoli (grade 2 WHO/ISUP). Immunohistochemistry revealed expression of CK7, AMACR, EMA, CK34βE12, CD10 (focal) and Vimentin (focal) in the neoplastic cell with negativity for CAIX. Cyclin D1 highlighted the squamoid cell islands.
Conclusion: Biphasic squamoid alveolar papillary renal cell carcinoma has been mainly described as a morphological variant of renal cell carcinoma (RCC). Its incidence has been estimated at less than 1% of papillary RCC. MET alterations and chromosome 7 trisomy have been recently reported in, respectively, 60% and 87,5% of BSA-PRCCs linking it to type 1 papillary RCC. Metastases occur in 9,4% of the cases but fortunately our patient is currently free of disease 13 months after the surgery.

E-PS-24-050
An unexpected presentation of renal cell carcinoma as a renal hilar lymph node metastasis without radiologically or macroscopically evident renal mass
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Background & objectives: It's extremely rare for renal cell carcinoma(RCC) to be diagnosed from metastasis without evidence of radiologically/macroscopically renal mass. The present case was diagnosed from lymph node metastasis, as there wasn't any renal mass. It was striking with many other features.
Methods: A 73-year-old woman was admitted to the hospital with abdominal pain. CT, PET/CT scans revealed a well-demarcated mass between the left kidney hilum and aorta (SUV-max=30.6), with a radiological appearance of lymphadenopathy. Fine-needle aspiration biopsy from the mass revealed a poorly differentiated, malignant epithelioid tumour with a preliminary diagnosis of sarcoma, due to epithelial-marker negativity. Patient underwent left radical nephrectomy.
Results: Macroscopically, a solid hilar mass, 9,5cm in long diameter, unrelated to the renal parenchyma/pelvicalyceal system was detected. No renal mass was noticed. Microscopically, tumour cells effacing the lymph node parenchyma were arranged in solid and alveolar pattern. They were polygonal with vesicular nuclei, prominent eosinophilic nucleoli, abundant eosinophilic cytoplasm, some with rhabdoid differentiation. Extensive necrosis was noted. Immunohistochemically, Pancytokeratin, EMA, PAX-8,Vimentin,RCCag, CD10, were positive, suggesting that the tumour was RCC metastasis. Based on these immunohistochemical findings, renal parenchyma was totally resampled, two distinct microscopic RCC foci (Low grade clear RCC-4mm, Chromophobe RCC-2mm) were

barely noticed in the renal cortex. Comparative NGS analysis of both metastatic and primary foci were planned.
Conclusion: Present case was interesting in different aspects. Unusual presentation posed a diagnostic pitfall. Despite of the metastatic foci forming a large mass with aggressive histological features, primary tumour foci were innocent, with milimetric, hardly detected nodules, low-grade histological features. Another striking feature was that these millimetric renal nodules showed different RCC types. We shared this case to raise awareness about this very rare presentation of RCC and to emphasize the importance of extensive sampling of the renal parenchyma when required.

E-PS-24-051
Metastasis of renal clear cell carcinoma to contralateral ureter twenty years later after radical nephrectomy: a challenging diagnosis
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Background & objectives: Metachronous metastasis of renal cell carcinoma (RCC) to the contralateral ureter is extremely rare. We report a rare case of RCC metastasized to the contralateral ureter twenty years later and highlight the clinicopathological features of this rare presentation.
Methods: A 58-year-old man with a history of a right radical nephrectomy for clear RCC 20 years ago and lost to follow-up presented an obstructive renal failure.
Results: MRI shows a left tumour of the upper ureter. The patient underwent a radical left nephroureterectomy. On gross examination, the upper ureter contained a white nodule extending over 1 cm with foci of haemorrhagic changes. The microscopic examination shows compact nests and sheets of cells with clear cytoplasm and distinct membrane growing beneath the urothelium and limited to the muscular propria of the ureter consistent with a metastasis of a clear RCC. Immunohistochemistry confirmed the diagnosis of contralateral metastasis of clear cell renal carcinoma grade 2 of the ISUP grading system. Tumour cells were positive for CD10, EMA, and vimentin and negative for AMACR and CK7.
Conclusion: Although clear RCC can metastasize to any location within the body, involvement of the contralateral ureter is very rare. This unusual diagnosis should be considered in any patient after treatment for RCC. Clear cell RCC has a worse prognosis than papillary or chromophobe RCCs, when matched for stage, and is more likely to present at an advanced stage or with existing metastases

E-PS-24-052
Primary small cell carcinoma of the kidney: a rare case report
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Background & objectives: Small cell carcinoma (SCC) is most commonly seen in the lung, but rare cases of extrapulmonary sites have also been reported. Primary SCC of the kidney is an extremely rare neoplasm representing < 1% of renal neoplasms.
Methods: A 27-year-old women without any previous disease, presented with a history of right lumbar abdominal pain for 2 months. A computed tomography scan of the abdomen revealed an ill-defined, large heterogeneous tumour in the upper pole of the left kidney, measuring 14,7cm and infiltrating the perirenal tissue. The patient underwent a left radical nephrectomy.
Results: Gross pathological examination of the surgical specimen showed a large mass measuring 10 cm. Cut sections were brownish with necrotic areas. The renal capsule was intact. On Histologic examination, the tumour was composed predominantly of nested growth pattern with ribbons associated with extensive necrosis areas. These nests are surrounded by delicate connective tracts in a neuroendocrine-like pattern. The tumour cells were small with indistinct cell borders, scant cytoplasm, hyperchromatic nuclei with fine granular chromatin, and high mitotic activity.
Immunohistochemical stains revealed that the tumour cells were strongly positive for CD56. The ki67 index was 60%. The tumour was staged as pT2a.
Conclusion: SCC of the kidney is a high neuroendocrine neoplasm with aggressive behaviour and a tendency to develop early nodal and disseminated metastatic disease. It is an extremely rare neoplasm, fewer than 60 cases have been reported in the literature.
The diagnosis of a SCC is histologic and immunohistochemical. SCC is mainly misdiagnosed as other small round cell tumours. However, it is much more important always to rule out the existence of a primary lung tumour metastatic to the kidney.

E-PS-24-053
The Prevalence of CHEK 1 and CHEK 2 mutations in prostate cancer in Jordan population: a retrospective cohort study
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Background & objectives: Prostate cancer (PCa) is one of the most common types of male cancers. This study aimed to investigate the occurrence of variations in mammalian checkpoint kinase 1/2 (CHEK1/CHEK2) genes as key signal transducers inside the genomic integrity checkpoints in PCa.
Methods: FFPE-PCa specimens of radical prostatectomies from 74 Jordanian patients were subjected to DNA extraction, polymerase chain reactions and Sanger sequencing to screen the mutations in selected exons of CHEK1 and CHEK2 tumour suppressor genes.
Results: The mean age of the study population was 72 years. The mean of the PSA was 60 ug/L. The analysis of the CHEK1 and CHEK2 genes showed the presence of two point mutations in CHEK1 and CHEK2 genes (2/74, 2.8%). Specifically, F281L (T/C) (1.4%) homologous missense point mutation in the CHEK2 gene and c.564A>AT (188 P>P/P) (1.4%) silent mutation in exon 6 (kinase domain) of CHEK1 gene. However, the 1100delC mutation was not detected in the studied PCa samples.
Conclusion: We found, and in line with previous studies, lack of association between CHEK1 mutations and PCa development. The presence of 1.4% of mutation in CHEK2 in our results supported the possible role of genetic variants in this gene and the development of PCa. Further studies are needed with larger cohorts to shed more light on these findings and to reveal the genetic predisposition of the CHEK2 gene in the development of PCa in Jordan and perform screening of more exons.

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E-PS-MD-01-001

Automation meets reliability: use of Oncomine™ Precision Assay on the Genexus™ System for accurate identification of cancer biomarkers in FFPE and liquid biopsy samples

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Background & objectives: We report the use of the Oncomine™ Precision Assay (OPA) with the Genexus™ System which provides a fast, accurate and comprehensive genetic profile across 50 key genes using DNA and RNA from FFPE tissues or liquid biopsy samples.
Methods: Contrived and clinical research samples with known variants were used for the OPA FFPE and liquid biopsy workflows (n = 30). NA quantification was completed using the Genexus™ purification instrument's Qubit™ feature after purification. Extracted NA was transferred to the Genexus™ sequencer for library preparation, sequencing, variant and QC reporting using the onboard Ion Torrent™ analysis software.
Results: The OPA assay only required 10ng of DNA and RNA from FFPE samples and 20ng of cfTNA from liquid biopsy samples. Genexus™ purification instrument onboard quantitation data showed successful extraction of NA exceeding the required yields for library preparation. Excess NA was automatically aliquoted into an archive plate and stored for future use. Sequencing results for four samples of FFPE or liquid biopsy were reported within 24 hours. Both Control and clinical research samples showed expected assay metrics including read coverage, molecular coverage, and uniformity. The results reported all expected variants at correct allele frequencies, including BRAF V600E, KRAS G12C, PIK3CA N345K, and AKT1 E17K.
Conclusion: The Genexus™ system provides a user-friendly workflow with automated NA purification, quantitation, sample dilution, library preparation, sequencing, and data analysis with minimal hands-on time that can be performed with limited expertise to obtain results within 24 hours. Reliable identification of variants from control and clinical research samples of FFPE and liquid biopsy origin with optimal assay metrics demonstrates the successful use of the OPA assay and Genexus™ system that can be confidently used in clinical oncology research.

E-PS-MD-01-002

RAS/BRAF mutations in colorectal cancer : assessment of its status in a north African population compared to European population

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Background & objectives: Kras/Nras/Braf mutation screening is recommended in metastatic colorectal cancer for personalized medicine therapy. Since epidemiology of colorectal cancer in north African population is different from European population, we aimed to compare mutational status in the two populations.
Methods: Ras/Braf screening was achieved using the Idylla technologies on formalin fixed paraffin embedded tissue sections. Spotting areas with the greatest amount of tumoral cells was performed on HE slides. A threshold of 10% tumoral cells was required. Then, 1 x 5 µm tissue section was prepared from the corresponding paraffin block.
Results: We tested Ras and Braf mutations in a series of 250 colorectal patients with or without metastasis.
Our results showed 58% of Ras (Kras and Nras) mutations and 3% of Braf V600 mutations. 56% of mutations were present in metastatic colorectal patients and 44% in non metastatic colorectal patients. Moreover it seems that we could not predict the type of mutation according to any histologic classification.
Conclusion: Ras/Braf mutation frequency in our population approaches occidental series.

E-PS-MD-01-003

Molecular markers in group 3 and group 4 medulloblastomas

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Background & objectives: Together, group 3 and group 4 medulloblastomas represent up to 70% of paediatric cases; however, their distinction can be challenging. The objective of the study is to evaluate five genes reported as potentially discriminated amongst both groups.
Methods: Seventy-five patients diagnosed with medulloblastoma and treated at Hospital Infantil de México Federico Gómez were included. Molecular classification was assessed by Polymerase Chain Reaction, based on 22 gene panel proposed by Northcott et al 2012, plus ANO2, DISC1, ARHGAP18, GMR8, PRDM6. The expression of the novel genes was evaluated between the four groups and compared with four cerebellar control samples.
Results: Using the 22 subgroup signature genes, samples were classified as 8/75 wingless, 27/75 sonic hedgehog, 22/75 group 3, and 18/75 group 4 medulloblastomas.
Thereafter, when compared between the four subgroups, mean fold change values for ANO2 were 4.00, 1.20, 8.46 and 10.18; for DISC1 were 17.36, 15.22, 12.28 and 19.72; for ARHGAP18 were 2.52, 4.28, 14.71 and 8.59; for GRM8 were 152.9, 814.7, 230.6 and 1381.9; and, for PRDM6 were 16.21, 11.57, 19.26, and 27.40, for wingless, sonic hedgehog, group 3, and group 4, respectively. Consequently, the overexpression of ANO2, DISC1, GRM8 and PRDM6 were consistent with group 4, while overexpression of ARHGAP18 with group 3 subgroup assignment.
Conclusion: This study confirms differential expression of the five genes analysed between the four main molecular subgroups of medulloblastoma, furthermore, help to differentiate amongst groups 3 and 4.
Outputs provide continued support for group 3 and group 4 distinction. Next step is to validate the set of genes by methylation or with an independent validation cohort of medulloblastomas. Supplementary studies may also provide insights to facilitate groups 3 and 4 subtypification using the evaluated genes.
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