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ABDOMINAL IMAGING

ORIGINAL ARTICLE

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Diagnostic performance of magnetic resonance imaging in preoperative local staging of rectal cancer after neoadjuvant chemoradiotherapy

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PURPOSE

This paper aims to investigate the diagnostic performance of magnetic resonance imaging (MRI) in predicting the pathologic stage of locally advanced rectal cancer (LARC) after neoadjuvant chemoradiotherapy (CRT) and the role of MRI in selecting patients with a pathologic complete response (ypCR).

METHODS

Restaging MRI (yMRI) examinations of 136 patients with LARC treated with neoadjuvant CRT followed by surgery were retrospectively analyzed by two radiologists. All examinations were performed on a 1.5 Tesla MRI machine with a pelvic phased-array coil. T2-weighted turbo spin-echo images and diffusion-weighted imaging were obtained. Histopathologic reports of the surgical specimens were the reference standard. The accuracy, sensitivity, specificity, positive and negative predictive values (PPV and NPV) of yMRI in predicting the pathologic T-stage (ypT), N-stage, and ypCR were calculated. The inter-observer agreement was evaluated using kappa statistics.

RESULTS

The yMRI results showed 67% accuracy, 59% sensitivity, 80% specificity, 81% PPV, and 56% NPV in identifying ypT (ypT0-2 versus ypT3-4). In predicting the nodal status, the yMRI results revealed 63% accuracy, 60% sensitivity, 65% specificity, 47% PPV, and 75% NPV. In predicting ypCR, the yMRI results showed 84% accuracy, 20% sensitivity, 92% specificity, 23% PPV, and 90% NPV. The kappa statistics revealed substantial agreement between the two radiologists.

CONCLUSION

Utilization of yMRI showed high specificity and PPV in predicting the tumor stage and high NPV in predicting the nodal stage; in addition, yMRI revealed moderate accuracy in the T and N classifications, mainly due to underestimating the tumor stage and overestimating the nodal status. Finally, yMRI revealed high specificity and NPV but low sensitivity in predicting the complete response.

KEYWORDS

Rectal cancer, magnetic resonance imaging, neoadjuvant chemoradiotherapy, neoplasm staging, surgical pathology

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Neoadjuvant chemoradiotherapy (CRT) is the standard initial treatment for patients with locally advanced rectal cancer (LARC). Neoadjuvant CRT induces tumor downstaging in approximately 50% of patients and creates a pathologic complete response (ypCR) in 15%–38% of LARC cases.[1,2] Neoadjuvant CRT provides the opportunity to perform sphincter-preserving surgery in patients with LARC by increasing the distance between the tumor and the anorectal junction. It can even offer a non-surgical treatment approach for some patients.[3] Additionally, it leads to a significant reduction in the number and size of met-

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astatic mesorectal lymph nodes.[4] Patients with LARC are restaged with a digital rectal examination, a colonoscopy, and rectal magnetic resonance imaging (MRI) after receiving neoadjuvant CRT.[5,6] Proper staging after CRT is essential to determine the optimal surgical strategy, such as sphincter-sparing surgery for tumors in the lower rectum or local excision for tumors confined to the rectal wall.[7]

MRI is the technique of choice for local staging, while positron emission tomography and computed tomography are more often used to detect distant metastases.[8] However, the reliability of restaging MRI (yMRI) remains controversial. Restaging with MRI after CRT is more challenging than the initial staging of cancer with MRI since it is difficult to distinguish small residual tumor areas from edema, fibrosis, and normal mucosa. Although the residual tumor has intermediate signal intensity, whereas fibrosis and scarring have low signal intensity on T2-weighted (T2W) images, the differentiation is still not easy, as the residual tumor may be found within scar tissue. Diffusion-weighted imaging (DWI) is useful in differentiating between viable residual tumor and treatment-related tissue changes.[9-11] Many studies have suggested that DWI plays a remarkable role in restaging.[12-17]

Restaging rectal cancer with MRI remains a challenge.[18-20] Studies that have investigated the performance of MRI in the staging of LARC after CRT revealed substantial discrepancies regarding tumor and lymph node staging and complete response evaluation.[15] Thus, this study investigates the diagnostic performance of MRI in predicting the pathologic stage of rectal cancer after CRT using histopathology as the gold standard. Additionally, the performance of MRI in selecting pathologic complete responders after CRT is analyzed.

Main points

- Restaging magnetic resonance imaging (MRI) showed high specificity and positive predictive value in predicting the tumor stage and high negative predictive value (NPV) in predicting the nodal stage.
- Restaging MRI revealed moderate accuracy in the T-stage and N-stage classifications, mainly due to underestimating the tumor stage and overestimating the nodal status.
- Restaging MRI revealed high specificity and NPV but low sensitivity in predicting the complete response.

Methods

Study population

The institutional review board approved this retrospective study (2021/28-11) and waived the informed consent requirement. Consecutive patients diagnosed with LARC who underwent neoadjuvant CRT followed by total mesorectal excision between December 2012 and January 2020 were retrieved from our hospital database. Patients who underwent rectal MRI after CRT were included in the study. The exclusion criteria were distant metastases, insufficient image quality, incomplete CRT, and mucinous tumors. The patient accrual is summarized in Figure 1.

All patients underwent rectal high-resolution MRI and DWI after neoadjuvant CRT. For all patients, 45-Gy radiotherapy to the pelvis was administered before surgery. Consequently, a 5.4-Gy boost in three fractions was applied to the primary tumor. After the first and fifth weeks of radiation therapy, patients received 400 mg/m^2/day fluorouracil and 20 mg/m^2/day leucovorin over three days. The yMRI was performed at approximately 6–8 weeks after the completion of neoadjuvant CRT.

Image acquisition

To minimize bowel motility, 20 mg of scopolamine butylbromide was injected intravenously 10 min before scanning, unless contraindicated. All examinations were performed on a 1.5-T MR machine (Philips Achiva Release 1.8, Eindhoven, The Netherlands) with a pelvic phased-array coil. The T2W turbo spin-echo images were obtained in sagittal, para-axial (perpendicular to the long axis of the tumor), and para-coronal (parallel to the long axis of the tumor) planes using a repetition time of 4,500 ms, a field of view (FOV) of 180–220 mm, a matrix size of 256 × 512, a slice thickness of 3 mm, an intersection gap of 0.8 mm, and an echo train length of 16. Fat-suppression techniques and contrast agents were not used. Diffusion-weighted (b: 0 and b: 1.000 s/mm^2) images were obtained in the sagittal and axial planes with a single-shot echo-planar sequence using a TR/TE of 4.200/95, a bank angle of 90°, a slice thickness of 5 mm, and a FOV of 350–400 mm. The in-line software automatically generated apparent diffusion coefficient (ADC) maps.

Image interpretation

Rectal MRI examinations performed after CRT for yMRI were evaluated independently by two radiologists who were blinded to the histopathologic staging (ypTNM) results. Initially, an independent blinded evaluation of the yMRI images of each patient was performed by two radiologists [F.O. (radiologist-1), H.C. (radiologist-2), with 22 and 6 years of experience reading rectal MR images, respectively], who had no knowledge of the results of the histopathologic exam-

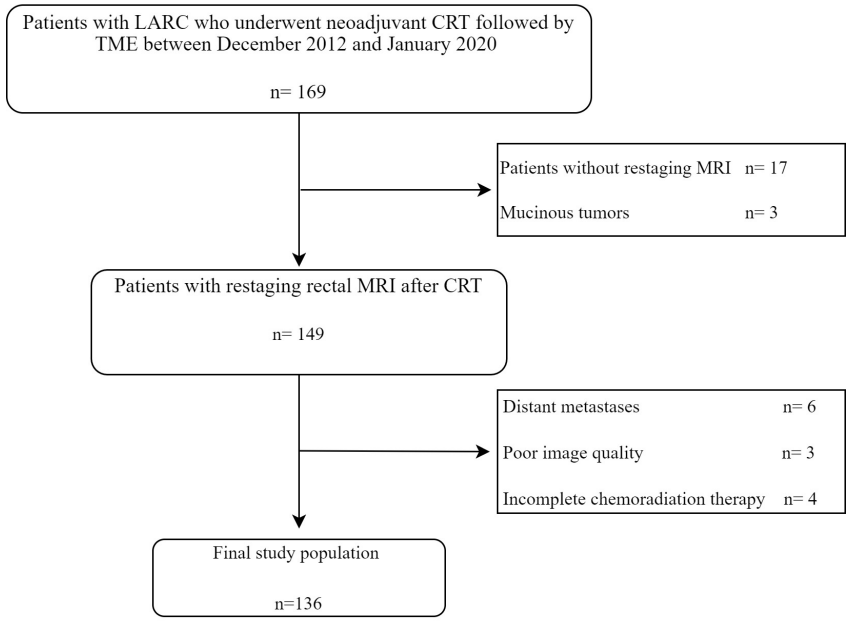


Figure 1. Flow chart of the study population.

LARC, locally advanced rectal cancer; CRT, chemoradiotherapy; MRI, magnetic resonance imaging, TME, total mesorectal excision

ination. The observers reached a consensus by discussing cases where they did not fully agree on the findings. The observers were able to review the rectal MRI obtained before neoadjuvant CRT to identify the treated tumor. The yT-stage (ypT), yN-stage (ypN), and the presence of radiologic complete response (ymrCR) were assessed using MRI. The yT-stages were defined according to the depth of tumor penetration into the rectal wall, mesorectum, and adjacent pelvic structures as follows: T1, infiltration into the submucosa; T2, infiltration into the muscularis propria; T3, infiltration beyond muscularis propria; and T4, infiltration to peritoneal reflection or other pelvic organs. The T-stage was primarily evaluated using high-resolution T2W images. On the T2W images, DWI and ADC maps were also evaluated to distinguish residual tumor from fibrosis. The signal intensity on DWI is usually high in the residual tumor and low in fibrosis. Subgroups of yT were defined as yT0-2 representing the early stage versus yT3–4 representing LARC.

According to the latest ESGAR guidelines, nodes with a short-axis diameter of <5 mm on yMRI are considered benign.[21] Nodes with a short-axis diameter of ≥5 mm are considered malignant in yMRI since there are no reliable criteria other than size for irradiated nodes. Only the T2W-MR images were evaluated for deciding on the nodal status.

The tumor response to neoadjuvant CRT was mainly evaluated qualitatively using DWI images and ADC maps. Nevertheless, the lack of anatomical details and the greater vulnerability to artifacts of DWI can introduce inaccuracy and variability in interpretation. Therefore, T2W images were reviewed to accurately assess the former tumor location. Lesions were considered to have restricted diffusion when the signal intensities on DWIs were higher than those of the prostate or small intestine.[22] The absence of any hyperintense signal that may belong to a residual tumor on DWI was accepted as a radiologic complete response (Figure 3). The patients who were qualitatively classified as ymrCR were compared with those reported to have ypCR.

Histopathologic evaluation

All histopathologic interpretations were conducted by pathologists experienced in rectal cancer (O.S., S.S., and M.U.; 22, 24, and 15 years of experience, respectively). Histopathology records were reviewed for the ypT, ypN, and presence of complete response. Pathologic T0-2 (ypT0-2) stages were accepted as early stage, while ypT3-4 stages were accepted as LARC. Subgroups of ypT included ypT0-2 representing the early stage and ypT3–4 representing LARC. Lymph nodes were grouped as ypN– and ypN+.

Statistical analysis

The reference standard was the histopathologic reports of the surgical specimens. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MRI in predicting ypT, ypN, and ypCR were calculated. Kappa statistics were used to evaluate agreement among the observers.

Results

Of the 136 patients included in this study, 50 (37%) were female and 86 (63%) were male, with a mean age of 63.2 ± 11.2 years (range: 33–88 years).

Regarding yMRI, early T-stage (yT0-2) was detected in 53.7% (n = 73) of the patients, while LARC (yT3-4) was detected in 46.3% (n = 63) of them. Regarding histopathology, ypT0-2 was found in 39.7% (n = 54) patients, and ypT3-4 was found in 60.3% (n = 82) patients. Correlations between the MRI-based T classification after CRT and ypT-stages are summarized in Table 1.

Regarding the lymph node assessment on yMRI, 43.4% (n = 59) of the patients had at least one lymph node metastasis, and 56.6% (n = 77) of the patients had no metastatic lymph node. Assessment of the surgical resection specimens revealed that 34.6% (n = 47) of patients had at least one metastatic lymph node, and 65.4% (n = 89) of patients had no metastatic lymph node. The correlation between the results of yMRI and histopathology for the nodal status is summarized in Table 2.

The radiologic complete response to CRT was detected in 9.6% (n = 13) of the patients

Table 1. Comparison of MRI-based T-stage classification after chemoradiation and postoperative pathologic T classification

ymrT-stage	ypT-stage						
	ypT0	ypT1	ypT2	ypT0-2	ypT3	ypT4	ypT3-4
ymrT0	2	0	4	6	1	0	1
ymrT1	1	0	0	1	1	0	1
ymrT2	9	4	21	34	28	2	30
ymrT0-2	12	4	25	41	30	2	32
ymrT3	3	1	8	12	38	2	40
ymrT4	0	0	1	1	6	4	10
ymrT3-4	3	1	9	13	44	6	50

The overall accuracy of yMRI in the T-staging of rectal cancer: 48%. MRI, magnetic resonance imaging; yMRI, restaging MRI; ymrT, MRI-based T classification after chemoradiation; ypT, postoperative pathologic T classification.

Table 2. Comparison of MRI-based N-stage classification after chemoradiation and postoperative pathologic N classification

ymrN	ypN	
	ypN+	ypN–
ymrN+	28	31
ymrN–	19	58

MRI, magnetic resonance imaging; ymrN, MRI-based N classification after chemoradiation; ypN, postoperative pathologic N classification.

on yMRI. The ypCR to neoadjuvant treatment was detected in 11% (n = 15) of patients. The correlation between the radiologic and histopathologic complete responses is summarized in Table 3.

The yMRI results showed 67% accuracy, 59% sensitivity, 80% specificity, 81% PPV, and 56% NPV in predicting ypT (ypT3-4 versus ypT0-2). The overall accuracy of yMRI in predicting each T-stage (T0/1/2/3/4) was 48%. In predicting the nodal status, yMRI revealed 63% accuracy, 60% sensitivity, 65% specificity, 47% PPV, and 75% NPV. In predicting the complete response to neoadjuvant CRT, yMRI showed 84% accuracy, 20% sensitivity, 92% specificity, 23% PPV, and 90% NPV. The value of kappa was 0.82 in T-staging, 0.79 in N-staging, and 0.74 in predicting ypCR according to the agreement analysis of the observers. The diagnostic performance of yMRI is summarized in Table 4.

Discussion

This study investigated the efficacy of yMRI in predicting the histopathologic stage after neoadjuvant CRT. In this study, the moderate accuracy of MRI in predicting the histopathologic stage can be related to understaging in the T-stage and overstaging in the N-stage. The yMRI results showed high specificity and moderate sensitivity in predicting the pathologic T-stage, whereas it showed moderate sensitivity and specificity in nodal staging. A qualitative assessment of DWI revealed high specificity but low sensitivity in predicting ypCR. Interobserver agreements were significant, but an experienced observer revealed a higher performance in all statistical measures (Table 4).

The pathologic examination of the treated tumor revealed fibrosis and/or mucin production. On T2W and high b-value DWI, fibrosis presents as low-signal intensity areas, while mucin-containing areas appear hyperintense. Both fibrotic and mucinous tissue changes may obscure small areas of residual tumor, reducing the accuracy of yMRI.[23] In the present study, the tumor stage was understaged in 25% of patients on yMRI (Figure 4). We hypothesized that a viable residual tumor concealed in the hypointense scar was the main reason for underestimating the T-stages. In contrast, Lee et al.[19] suggested that diffusely infiltrated hypointense tissue in the mesorectal fascia secondary to CRT causes T-overstaging and decreases the accuracy of yMRI. Moreover, the submucosal edema adjacent to the tumor presented as a hyperintense signal on T2W images and may be misinterpreted as a residual tumor.[23] The combination of T2W imaging and DWI can be helpful to circumvent these pitfalls for response evaluation after neoadjuvant CRT.[23] The T2W images should be used as a reference for accurate identification of the tumor site when assessing DWI and ADC maps (Figures 2, 3).[24]

After CRT, both benign and malignant nodes shrank, and approximately 44% disappeared.[25] There are no specific morphological characteristics for characterizing metastatic and benign nodes on yMRI.[21] In addition, morphology may be difficult to assess due to the shrinkage of the lymph nodes after CRT. Note that DWI successfully detects lymph nodes, but it is insufficient to distinguish between benign and malignant tumors.[26] After CRT, node size in the short axis is more reliable than other criteria for assessing residual metastatic disease.[8] Staging the N-classification on yMRI was more challenging than T-staging, and the accuracy of N-staging was slightly lower than T-staging. The yMRI results showed moderate accuracy, sensitivity, and specificity in predicting the metastatic lymph nodes in our study. The overall accuracy of yMRI in predicting ypN was 63%, which is similar to Lee et al.[19] The NPV for nodal restaging was high (up to 75%) in our study, which is partly due to the high chance of sterilization of the remaining nodes after irradiation.[27] According to the literature, 25% of nodes are overstaged.[21] In the present study, the overstaging rate was 22.8% for ypN classification. Representative T2W images are shown in Figure 5. Despite technological advances in MRI, the accuracy of post-CRT lymph node characterization remains low.[15] We suggest that the reason for the reduced accuracy of yMRI is the lack of reliable criteria other than size for evaluating the irradiated lymph nodes after CRT.

An accurate assessment of the clinical response to neoadjuvant CRT is essential, as the non-surgical approach is now an option for selected patients with clinical complete response.[28] In selected patients with LARC, the "watch and wait" strategy is associated with good cancer control, along with lower morbidity and better quality of life than conventional treatment.[29] However, an in-depth analysis of this strategy is still needed, as there are controversies that can be resolved by consensus among the specialists involved in treating these patients.

Histopathologic complete response rates reported in previous studies range from 15% to 38%.[1,2,6,30,31] In this study, ypCR was present in 15 (11%) of 136 patients, and the accuracy of MRI in predicting the complete response was 84%. In general, the diagnostic performance of MRI in detecting the complete response in our study is consistent with similar studies in the literature, although the accuracy of these studies varies between 50% and 90%.[15,18] Utilization of yMRI revealed high specificity and NPV and low sensitivity and PPV in the assessment of ypCR. Compared to

Table 3. Comparison of radiologic and pathologic complete response

ymrCR	ypCR	
	ypCR+	ypCR–
ymrCR+	3	10
ymrCR–	12	111

ymrCR, radiologic complete response; ypCR, pathologic complete response.

Table 4. Diagnostic performance of MRI performed after chemoradiotherapy in the evaluation of the T-stage (ypT3-4 versus ypT0-2), N-stage (ypN-positive versus ypN0), and complete response (ypCR+ versus ypCR–)

	Sensitivity (%)			Specificity (%)			PPV (%)			NPV (%)			Accuracy (%)			IOA (kappa)
	R1	R2	**C**	R1	R2	**C**	R1	R2	**C**	R1	R2	**C**	R1	R2	**C**	R1-R2
T-staging	59	57	**59**	80	70	**80**	81	75	**81**	56	52	**56**	67	63	**67**	**0.82**
N-staging	60	54	**60**	65	58	**65**	47	40	**47**	75	71	**75**	63	57	**63**	**0.79**
CR	20	14	**20**	92	87	**92**	23	11	**23**	90	89	**90**	84	78	**84**	**0.74**

MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value; IOA, interobserver agreement; CR, complete response; R1, radiologist 1; R2, radiologist 2; C, consensus.

T2W images, DWI can display smaller tumor sizes, but higher interobserver agreement can be achieved.[32] In our experience, the presence of diffusion restriction in post-CRT DWI is useful in demonstrating the presence of a residual tumor. The specificity and NPV of DWI in anticipating the complete response were high (92% and 90%, respectively) since the presence of a residual tumor can be demonstrated with a high b-value DWI. Potential explanations for the low sensitivity and PPV of restaging DWI in this study include the possibility of small residual tumor foci, even in the absence of diffusion restriction, and the low rate of ypCR (11%) in our patient population. The poor spatial resolution of DWI obtained using the 1.5 T MR scanner may have led to misinterpretations in estimating ypCR. Increased spatial resolution and higher SNR can be achieved with 3T MR systems. The misinterpretation of the T2 shine-through is a major pitfall for DWI.[27] ADC maps were inspected in each case to look for a corresponding area of low signal to avoid this pitfall. T2 dark-through is another trap that is attributed to hypointensity that can sometimes be seen on the ADC maps in fibrotic areas.[33] The reason for this low signal is the high amount of collagen rather than the residual tumor (Figure 2). It is essential

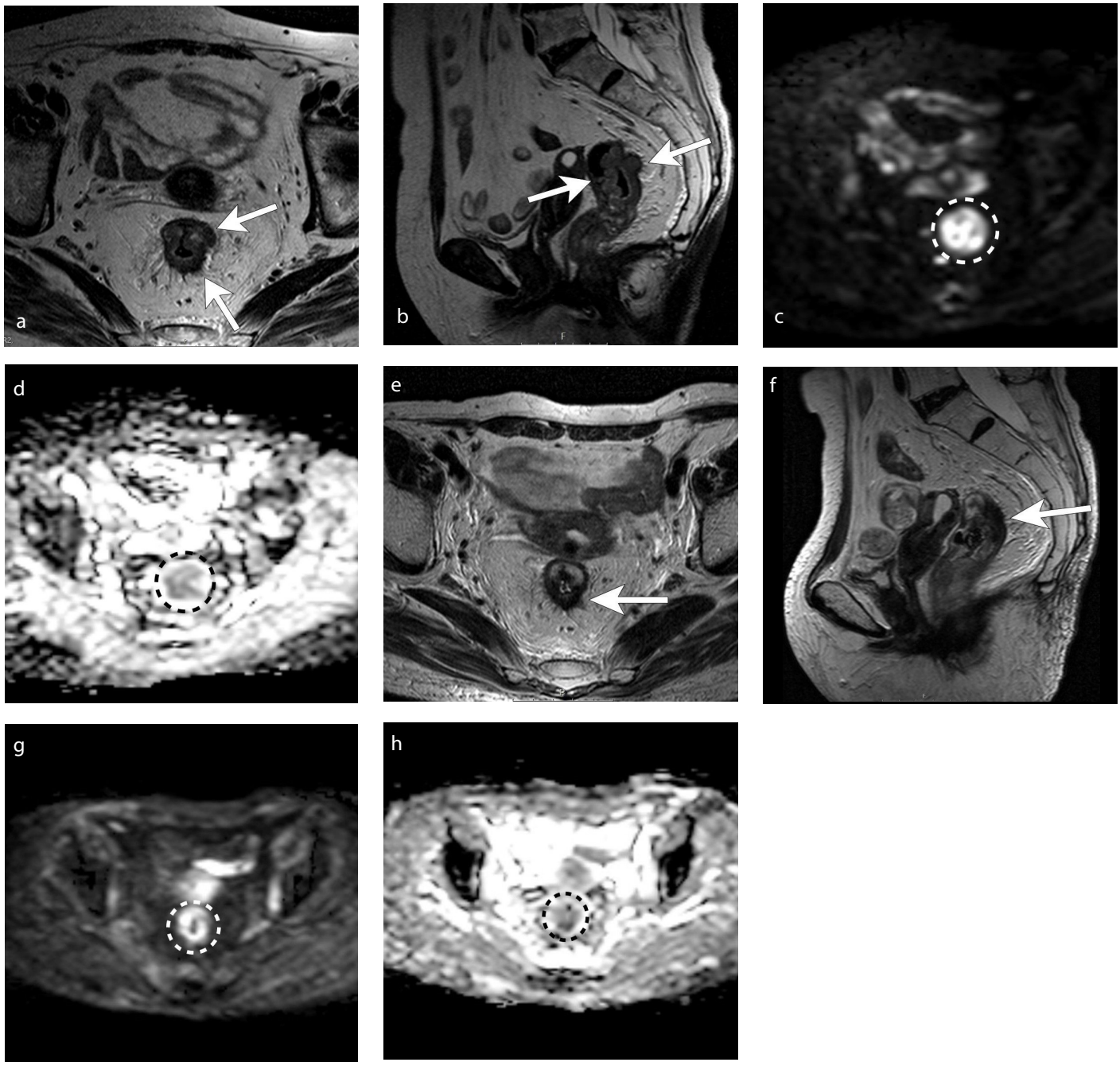


Figure 2. An 83-year-old woman with rectal adenocarcinoma. **(a-d)** Baseline rectal magnetic resonance (MR) images. T2-weighted (T2W) MR images in axial **(a)** and coronal planes **(b)** demonstrate the tumor infiltrating the mesorectal fat (arrows). Axial diffusion-weighted (DW) image **(c)** and apparent diffusion coefficient (ADC) map **(d)** demonstrate restricted diffusion (dashed circles). **(e-h)** Restaging MR images. The T2W MR images in the axial **(e)** and coronal planes **(f)** reveal that the tumor is smaller and confined to the muscularis propria (arrows). The axial DW image **(g)** and ADC map **(h)** reveal persistent restricted diffusion (dashed circles). The patient was classified as , MR imaging-based T classification 2 after chemoradiation, which is consistent with histopathology (postoperative pathologic T classification 2).

to evaluate the ADC maps with high b-value DW images, as fibrosis will be hypointense on DWI, while viable residual tumor will be hyperintense.

It is challenging to anticipate the histopathologic stage by evaluating only conventional MRI. Given the importance of a reliable diagnosis of complete response, new techniques are being studied, including dynamic contrast imaging,[34] magnetic transfer ratio,[35] and texture analyses.[36-38] Further, positron emission tomography and T1 mapping may help predict and evaluate tumor response to CRT.[39,40] More accurate restaging can be performed with MRI by utilizing treatment-related changes in the tumor volume and metabolism.[40] However, these techniques are still not used in routine practice, as there is not enough evidence to prove their effectiveness.

Our study has several limitations. First, this is a retrospective, single-center study. Therefore, further studies, especially prospective and multicentric ones, are needed to evaluate the diagnostic performance of yMRI and define the most reliable parameters in predicting the ypT, ypN, and complete response after CRT. Second, some patients did not receive scopolamine butylbromide intravenously due to contraindications. In addition, our 1.5 T MR scanner is routinely

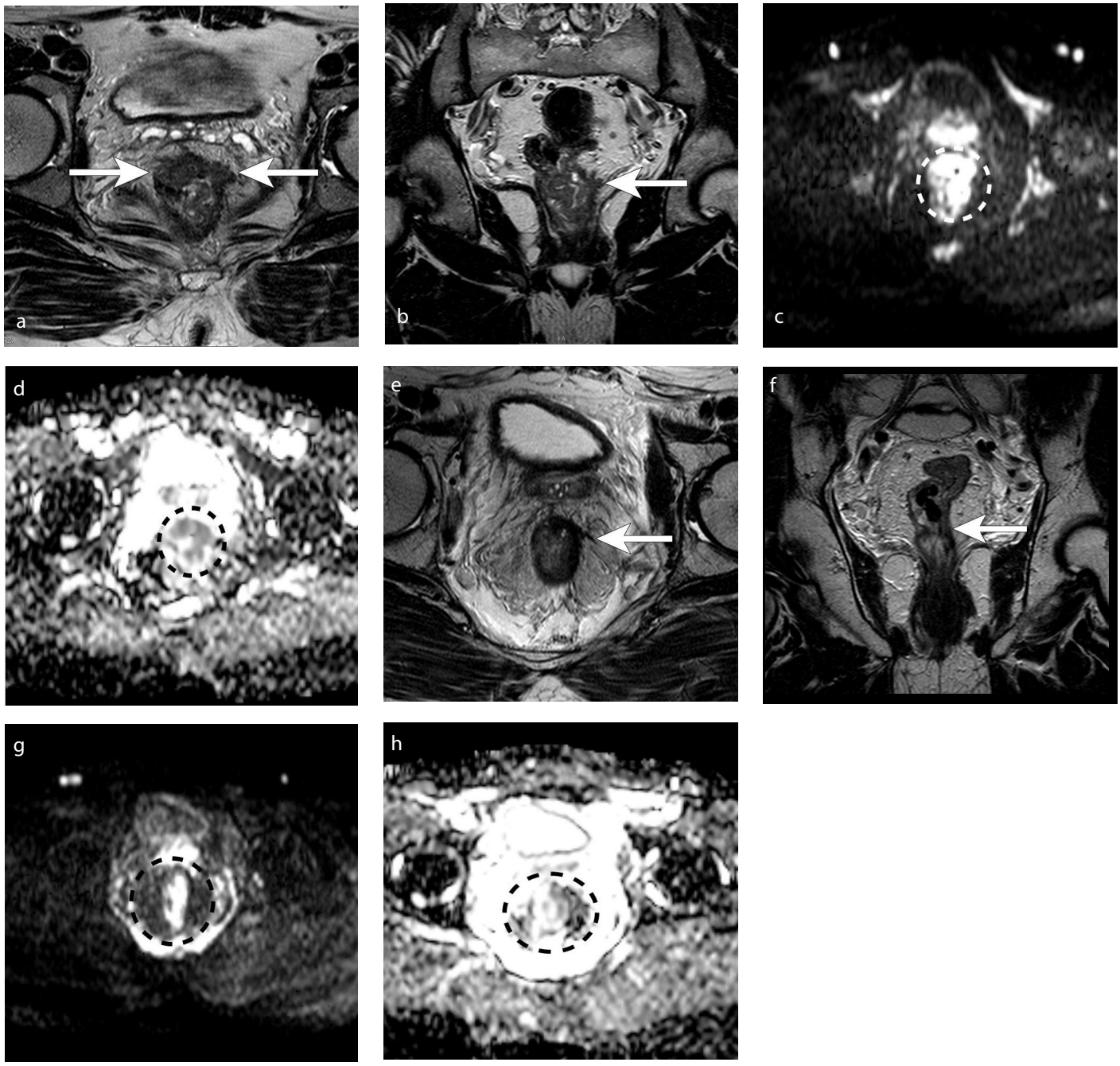


Figure 3. A 42-year-old man with locally advanced rectal cancer, treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision. **(a-d)** Baseline rectal magnetic resonance (MR) images. T2W MR images in axial **(a)** and coronal planes **(b)** demonstrate the tumor infiltrating beyond muscularis propria (arrows). Axial diffusion-weighted (DW) image **(c)** and ADC map **(d)** demonstrate restricted diffusion (dashed circles). **(e-h)** Restaging MR images. T2-weighted MRI images in the axial **(e)** and coronal planes **(f)** show that the tumor is completely replaced by low-signal-intensity fibrosis (arrows). The axial DW image **(g)** and ADC map **(h)** reveal no restricted diffusion in the former tumor location (dashed circles). A complete tumor response (ypT0N0) was confirmed at histopathology.

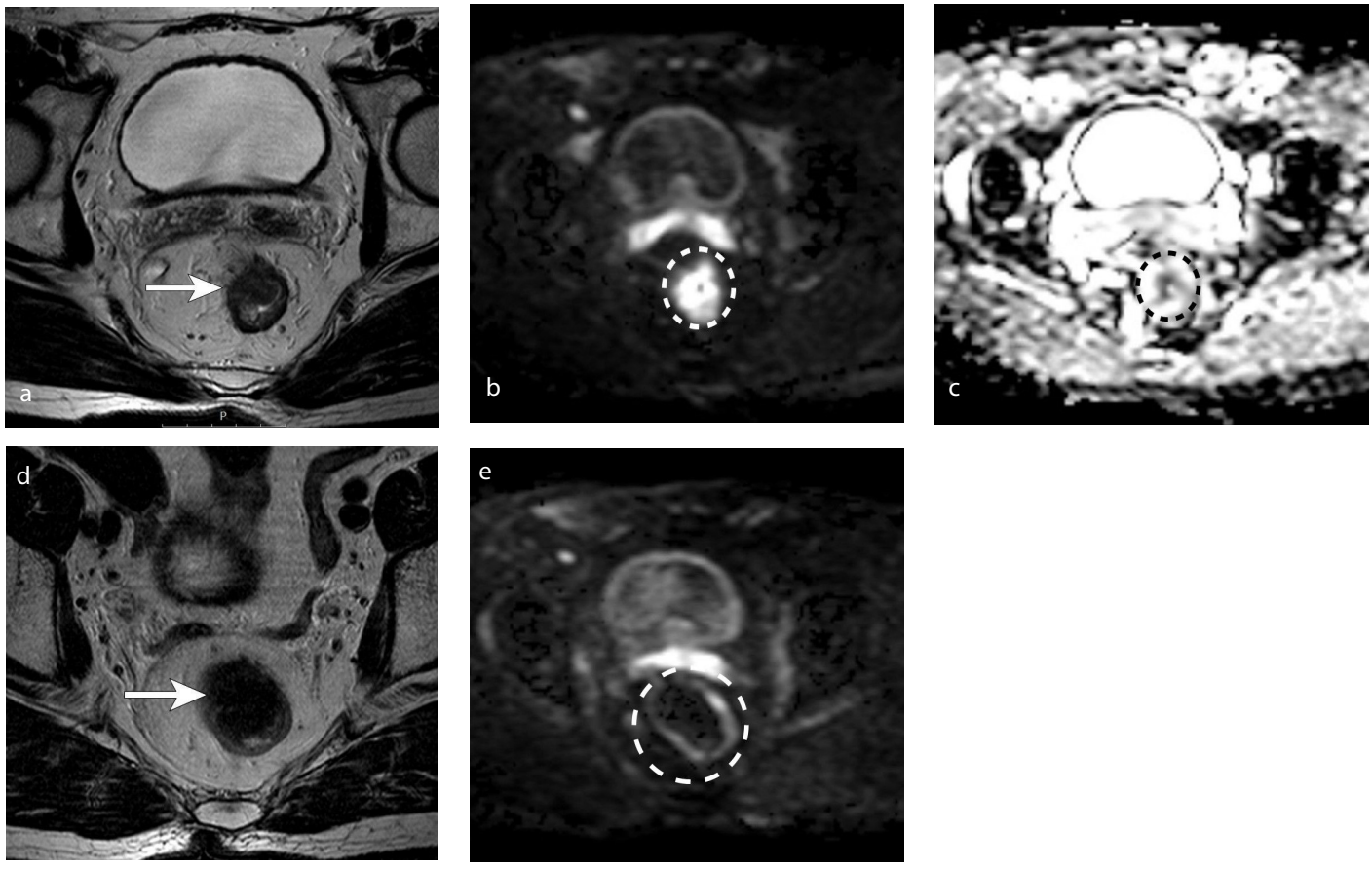


Figure 4. A 57-year-old man with rectal adenocarcinoma who underwent neoadjuvant chemoradiotherapy. **(a-c)** Baseline rectal magnetic resonance (MR) images. Axial T2-weighted (T2W) MR image **(a)** demonstrates a stage T3 tumor with intermediate signal (arrow). Axial diffusion-weighted (DW) image **(b)** and apparent diffusion coefficient (ADC) map **(c)** reveal restricted diffusion (dashed circles) in the tumor location. **(d-e)** Restaging MR images of the patient. The axial T2W MR image **(d)** reveals complete disappearance of the tumor signal with fibrotic low signal change. The axial DW image **(e)** shows no hyperintense signal in the former tumor location (dashed circle), and the patient was classified as complete response. The histopathologic staging was postoperative pathologic T classification 2.

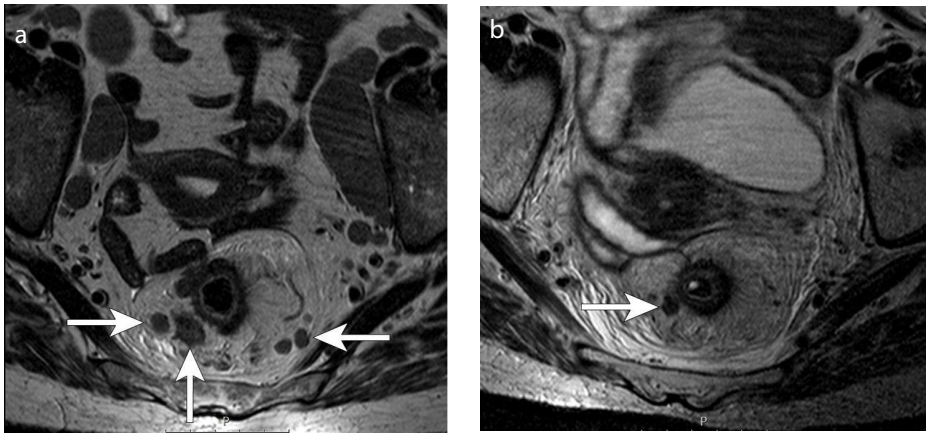


Figure 5. A 75-year-old female with locally advanced rectal cancer. **(a)** Baseline axial T2-weighted (T2W) magnetic resonance (MR) image **(a)** shows multiple metastatic mesorectal lymph nodes (arrows). Post-treatment axial T2W MR image **(b)** shows a lymph node with a short axis >5 mm (arrow), and the patient was classified as MRI-based N classification after chemoradiation +, and the histopathologic staging was postoperative pathologic N classification 0.

scheduled for a software upgrade, which might have improved the image quality over time. However, these changes did not affect or change the main protocol parameters. Additionally, poor spatial resolution of DWI was a potential challenge that may have caused misinterpretations in predicting ypCR.

In conlusion, yMRI revealed moderate accuracy in the T and N classifications, mainly due to underestimating the tumor stage and overestimating the nodal status. The yMRI results showed high specificity and PPV in predicting the tumor stage and high NPV in predicting the nodal stage; in addition, yMRI revealed high specificity and NPV but low sensitivity in predicting the complete response. Estimating the nodal stage and complete response using MRI after CRT remains a major challenge.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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