T.C

DOKUZ EYLÜL ÜNİVERSİTESİ

SAĞLIK BİLİMLERİ ENSTİTÜSÜ

DENEYSEL PERİTONEAL KARSİNOMATOZ MODELİNDE HİPERTERMİK İNTRAPERİTONEAL KEMOTERAPİNİN ETKİNLİĞİNİN ARAŞTIRILMASI

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ONKOLOJİ ANABİLİM DALI

TEMEL ONKOLOJİ PROGRAMI

DOKTORA TEZİ

İZMİR

OCAK 2023

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İZMİR

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DOKUZ EYLÜL ÜNİVERSİTESİ

SAĞLIK BİLİMLERİ ENSTİTÜSÜ MÜDÜRLÜĞÜNE

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Dokuz Eylül Üniversitesi Sağlık Bilimleri Enstitüsü Tez Yazım Kurallarına uygun olarak hazırlayıp sunduğum "**Deneysel peritoneal karsinomatoz modelinde hipertermik intraperitoneal kemoterapinin etkinliğinin araştırılması**" başlıklı Doktora tezim içinde elde ettiğim verileri, bilgileri, belgeleri akademik ve etik kurallar çerçevesinde elde ettiğimi, değerlendirme ve sonuçları bilimsel etik ve ahlak kurallarına uygun olarak sunduğumu, tezimde yararlandığım eserlere bilimsel kurallara uygun atıfta bulunarak kaynak gösterdiğimi, tezimin özgün olduğunu, tezimin çalışma ve yazımında patent ve telif haklarını ihlal edici bir davranışımın olmadığını, aksi bir durumda aleyhime doğabilecek tüm hak kayıplarını kabullendiğimi beyan ederim.

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KISALTMALAR

PK : Peritoneal karsinomatozis

HİPEK : Hipertermik intraperitoneal kemoterapi

EPİK : Erken postoperatif intraperitoneal kemoterapidir

NİPEK : Normotermik intraperitoneal kemoterapi

KRK : Kolorektal kanser

PKİ : Peritoneal kanser indeksi

SRC : Sitoredüktif cerrahi

İPİP : İntraperitoneal infüzyon pompasıyla

MMC : Mitomisin C

NİPEK : Normotermik intraperitoneal kemoterapi

5-FU : 5-Fluorourasil

GAG : Glukozaminoglikanlar

DEÜTFDHAL : Dokuz Eylül Üniversitesi Tıp Fakültesi Fakültesi Deney Hayvanları Laboratuarı

PBS : Fosfat tamponlu salin

i.p. : İntraperitoneal

H & E : Hematoksilen ve eozin

IL-1ß : İnterlökin 1 beta

VEGF : Vasküler endotelyal büyüme faktörü

IL-6 : İnterlökin 6

TNF-β : Tümör nekroz faktör beta

IL-8 : İnterlökin 8

ESM : Ekstraselüler Matriks

KİF : Kanserle ilişkili Fibroblast

EMG-MMG : Epitelyal-Mezenkimal Geçiş - Mezetelyal-Mezenkimal Geçiş

LOX1 **:** Lizil Oksidaz benzeri protein 1

TWIST **:** TWIST Transkripsiyon faktör

LYVE-1 **:** Lenfatik damar endotelyal hyaluronan reseptörü-1

Ang-1 **:** Anjiyopoietin-1

Ang-2 **:** Anjiyopoietin-2

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Doktora Tezi

Berke MANOĞLU

DOKUZ EYLÜL ÜNİVERSİTESİ SAĞLIK BİLİMLERİ ENSTİTÜSÜ

Onkoloji Anabilim Dalı

ÖZET

Çalışmamız da (1)atimik farelerde peritoneal karsinomatoz (PK) modeli oluşturularak, bu modelde kendi geliştirdiğimiz peritoneal infüzyon pompasıyla intraperitoneal kemoterapi verilmesi, (2)intraperitoneal kemoterapi etkinliklerinin farklı ısı ve ilaçlarda karşılaştırılması amaçlanmaktadır.

Peritoneal karsinomatoz modeli, CC531 kolon karsinomu hücre hattı kullanılarak atimik farelerlerde oluşturulmuştur. PK oluşmuş modeller, her biri yedi hayvandan oluşan dört gruba randomize edildi: grup 1: kontrol(n = 7), grup II: mitomisin C(MMC) ile normotermik intraperitoneal kemoterapi (NİPEK) (n = 7), grup III: mitomisin Cile hipertermik intraperitoneal kemoterapi (HİPEK) (n = 7), grup IV: 5-Fluorourasil(5-FU) ile normotermik intraperitoneal kemoterapi(n=7) uygulandı.

Tüm hayvanlarda, tümör gelişimi sağlandı. Tümör yükü tedavi grubu III de anlamlı olarak azalırken, diğer gruplarda anlamlı bir fark saptanmamıştır(p=0.034).PK fare modelinde, hippertermik intraperitoneal MMC uygulaması en yüksek tümörosidal etkiye sahipti.

PK modelimiz, HİPEK ve İPİP etkinliğini değerlendirmemizi sağlamıştır. Bundan sonraki çalışmalarda farklı ilaç etkinliklerinin, oluşturduğumuz PK modellerinde değerlendirilmesi planlanmaktadır.

Anahtar kelimeler: peritoneal karsinomatoz modeli, kolorektal kanser, HİPEK

Tez Sayfa Adedi: 87

Danışman: Prof. Dr. Tuğba Yavuzşen

INVESTIGATION OF THE EFFECTIVENESS OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN EXPERIMENTAL PERITONEAL CARCINOMATOSIS MODEL

PhD Thesis

Berke Manoglu

DOKUZ EYLÜL UNIVERSITY GRADUATE SCHOOL OF HEALTH SCIENCES

Department of Oncology

ABSTRACT

In our study, it is aimed to (1) create a peritoneal carcinomatosis (PC) model in athymic nude mice, administer intraperitoneal chemotherapy with the peritoneal infusion pump we developed in this model, and (2) compare the intraperitoneal chemotherapy efficacy at different temperatures and drugs.

The peritoneal carcinomatosis model was established in athymic nude mice using the CC531 colon carcinoma cell line. Models with PC were randomized into four groups of seven animals each: group I, control group (n=7), group II normothermic intraperitoneal chemotherapy(NIPEC) with mitomycin C(MMC)(n=7), group III hyperthermic intraperitoneal chemotherapy(HIPEC) with mitomycin C (n=7), group IV NIPEC with 5-Fluorouracil (5-FU) were applied.

Tumor development was achieved in all animals. While the tumor burden decreased significantly in treatment group III($p=0.034$), no significant difference was found in the other groups. In the PC mouse model, hyperthermic intraperitoneal administration of MMC had the highest tumoricidal effect.

Our PC model provided a good opportunity to examine the efficacy of HIPEC and IPIP. In future studies, it is planned to evaluate different drug efficacy in the PC models we have created.

Key words: peritoneal carcinomatosis model, colorectal cancer, HIPEC

Page Number: 87

Advisor: Prof. Dr. Tuğba Yavuzşen

1. GİRİŞ VE AMAÇ

Klinik olarak peritoneal karsinomatoz, over, kolon ve mide kanserinde yaygın olan kötü progresyonu temsil eder[1]. Over kanseri, kadınlarda jinekolojik kanser nedeniyle beşinci ölüm nedenidir. Hastaların % 70' inde ileri hastalık evresinde peritoneal karsinomatoz teşhisi konmaktadır[2,3]. Kolon kanserinde hastaların % 8'inde birincil ameliyat sırasında izole peritoneal ekim yapılır ve nüks olan hastaların % 25' inde periton karsinomatoz görülür[4,5]. Kolorektal kansere(KRK) bağlı gelişen peritoneal karsinomatozlu (PK) hastalarda sistemik kemoterapi ile ortalama 1 yıllık sağkalım sağlanabilirken, sitoredüktif cerrahi (SRC) ve hipertermik intraperitoneal kemoterapi (HİPEK) ile 5-yıllık sağkalım %40-58'e ulaşabilmektedir[6]. Bu nedenle SRC ve HİPEK'in seçilmiş hastalarda standart tedavi olarak yapılması önerilmektedir[7]. Sistemik kemoterapiye karşı daha başarılı olmasına karşın SRC ve HİPEK konusunda yeterli bilimsel kanıt oluşmamıştır. Sadece hipertermi kanser hücreleri üzerinde sitotoksik etkiye sahipken kemoterapi ile birlikte birbirlerinin etkisini potansiyalize etmektedirler [8]. Sistemik kemoterapi ile karşılaştırıldığında kemoterapinin intraperitoneal olarak verilmesi tümör hücreleri üzerinde daha yoğun konsantrasyonda kemoterapi verilmesini sağlarken sistemik toksisite de daha az olmaktadır[9]. Tüm bu etkiler nedeni ile HİPEK uygulandığında sistemik kemoterapiye göre 20-50 kat daha fazla tümörisidal etki oluşmaktadır[10].

Çalışmamızda CC-531(kolon adenokarsinom hücre hattı) kullanılarak atimik farelerde peritoneal karsinomatoz(PK) modeli oluşturulması ve bu modelde kendi geliştirdiğimiz infüzyon pompasıyla intraperitoneal kemoterapi verilmesi planlanmaktadır. Farklı ısılarda farklı kemoterapötik ajanlar uygulanarak gruplar arası etkinlik karşılaştırması yapılacaktır.

2. GENEL BİLGİLER

2.1. Periton Anatomisi, Histolojisi, Fizyolojisi ve Patolojisi

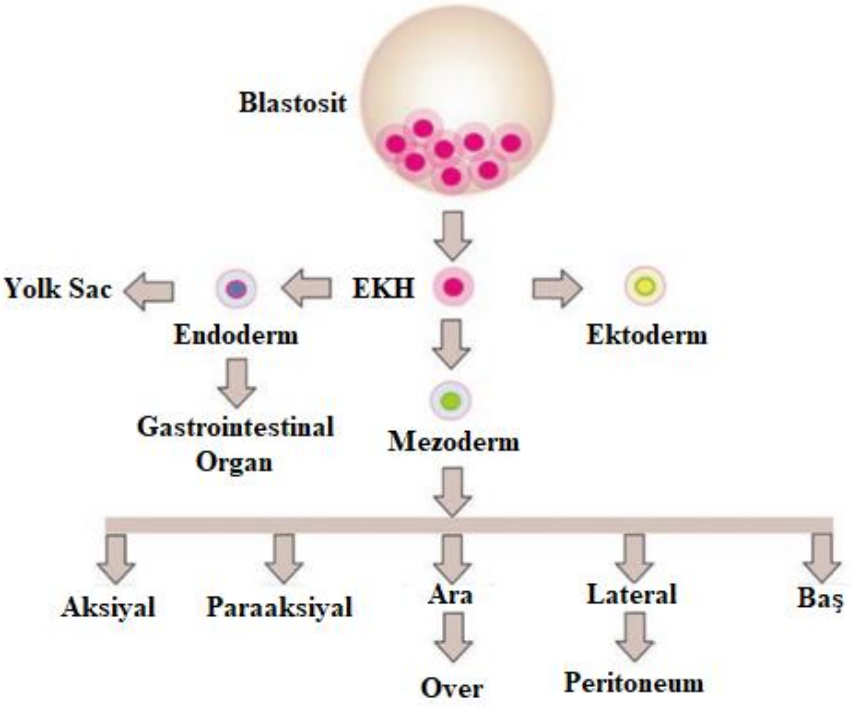
2.1.1. Genel Bilgiler

İnsan vücudundaki en büyk seröz membran peritondur ve yaklaşık 2m² alana sahiptir. Periton vücudun, en geniş ve kompleks seröz membranıdır. Erkeklerde peritoneal boşluk kapalı, kadınlarda ise ekstraperitoneal pelvis ve fallop tüpleri vasıtasıyla uterus ile bağlantılıdır. Periton paryetal ve visseral periton olarak ikiye ayrılır. Parietal periton (toplam periton alanının yaklaşık %30'u) karın duvarını ve visseral periton (alanın yaklaşık %70'i) karın içi organları kaplar. İki periton tabakası, arasındaki seröz sıvı ve aralarındaki periton boşluğu sayesinde birbirleri üzerinde kayar. Periton, toraksta torakal boşluğu kaplayan pariyetal plevra ile akciğeri kaplayan visseral plevranın abdomende yer alan eşdeğeridir. Plevral boşlukta olduğu gibi normal şartlarda peritoneal kavite görülmez. Ancak, sıvı, gaz birikimi veya kitle ile distandü hale geldiği durumlarda görülebilir[11].

2.1.2. Embriyoloji

İnsan vücudu gelişir üç germ tabakasından gelişir. Bunları sıralayacak olursak endoderm, mezoderm ve ektodermdir. Bunlar temel olarak daha sonra farklılaşan farklı doku türleridir ve vücudun çeşitli özel organlarına dönüşürler. Periton lateral plak mezoderminden gelişir. Yumurtalıklar da ara plaka mezoderminden gelişir(Şekil 1). Klinikte karar vermek için, bu farklı embriyolojik yapılar önemlidir. Çünkü epitelyal ve mezotelyal belirteçlerin farklılaşması peritoneal tümörlerin kökeninin belirlenmesine sağlar. Tersine, yumurtalık yüzey epiteli ve peritonun benzer embriyolojik kökeni de yumurtalık karsinomu ve primer papiller peritoneal karsinom arasındaki immünohistokimyasal farklılaşmanın zorluğunu açıklar. Bununla birlikte, mezodermal kökene rağmen, seröz membranların epitelleri birleşme bağlantıları, apikobazal oryantasyon, sitokeratinler ve yüzeysel mikrovilluslar gibi birçok benzerlik gösterir. Dolayısıyla çeşitli peritoneal tümörlerin ayırıcı tanısı modern inceleme ve tanı yöntemleri olmasına ragmen zor olabilir. Peritonun karmaşık innervasyonun açıklaması da

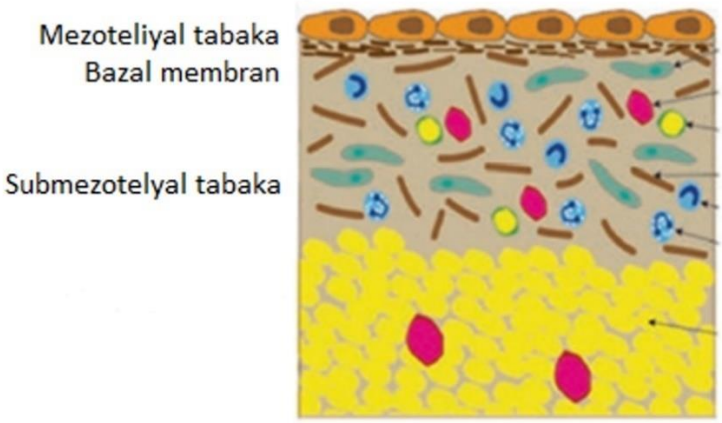
embriyolojik gelişimde cevap bulur. Embriyogenez sırasında, Vagus sinirinin alt ganglionlarından ve dorsal kök gangliyonlarından gelen aksonlar bağırsağa doğru büyüyerek ekstrinsik innervasyon oluşturur. Enterik organlara ulaştıklarında, innervasyona izin vermek için büyümeye devam ederler. Pariyetal peritonun serebrospinal sinirleri(T6–T12) alt torasik dermatomlar ile aynı segmental yapıdan köken alırlar. Bu enterik sinir sistemi nöral krestten köken alır. Bağırsak yolu ve onun uzantılar orta hat organları olarak büyürler. Bu organların splanknik innervasyon bilateraldir ve visseral ağrıları orta hatta hissedilir. Visseral peritonun kendisi inerve edilmemiştir[11,12].



Şekil 1 Mezotelyum Embriyolojisi(EKH: Embriyonik Kök Hücre)

2.1.3. Morfoloji

Periton üç tabakadan oluşur: Mezotelyumun kendisi, bazal membran ve submezotelyal tabakadır(Şekil 2).



Şekil 2 Mezotelyum Morfolojisi

2.1.3.1. Mezotelyum

Serozanın kendisi merkezinde oval bir çekirdeği ve sitoplazması olan basit bir mezotelyal hücre tabakasından oluşur. Uzamış ve yassı hücrelerin çapları yaklaşık 25 mikron kadardır. Mezotelyal hücreler, epitel benzeri bir tabaka oluşturur ve apikal yüzeylerinde mikrovilluslara vardır. Ancak bu morfoloji karın bölgesinin farklı bölgelerinde değişiklik gösterir. Mikrovillusun uzunluğu ve sayısı işlevsel adaptasyona bağlı olarak organ ve konuma göre değişiklik gösterir. Mezotel hücreleri parankimatöz organlarda(visseral periton) küboidal bir şekle sahiptir. Ancak diyaframın peritoneal tarafında, yassıdır(parietal periton). Yassı mezotel hücreleri dış uyaranlarla(hücre hasarı gibi) küboidal şekle dönüşebilirler. Bu hücreler daha sonra bazen belirgin nükleoller, mitokondri ve kaba endoplazmik retikulum gibi artan hücre organelleri ile genişlemiş bir çekirdek gösterebilirler. Mezotel hücreleri yüzeyindeki microvilluslardan vücudu enfeksiyona ve tümör yayılımına karşı koruyabilen glikozaminoglikanlardan (GAG)

oluşan koruyucu bir tabaka olan glikokaliksi salgılar. Bu özellik için oldukça hidrofilik olan ve sulu bir polimer oluşturan Hyaluronik asit oldukça önemlidir[13-15].

2.1.3.2. Bazal Membran

Mezotel hücrelerinin altında ince bir bazal membran bulunur. Bazal membran alttaki kandamarları, sinirler ve lenfatik sistemden zengin stromal tabakayla bağlantılıdır. Bu mekanik bağlantı visseral peritonda, pariyetal peritona göre daha belirgindir. Bu fark visseral peritonektomi yapılabilirken, pariyetal peritonektominin yapılamamasının nedenini açıklamaktadır. Bazal membranda, iki veya daha fazla mezotel hücresinin birleşme yerinde küçük açıklıklar vardır. Bu yapılar lenfatik stomalardır.

2.1.3.3. Submezotelyal stroma

Submezotel stroma, üstündeki hücreleri besleyen kan damarlarını, sinirleri içerir, organlara ve diğer yapılara olan bağlantılarda önemli bir rol oynar. Ayrıca bu katman yoğun bir lenfatik sisteme sahiptir, rmakrofajlar, lenfositler ve adipositleri içermektedir. Abdominal submezotelyal tabakası, toraksın submezotelyal tabakası ile anatomik olarak süreklidir, bu da malign tümörlerin abdomenden, toraksa sık geçişinin nedenini açıklamaktadır[16,17].

2.1.3.4. Peritoneal Lenfatik Sistem

Lenfatik sistem periton boşluğundaki proteinlerin, lipidlerin ve sıvıların kan dolaşımına taşınmasında önemli bir rol oynar. Bu subdiyafragmatik lenfatik damarlar abdominal kavitenin %80'ini drene ederek diğer lenfatik kanallara ve venöz dolaşıma geçişi sağlar. Fizyolojik durumda, karın içerisinde aktif absorpsiyon, olduğu için sadece birkaç mililitre sıvı vardır. Periton boşluğunda sıvı alımı ve absorsiyonu arasında denge bozulursa karın içerinde assit oluşur. Örneğin lenfatik damarların tümör hücreleriyle tıkanması sonucu yetersiz bir absorsiyon hali oluşacak ve sonucunda batın içi assit oluşacaktır. Bu patolojik durum peritoneal metastazlı hastaların yarısında görülür[18].

a. Lenfatik Stoma: Lenfatik stomalar, son lenfatik sistemle doğrudan bağlantılıdır. Periton boşluğundan, assit, bakteri, tümör hücreleri ve diğer partiküllerin temizlenmesini sağlarlar. Periton boşluğundaki dağılımları değişkendir ve bölgeseldir. En sık olarak diyaframın yüzeyinde, büyük omentumda, falsiform ligamentte, kolonun epiploik uzantılarında, mezenterler arasında, ince bağırsakta ve Douglas poşunda yer alırlar. Lenfatik stomalar genellikle kapalıdırlar, ancak intraabdominal basınç artışı gibi çeşitli uyaranlara bağlı olarak açılabilirler[19].

b. Milky Spot: Lenfatik kanalın peritoneal açıklığında yer alan küçük lenfatik stomalardır. Esas olarak makrofaj ve lenfosit deposundan oluşurlar. Hümöral ve hücresel immün sistemde önemli rol oynarlar. Mikroskopik olarak milk spotlar periton boşluğu, kan akımı ve çevreleyen büyük omentum arasında sıvı alışverişine izin veren glomerüler bir kan damarı ağı içerir. Hücresel bileşenler omental glomerüllerin çevresinde bulunurlar. Karakteristik olarak devamlılık göstermeyen gözenekleri olan mezotel tabakasının hemen altında yer alırlar ve stomalar peritoneal kaviteyle doğrudan iletişime izin verir. Elektron mikroskobu gösteriyor ki aktive olmuş milky spotlardan gelen makrofajlar, membran aktivitelerini önemli ölçüde değiştirebilir ve milky spotların hücreler arası stomaları yoluyla periton boşluğuna göç edebilir[20,21].

2.1.3.5. Peritoneal Vaskülarizasyon

Submezotelyal tabaka, kan ve lenf damarları içermektedir. Peritondaki kan akış hızı 60-100ml/dakika olarak bilinmektedir ve kardiyak out put' un yaklaşık %1-2' sini oluşturmaktadır. Pariyetal periton, sirkumfleks, iliak, lomber, interkostal ve epigastrik arterler tarafından beslenir. Büyük paralel kan damarları ve bunların dikey dallarından oluşan dörtgen bir ağ oluşturur. Pariyetal venöz damarlar inferior vena cava ya drene olur. Visseral periton kanlanımı splanknik organların üç ana arterinden alır. Bunlar çöliyak arter, superior ve inferior mezenterik arterlerdir. Bu arterleri oluşturan küçük arterlere çoklu bifurkasyonlar yaparak geniş bir ağ oluştururlar. Visseral peritonun venöz drenajı portaya olur. Periton tarafından emilen ilaçların ilk metabozlize edildiği yer karaciğerdir. Hem peritoneal inflamasyon durumunda hem de tümör invazyonu olduğunda,

neoanjiyogenez indüklerlenir, bu da mikrovasküler ağın aşırı büyümesine neden olur. Bu vasküler yapılar anatomik olarak bozukturlar ve kanın ekstravaze olmasına neden olurlar. Peritoneal karsinomatoz makroskopik olarak görülmeden önce diffüz anjiyogenez görülebilir. Peritoneal kılcal damarların neovaskülarizasyona bağlı yüzey alanının artması, peritonun kanlanımınında artmasına neden olur[22-24].

2.1.4. Peritonun Görevleri

Serozal membranların ana morfolojik bileşeni olmasının yanı sıra, mezotelyal hücrelerin anahtar fonksiyonel rolleri vardır. Mezotel hücrelerinin temel görevlerinden biri abdominal organların hareket etmesini sağlayan pürüzsüz bir yüzey oluşturmaktır. Ayrıca, mezotelyal hücrelerinin, dokudaki farklı süreçlerde çeşitli fizyolojik ve biyolojik işlevlere sahiptirler. Örneğin iyileşme, fbrinoliz, enflamasyonun düzenlenmesi, epitelyal-mezenkimal geçiş ve intraperitoneal tümör hücresi çoğalması gibi görevlerde yer alırlar. Araştırmalar, mezotel hücrelerinin periton diyalizi, doku hasarı, iyileşme ve tümör hücre çoğalması gibi farklı stres koşullarındaki rolünü vurgulamıştır. Ek olarak, son zamanlarda yapılan bir genetik analiz, mezotelyum çevreleyen visseral adipoz doku obezitede doku disfonksiyonun da, fibrosis gelişiminde ve inflamasyon da potansiyel bir oyuncu olabileceğini gösterdi[25,26].

2.1.5. Moleküler Patoloji ve Peritoneal Metastaz

Metastaz, tümörün orijinine, tümörün lokalizasyonuna ve tümör tipine göre değişmektedir. Gastrointestinal adenokarsinomlar genellikle metastaz yapma eğilimindedir. Karaciğer, müsinöz kolorektal karsinomlar ve taşlı yüzük hücreli karsinomların peritoneal metastaz geliştirme olasılığı daha yüksektir. Kolon karsinomları ve mide karsinomları peritoneal boşluğuna metastaz yapar, sıklıkla over metastazlarına yol açar(Krukenberg tümörleri) ve genellikle periton metastazları ile aynı anda teşhis edilirler. Peritoneal karsinomatoz, tümör hücrelerinin primer tümörden ayrılması, tümör hücrelerinin çoğalması, periton boşluğu boyunca taşınması ve peritoneal yüzeye tutunmasından oluşan çok adımlı bir süreçtir. Ardından invazyon, neovaskülarizasyon ve tümör büyümesi basamakları gelir. Bu sürecin regülasyonunda birbirbirine bağlı

kompleks karmaşık yolaklar ve mediatörler görev alır. Örneğin, neoanjiyogenez, metastaz için esastır ve tümör büyümesini uyaran asit oluşumunda yer alan vasküler endoteyal büyüme faktörü (VEGF) tarafından düzenlenir. Bu nedenle peritoneal karsinomatozda yer alan moleküler adımları anlamak, tedavi stratejileri için çok önemlidir[27].

a. Primer Tümörden Ayrılma: Tümör hücreleri primer tümörden serozal infiltrasyonla veya komşu organlara invazyon ile ayrılırlar. Pek çok hastada bu tür tümör hücreleri, belirgin peritoneal metastaz olmadan peritoneal sitolojide saptanabilir ve bu kötü bir prognoz ile ilişkilidir. Benzer şekilde, tümör perforasyonu veya ameliyat sırasında lenfatik damarların transeksiyonu tümör hücrelerinin karın boşluğuna yayılmasına neden olabilir.

b. Çoğalma ve Peritoneal Alana Göç: Primer tümörden ayrıldıktan sonra, tümör hücreleri fizyolojik sıvı akışı nedeniyle periton boşluğuna yayılır. Tümör hücrelerinin periton boşluğu boyunca aşırı yayılması, özellikle assit oluşturan, ilerlemiş yüksek dereceli seröz over tümörlerinde yaygın olarak görülür. Yayılma, peritoneal sıvının hareketlerini takip eder ve abdominal anatomiden etkilenir. Örneğin, overyal bir tümör tipik olarak, Morrison poşundaki sağ kolon sulkusu boyunca ve peritoneal metastazların en sık bulunduğu sağ diyaframa doğru hareket eder. Aksine, gastrik karsinomun sol subfrenik boşluğa yayılma olasılığı sağa göre daha fazladır. Bu nedenle, birkaç abdominal kompartmanda pozitif peritoneal sitolojinin daha kötü bir prognoz ile ilişkili olması şaşırtıcı değildir[22-24,28].

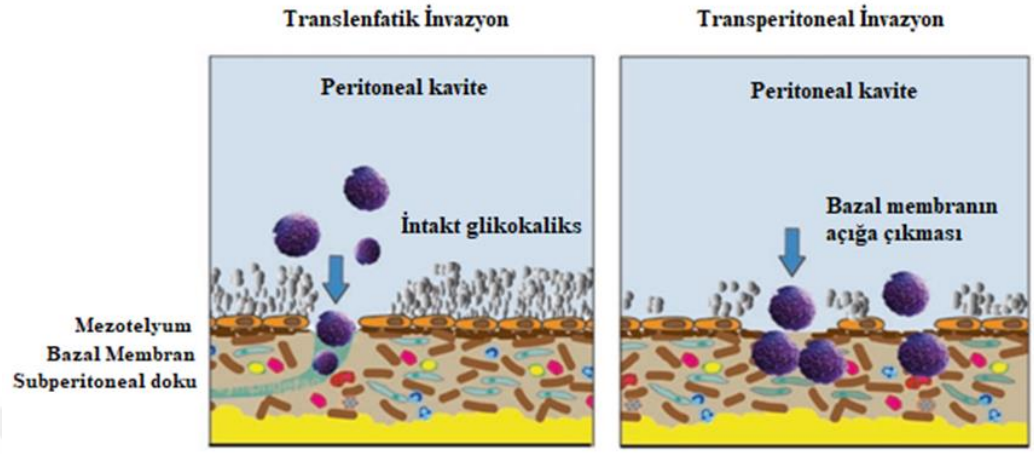
c. Periton Yüzeyine Tutunma: Bozulmamış mezotel tabakası, tümör adezyonu ve invazyonuna karşı mükemmel koruma sağlar[83]. Mikrovilluslar ince bir peritoneal sıvı tabakasıyla(60 μm) kaplıdır. Bunun yanısıra, glikozaminoglikanlar, fosfolipitler, proteoglikanlar, sürfaktan ve pıhtılaşma preküsörleri, mezotel hücreleri tarafından salgılanır. Mezotelyal hücreler tarafından lokal olarak üretilen, hiyalüronik asit glikokaliksin diğer bir ana bileşenidir. Tümör hücrelerine ve yapışmalarına karşı koruyucu bir glikokaliks tabakası oluşturur. Tümör hücrelerinin tutunma yeteneği mezotel hücreleri tarafından, daha sonra çoğalmaları için tümör hücresi ve mezotel hücresi arasındaki iletişim tarafından belirlenir. Tümör hücreleri, sağ diyafram veya omentum majus gibi

ekstraselüler matrikse serbestçe erişilebilen mezotel bölgelerine yapışmayı tercih eder. Ameliyattan sonra peritoneal hasralanan alanlarda tümör hücresinin yapışması ve daha sonra invazyonu için tercih edilen bölgelerdir[29,30].

d. Mezotelyuma İnvazyon: İki tip peritoneal invazyon görülmektedir: translenfatik invazyon ve transperitoneal invazyondur (Şekil 3).

Translenfatik İnvazyon Yolu: Bu en yaygın invazyon modelidir. Tümör hücreleri önce milky spotlardaki savunma hücreleri tarafından periton boşluğundan inaktive edilir ve ardından lenfatik stoma yoluyla boşaltılır. Bu etkili savunma mekanizması tümör hücreleri tarafından alt edilirse local tümör invazyonu meydana gelir. Bu invazyon lenfatik stomadan zengin omentum majus, diyafragma kubbesi ve falsiform ligament gibi bölgelerde olur.

Transperitoneal İnvazyon Yolu: Yayılım mezotelyumun kendisi yoluyla gerçekleşir. Bu ancak glikokaliks hasar görürse, mezotelyal hücreler küçülürse, bazal membran açığa çıkar ve yara iyileşme süreçleri tetiklenir, fibrin üretimi ve tümör hücrelerinin yapışması ile invazyon süreci başlar. Kanserli hücreleri, mezotelyal ayrışmayı destekleyen çeşitli hücre adezyon moleküllerini kullanır, mezotelyal hücrelerin ayrılmasını sağlarlar, kendileri bağlanırlar. Ratlarda yapılan çalışmalarda tümör hücrelerini karın içerisine enjekte ettikten sonra, mezotel hücrelerinin döküldüğü gözlemlenmiştir. Benzer gözlemler intraperitoneal IL-6, TNF-β ve IL-8'in enjeksiyonu sonrasında görülmüştür. Yapılan deneysel hayvan modellerinin tümünde, tümör hücreleri mezotel hücrelerinin kendilerine değil, altta yatan bağ dokusuna tutunmuşlardır. Ayrıca elektron mikroskobu görüntüleri peritoneal ilişkili tümörlerde, mezotel hücrelerinin doğrudan tümör kitlesinin altında olmadığını ortaya çıkardı. Bu da mezotelyal hücrelerin tümör hücrelerinin tutunduğu alanlardan ayrıldığını göstermektedir[31-33].



Şekil 3 Translenfatik invazyon ve Transperitoneal invazyon

2.1.6. Neoanjiyogenez

Peritoneal metastazlar, birkaç milimetreden fazla büyümek için, ek bir besleyici vasküler sisteme ihtiyaç duyarlar. Tümörler geliştiğinde veya peritona metastaz yaptığında, daha fazla büyümeleri konakçı dokuya etkili bir şekilde invazyon yapmalarına bağlıdır. Bunun nedeni de yüzeysel kan damarlarıyla yakın temasta olmalarını sağlamaktır. Bu nedenle, peritoneal metastazların omentum majus gibi oldukça vaskülarize dokularda veya mezenterik damarlar boyunca, örneğin mezenter ile ince bağırsak arasındaki sınırda başlama ve büyüme eğilimi vardır. Endotel büyümesini çeşitli endojen faktörler etkiler. Özellikle, anjiyogenezin ana aracısı olan VEGF, çeşitli tümör tiplerinin peritoneal yayılmasında önemli rol oynar alır ve bunun sonucunda assit gelişir. Yüksek vaskülarize tümörler VEGF aracılı neoanjiyogenezde ilaçlara çok bağımlıdır. Peritoneal tümörler plazma ve assit sıvısına geçebilen yüksek seviyede VEGF eksprese ederler. Bu, diffüz anjiyogenezin neden peritoneal metastazın erken evresi olmasına ragmen gözlemlendiğini açıklar. Bu dönemde sadece birkaç tümör nodülü makroskopik olarak tespit edilebilir. VEGF bir dizi olayın başlamasını sağlar. Bunların başında vasküler permabilite artışı vardır. Plazma proteinlerin, fibrinojen ve diğer damar içi maddelerin ekstravaze olmasına neden olur. Ekstravasküler koagülasyon kaskadının başlamasına

sebep olur. Ekstravasküler fibrin jelinin birikmesi, geçici bir stroma görevi görür ve hücre göçü için mükemmel bir matris oluşmasına neden olur. İkinci olarak VEGF anjiyogenez ve arteriovenogenezisin indüksiyonunu sağlar. Fibrinin, granülasyon dokusu ile yer değiştirmesi (yüksek derecede vaskülarize bağ dokusu oluşur), vasküler rezorpsiyon ve kolajen sentezi, yoğun lifli bir bağ dokusu tabakasının oluşmasına neden olur. Peritoneal metastazlarda VEGF, peritoneal hipersekresyonda da önemli rol oynar. Tümör hücreleri tarafından VEGF salgılanması, hayvan modelinde mast hücrelerinin, endotel hücrelerinde degranülasyon olmadan periton boşluğunda sıvı birikmesini arttırdı ve mikrovasküler geçirgenliği indükledi. Tek başına VEGF üretimi, kılcal damarlarda protein geçirgenliğinin artmasına neden olmak için yeterliydi. Yapılan bazı çalışmalarda insanlarda, VEGF seviyeleri malign asitte, sirotik aside göre daha yüksek bulunmuştur[34,35]. Başka çalışmalarda ise, pro-anjiyojenik VEGF'nin rolü, özellikle endotel hücrelerinin büyümesi, migrasyonu, endotel bariyerinin artan geçirgenliği, plazma proteinleri ve ekstraselüler matriksin değişmesi olarak saptanmıştır. Neovaskülarizasyon sadece kapiler geçirgenliği arttırmakla kalmaz; aynı zamanda kapiler filtrenin yüzey alanını çoğaltır, böylece protein ekstravazasyonunu ve değişen onkotik basıncın artmasına neden olur. Starling etkisindeki major parameter olan VEGF, sıvı kaybının artmasına ve periton boşluğunda sıvı birikimin artmasına neden olur[36]. Permabilite artmış, yeni oluşan vasküler yapılar, normal vaskülerlerden farklıdır. Neo anjiyogenez sırasında, önceden var olan küçük venüller ve kılcal vaskülerler genişlemiş ana damarlar halini birkaç gün içinde alırlar[37]. Bu genişlemiş ana damarların oluşması bazal membranın bozulmasına neden olur. Bu oluşan membranlar sert, sıkıştırılamaz yapılardır. Normal venüllerin ve kılcal vaskülerlerin genişlemesini %30 oranında sınırlayan tip IV kollajen, laminin ve proteoglikanlar içerirler[38]. Bu nedenle bazal membran, ana damarların normal mikrodamarların boyutunun 4 ila 5 katına kadar büyümesine izin verecek şekilde parçalanmalıdır.

a. Tümör Büyümesi: Tümör hücreleri peritona bağlandıktan ve mezotel tabakasına invaze olduktan sonra, daha fazla çoğalabilmeleri için submezotelyal bağ dokusuna kararlı bir şekilde bağlanmaları gerekir. Son veriler, bağ dokusunun insan mezotel hücrelerinin,

epitelyal-mezenkimal geçişini(EMG) indüklediğini göstermiştir. Bağ dokusu tabakasındaki tümör hücrelerinin, daha fazla çoğalması ve hayatta kalmaları tümörün mikro ortamı ile etkileşimi gerektirir. Bu bağlamda, kanserle ilişkili fibroblastlar(KİF) çok önemli bir rol oynamaktadır. KİF, ekstraselüler matriksin çeşitli büyüme faktörlerini ve bileşenlerini üretebilir, böylece tümörün vaskülarizasyonunu ve büyümesini hızlandırır. KİF' in kökeni hala belirsizdir. Fakat, farklı hücre tiplerinden, farklı tümörlerden ve farklı tümör alanlarından kaynaklanabilirler. En olası kökenlerden biri yerel peritoneal fibroblastlardır, ancak kemik iliğinin öncü hücreleri, endotel hücreleri, epitel veya peritoneal mezotel hücreleri de tartışılmıştır[39].

b. Epitelyal-Mezenkimal Geçiş (EMG) ve Mezotelyal-Mezenkimal Geçiş (MMG)

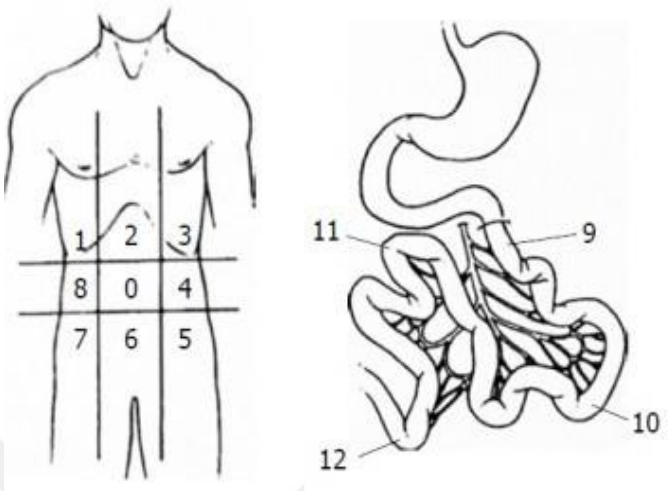
Epitelyal-mezenkimal geçiş (EMG) bir normal embriyogenez, doku onarımı süreçleri sırasında, organ fibrozisi, malign transformasyon ve kanser gelişimi gibi birçok patolojide meydana gelen temel biyolojik bir süreçtir. Belirli büyüme faktörlerine ve/veya stres faktörlerine maruz kaldığında, epitel morfolojik olarak karmaşık bir geçişe uğrayabilir ve mezenkimal fenotip haline gelebilir. Epitel hücreler arası bağlantılarının yanı sıra bazal membrana olan bağlantılarını ve apikobazal hücre bağlantılarını kaybeder. Daha sonra bazal membrana göç ve invazyonu sonrası, hücre iskeletini değiştirir, epitelyal hücreden mezenkimal fenotipe tam dönüşüm meydana getirir. Mezotel hücreleri ayrıca EMG potansiyeline sahiptir. Çünkü bazı epitel benzeri özelliklere ve işlevlere sahiptirler[40]. Mezotel hücrelerinin bu dönüşüm sürecine mezotelyal-mezenkimal geçiş(MMG) denir. Mezotel hücrlerinde, periton diyalizine bağlı periton hasarı oluştuğu durumlarda veya kanserle ilişkili fibroblast aktivasyonu sonucunda mezotelyal-mezenkimal geçiş olabilir. Tümör hücrelerinin kendileri ayrıca EMG sonucunda daha invaziv fenotiplere dönüştürülebilir. Bu durumda mezotel hücrelerini mezotelyal mezenkimal geçişe yönlendirebilir[41]. MMG, bazı mezenkimal belirteçlerin ekspresyonunu sağlar. Fibronektin, vimentin, fibroblast spesifik protein-1, düz kas aktini ekspresyonunu arttırırken aynı zamanda hücre polaritesini değiştirir ve hücre göçüne neden olur[42].

2.2. Peritonitis Karsinomatozada Evreleme Yöntemleri

Peritoneal karsinomatozlu hastaların büyük bölümüne(%50<) primer kanser cerrahisi sırasında tanı konulur[43]. Özellikle ince barsaklar ve mezosu üzerindeki tanecikli hastalık(miliyer tutulum), barsak obstrüksiyon bulguları ve assit varlığı ileri hastalığın göstergesidir. Peritoneal Kanser İndeksi, Gilly Peritoneal Karsinomatoz Evreleme İndeksi ve Hollanda Basitleştirilmiş Kanser İndeksi gibi çeşitli evreleme sistemleri peritonitis karsinomatozisin yaygınlığının tanımlanmasında kullanılmaktadır[44-46]. Bunların arasında en yaygın kullanılanı Peritoneal Kanser İndeksi'dir.

Peritoneal Kanser İndeksi 1996 yılında Sugarbaker ve Jacquet tarafından bildirilmiştir[45]. Peritoneal Kanser İndeksi, karın içerisindeki kanser implantlarının büyüklüğünü ve dağılımını değerlendirmektedir. Peritoneal Kanser İndeksi'nde abdomen çizgilerle 0'dan 8'e kadar numaralandırılarak dokuz bölgeye ayrılmıştır. İnce bağırsaklar da dört bölgeye ayrılmıştır(Şekil 5). Tümör implantlarına ise büyüklüğüne göre 0-3 arasında puan verilmektedir. 0: implant yok, 1: çapı 0,5 cm'ye kadar olan implantlar, 2: çapı 0,5 cm'den büyük ancak 5 cm'den küçük implantlar, 3: çapı 5 cm'den büyük implantların görüldüğünü ifade etmektedir. Bu yöntem ile 39 puan üzerinden bir puanlama yapılarak hastalığın yaygınlığını değerlendirilmektedir. Puanlamalara göre bir inoperabilite kriteri yoktur. Ancak etkin bir sitoredüktif cerrahinin nasıl yapılabileceği hakkında bize bu indeks yol gösterici olmaktadır[44,47].

Elias ve arkadaşlarının çalışmasında kolorektal peritonitis karsinomatozis nedeniyle Sitoredüktif Cerrahi ve HİPEK prosedürü uyguladıkları hastaları analiz etmişler. Peritoneal Kanser İndeks puanı 16'dan küçük olan hastalarda daha iyi bir sağkalım oranı olduğunu saptamışlar[48]. Sugarbaker'a göre ise PKİ puanı 20' nin altında olan hastalarda sağkalımın daha iyi olduğu belirtilmiştir[49].



Şekil 4 Peritonel kanser indeksinde yer alan anatomik yapılar

Anatomik bölgeler[44]

0 Santral: Omentum majus, transvers kolon

1 Sağ üst: Karaciğer sağ lob superior yüzü, sağ hemidiyafragma

2 Epigastrik: Karaciğer sol lobu, omentum minus, falsiform ligaman

3 Sol üst: Sol hemidiyafragma, dalak, pankreasın kuyruğu, mide

4 Sol flank: İnen kolon, sol abdominal alan

5 Sol alt: Sigmoid kolon, sigmoid kolonun lateralinde yer alan pelvik yüz

6 Pelvis: Overler, fallop tüpler, uterus, internal genital organlar, mesane, douglas boşluğu, rektosigmoid kolon

7 Sağ alt: Sağ pelvik yan duvar, apendiks ve çekum

8 Sağ flank: Sağ abdominal alan, çıkan kolon

9 Üst jejunum, 10 Alt jejunum, 11 Üst ileum, 12 Alt ileum

2.3. Sitoredüktif Cerrahi ve Hipertermik İntraperitoneal Kemoterapi

Peritonitis karsinomatozanın lokorejyonel bir hastalık olduğunu ve küratif tedavi edilebileceğini ilk olarak Sugarbaker 1981 yılında söylemiştir. Makroskopik hastalığın sitoredüktif cerrahi ile azaltılması, daha sonra mikroskopik hastalığın tedavisi için hipertermik intraoperatif intraperitoneal kemoterapi uygulanması gerektiğini Sugarbaker protokolü adı altında yayımlamıştır. Bu yöntemle kolorektal kaynaklı peritoneal metastazlı hastalarda 5 yıllık sağkalım oranının %45'e kadar çıktığını gösterilmiştir. Bu prosedürdeki morbidite ve mortalite oranlarına baktığımızda sırasıyla %25, %1,5 olarak bildirilmiştirBu yöntem peritoneal karsinomatoz tedavisinde altın standart olarak kabul edilmiştir. Ancak morbiditesi ve maliyeti yüksek olması nedeniyle sadece tecrübeli onkolojik cerrahlar tarafından seçilmiş hastalar üzerinde belirli merkezlerde uygulanabilmektedir[50].

3. GEREÇ VE YÖNTEM

Çalışma; Dokuz Eylül Üniversitesi Tıp Fakültesi Fakültesi Deney Hayvanları Laboratuarı'nda (DEÜTFDHAL) Ocak – Temmuz 2022 tarihleri arasında Üniversite Yerel Hayvan Etik Kurulu onayı alınarak yapıldı (Protokol No:03/2018). Peritoneal karsinomatoza (PK) modeli oluşturulma sürecinde, DEÜTFDHAL üretilen, erkek 28 adet 7-8 haftalık atimik fare (nude mause) kullanıldı. Nude fareler DEÜTFDHAL iklimlendirilmiş, hava ile filtrelenmiş bir laminer akış kabininde yedili gruplar halinde kafeslenerek izlendi. Işınlanmış gıda ve otoklavlanmış ters osmozla işleme tabi tutulmuş su ile beslenip, tüm işlemlerin, bir laminer akış davlumbazında steril koşullar altında gerçekleştirildi.

Tablo 1 Kullanılan malzeme ve cihazlar

Kullanılan Malzeme/Cihaz	**Marka**
Fetal Dana Serum (FBS)	Cegrogen
DMEM Kültür Ortamı	Cegrogen
Penisilin/Streptomisin antibiyotik	Cegrogen
Fosfat Tamponlu Tuz Çözeltisi (PBS)	Cegrogen
Tripsin/EDTA enzimi	Biochrom
25 cm^2 hücre kültür kabı	Grainer Bio-one
75 cm^2 hücre kültür kabı	Grainer Bio-one
175 cm^2 hücre kültür kabı	Grainer Bio-one
Dimetil sülfoksit (DMSO)	Merck
Otoklav	Hirayama
CO_2 inkübatörü	Thermo
Laminar Akımlı Kabinet	ESCO/Nüve
-80^0 Derin Dondurucu	Thermo

3.1. Tümör ekimi:

CC-531 kolon adenokarsinom hücre hattından elde edilen kanser hücreleri nemlendirilmiş % 5 CO_2 atmosferi altında 37 ° C' de inkübe edilerek, logaritmik büyüme evresi boyunca hasat edildi. Ardından hücreler intraperitoneal enjeksiyon için fosfat tamponlu salin (PBS) içerisinde yeniden süspanse edildi. Hayvan laboratuvarı laminar akış davlumbazında gerekli sterilizasyon sağlanarak, süspanse hücreler 16 mm uzunluğa ve 0.45 mm çapında bir iğne kullanılarak intraperitoneal(i.p.) enjeksiyon ile verildi. Tüm gruplara enjekte edilecek miktar, daha önceki çalışmalar örnek alınarak 200µl PBS içinde $5x10^6$ hücre, 0,3cc, olarak belirlenmiştir[8](Tablo-1). Tümör varlığı tespit edildikten sonra (10.gün) denekler dört gruba ayrıldı. Grup-I, Kontrol Grubu, (serum fizyolojik normotermik olarak uygulandı), Grup-II, Normotermik Kemoterapi (mitomisin C),Grup-III, Hipertermik Kemoterapi (mitomisin C),Grup-IV, Normotermik Kemoterapi (5-Fluorourasil)(Tablo-2).

Tablo 2 Gruplar ve intraperitoneal tedavi prosedürleri

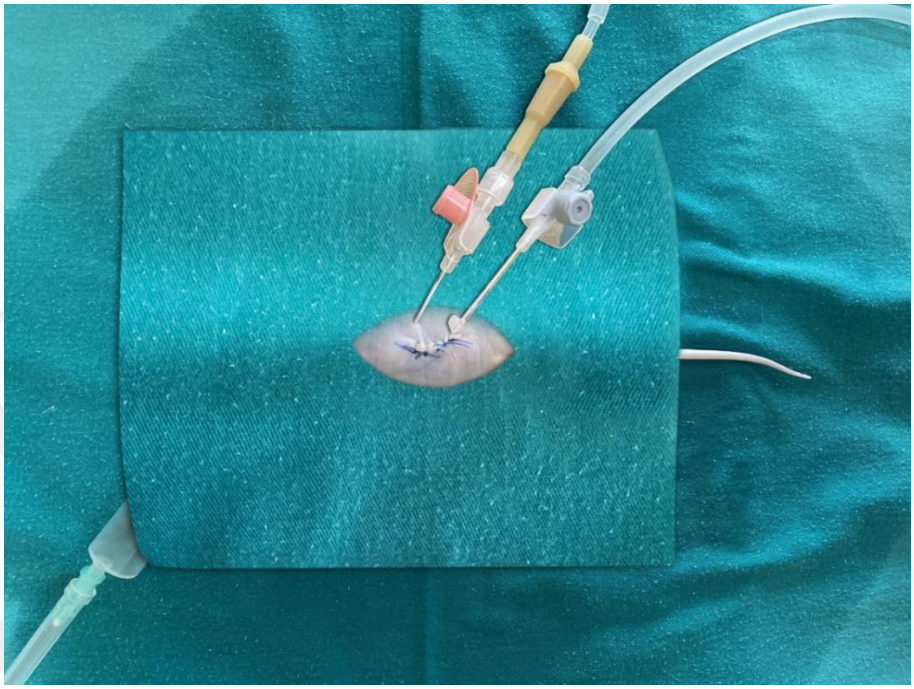
GRUPLAR	***İntraperitoneal Tedavi Prosedürü***
Grup I*(Kontrol)*	Normotermik(37º) Serum Fizyolojik
Grup II	Normotermik(37º) MMC
Grup III	Hipertermik(41º) MMC
Grup IV	Normotermik(37º) 5 FU

MMC: Mitomisin C, 5 FU: 5 Florourasil

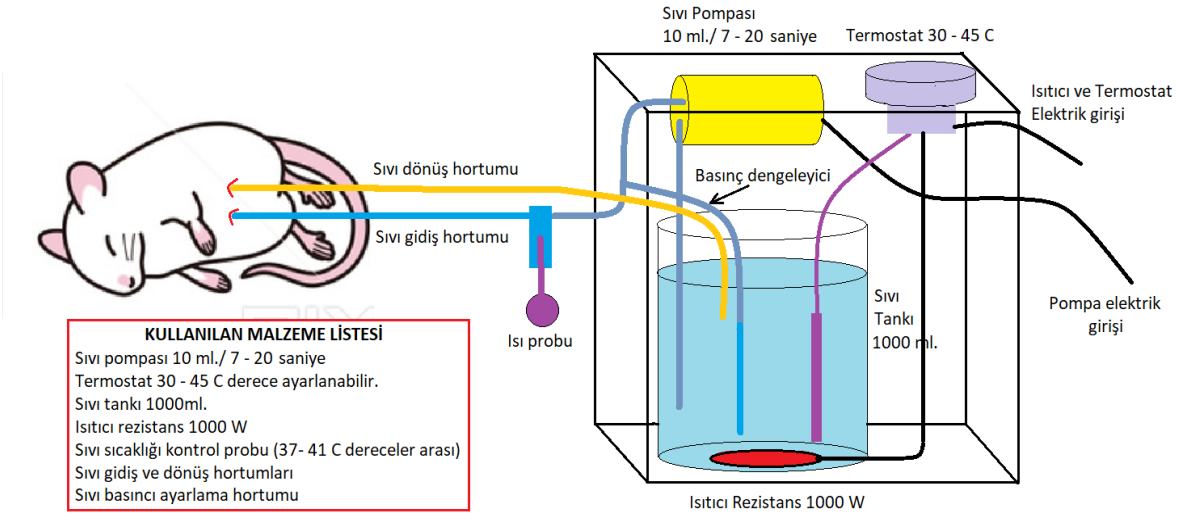
3.2. Cerrahi İşlem ve HİPEK Prosedürü:

Anestezi uygulaması öncesinde fareler tartıldı. Ortalama 34gram(±2gr) gelen farelere; dietil eter inhalasyon anestezi uygulandı. Anestezi sonrası; karın cildi povidone iodine ile temizlendi. Gerekli sterilizasyon şartları denekler steril örtülerle örtülerek sağlandı. Yaklaşık 1cm' lik orta hat insizyonu yapılarak karına girildi. PK varlığı kanıtlandı. İntraperitoneal infüzyon pompasının(İPİP) giriş ve çıkış kateterleri karına lateralden yerleştirildikten sonra orta hat insizyonu 4/0 prolen sütürler ile primer kapatıldı(Şekil-5). Ardından belirlenen gruplara uygun olarak farklı kemoterapötik ajanlar (5 florourasil 400mg/m², mitomisin C 20mg/m²) normotermik (37ºC) ve hipertermik (mitomisin C 20mg/m²) (41ºC) olarak 45 dakika verildi. Bu işlem tarafımızdan prototip olarak geliştirilmiş, İPİP ile gerçekleştirildi(Şekil-6). İntraoperatif olarak gerekli doku sıcaklığı HİPEK grubunda 4-6 dakika içinde ulaşıldı. Kararlı sıcaklıklar daha sonra ortalama 40.5°C ± 0.5 ile 45 dakika daha muhafaza edildi. Karın içerisini doldurmak için gereken hacim yaklaşık 5 ml idi. Cihazın kendi termostatı yardımıyla karın içerisine verilen ve alınan sıvının derecesi kontrol edilerek ısının sabit tutulması sağlandı. Kemoteröpötik ajanlar mitomisin C konsantrasyonu 20mg/m², 5 florourasil 400mg/m², olarak 30cc %0,9 NaCl içerisinde hazırlanarak verildi. Bu işlem laboratuvar ortamında, güvenlik önlemleri alınarak yapıldı. Hayvan vücut metrekaresi [A(m²) =kW(2/3)(k=3)] formül kullanılarak hesaplandı. Peritoneal perfüzyon 45 dakika sürdürüldü. İşlem tamamlandıktan sonra perfüzyon kanülleri karın dışarısına alındı. Sistemin sıvı kazanı her

işlem sonrası siterilize edildi. Tüm infüzyon hortumları ve kanüller, her işlem sonrası değiştirildi. Sterilizasyon her denek için optimal şartlarda sağlandı.



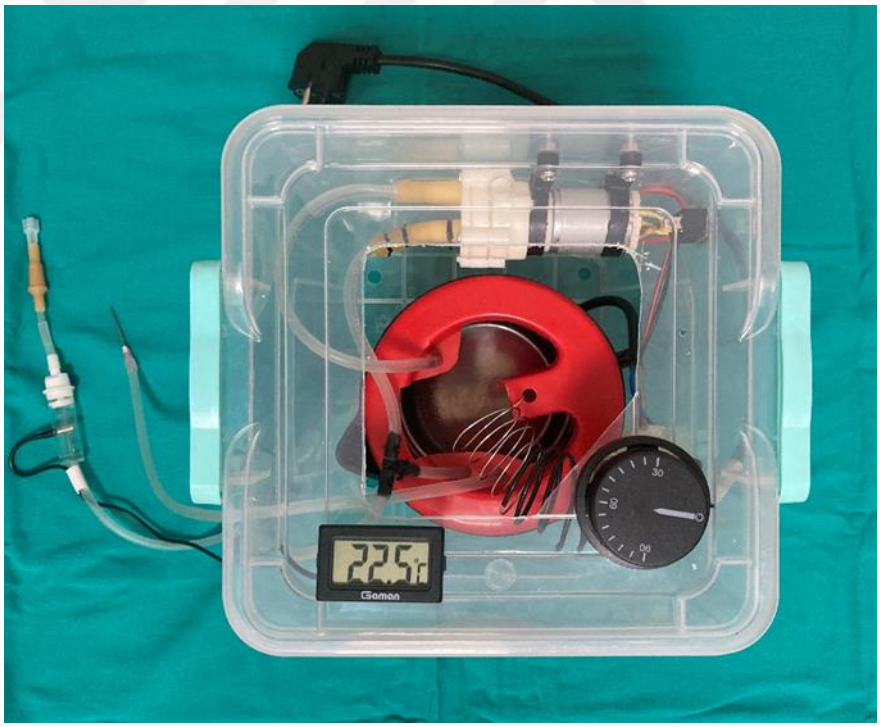
Şekil 5 İntraperitoneal kemoterapi uygulaması önce modelin hazırlanması, kateterlerin yerleştirilmesi



Şekil 6 İntraperitoneal İnfüzyon Pompa Sistemi Çalışma Şeması

3.3. İntraperitoneal İnfüzyon Pompası(İPİP):

Tarafımızdan tasarlanan ve geliştirilen intraperitoneal infüzyon pompası(İPİP), 1000mililitrelik sıvı tankı, sıvı pompası, 30-45derece aralığını kontrol edebilecek termostat, ısıtıcı resistansı(1000W), sıvı sıcaklığı kontrol probu, sıvı gidiş ve toplama kanülleri, sıvı basıncı ayarlama kanülünden oluşmaktadır(Şekil-7). Sıvı çıkış kanülünden, karın içerisinden gelen sıvının ısısı ikinci kontrolden geçerek sabit sıcaklık sağlanmaktadır. Sıvı pompasının debisi ayarlanabilmektedir. Geliştirdiğimiz İPİP sistemi ile farklı türde oluşturulan PK modellerine intraperitoneal kemoterapi uygulanabilir.



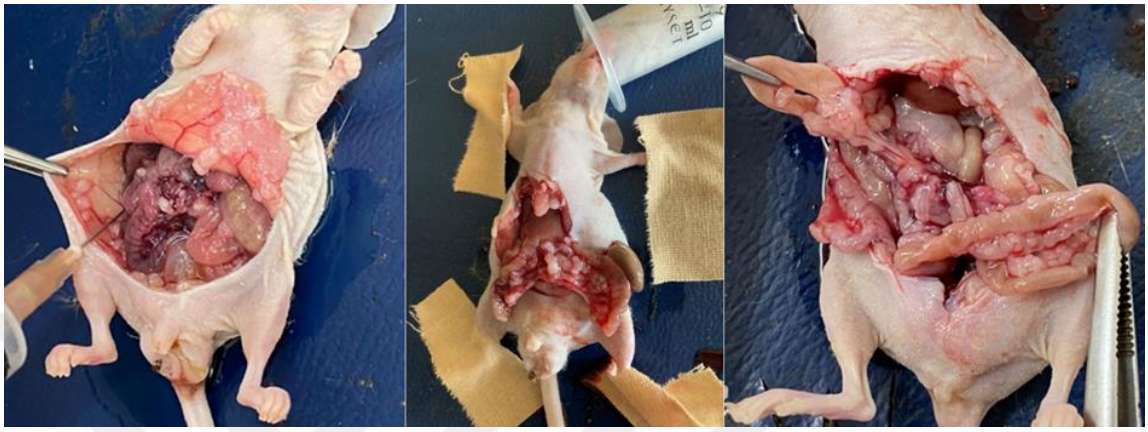
Şekil 7 İntraperitoneal İnfüzyon Pompası(İPİP)

a. Denek Takibi, Sakrifikasyon, Verilerin Toplanması:

Günlük takipleri yapılan denekler, intraperitoneal kemoterapi infüzyonundan 5 gün sonra laparotomi yapılarak değerlendirildi. Peritoneal karsinomatoz indeksi(PCI)

belirlenerek, skorlama yapıldı. Tutulan organ ve tümör çapına göre puanlama yapıldı (Skorlama 8 puan üzerinden değerlendirildi). İnce barsak ve/veya mezenter tutulumu: 1puan, periton tutulumu: 1puan, diyafragma tutulumu: 1puan, asit (+): 1puan, diğer organlar: 1puan). Tümör çapları ölçülerek skorlandı(0 makroskopik tm yok, nodül çapı 2mm≥ 1puan, nodül çapı 2-5mm ya da >5 nodül sayısı 2puan, nodül çapı 5mm≤ ya da >10 nodül sayısı 3puan)(Şekil-8). Asit aspire edildi, miktar ölçümü gerçekleştirildi. İnce barsak, periton, karın içi doku ve sıvı örnekleri alınarak, denekler sakrifiye edildi. Sonrasında alınan doku ve karın içi sıvı örnekleri histopatolojik, biyokimyasal olarak değerlendirildi. Doku örnekleri %10 formaldehit içerisinde fikse edilerek, kasetlendi, doku takibi sonrası paraffin bloğa gömülerek. 5 µm'lik dondurulmuş kesitler, optimum kesit yüzeyinden elde edildi. Kesitler daha sonra hematoksilen ve eozin (H & E) ile boyanarak ve Olympus X50 ışık mikroskopisi altında incelendi. Dokular tümör varlığı, paterni, differansiyasyonu, apoptoz, mitoz ve nekroz açısından değerlendirildi. Işık mikroskobunda 40' lık objektif altında 400 kat büyütülerek farklı 10 tümör alanında toplam mitoz sayısı hesaplanarak değerlendirme yapıldı. Apoptoz sayısı 5000hücre değerlendirilerek 1000hücredeki oran belirlenerek hesaplandı. Dokular tümör nekrozu olup olmadığına değerlendirildi. Kanserli dokudaki lenfatik damar endotelyal hyaluronan reseptörü-1(LYVE-1), Anjiyopoietin-1(Ang-1) ve Anjiyopoietin-2(Ang-2) boyanma şiddeti, ekspresyon düzeyleri immunohistokimyasal yöntemlerle incelendi. Batın içi sıvı enjektörle tüpe alınıp santrifüj edildi, üst kısım biyokimyasal çalışmalar için kullanıldı. Çökelti lam üzerine damlatılıp, kurutulup methanol ile fikse edilerek ve giemsa ile boyanıp ışık mikroskobunda tümör açısından değerlendirildi. Deneklerin karın içi sıvıları santrifüj sonrası kalan süpernatanlarında Lizil Oksidaz benzeri protein 1 (LOXL1) (USCN) ve TWIST Transkripsiyon faktör (TWIST) (USCN) fare uyumlu ELISA kitleri kullanılarak çalışıldı. VEGF düzeyleri asit sıvılarında örnekler dilüe edilerek fare uyumlu ELISA kiti (Finetest) uygulama basamakları gözetilerek çalışıldı. Standartlardan elde edilen absorbans değerlerine göre her bir teste ait standart grafikleri oluşturuldu. Örneklerden elde edilen absorbanslardan konsantrasyonlar hesaplanarak ifade edildi. LOXL1 ELISA kitinin ölçüm aralığı 78-5000 pg/mL ve testin sensitivitesi 29 pg/ml idi. TWIST testi için kitin ölçüm aralığı 0,156-10 ng/mL olup, testin sensitivitesi 0,056 ng/mL

idi. VEGF testi için kitin ölçüm aralığı 15-1000 pg/mL olup, testin sensitivitesi 9.375 pg/mL idi.



Şekil 8 Farelerde Peritoneal Karsinomatoz İndeksi Tayini, Asit Miktarı Ölçümü

b. İstatistiksel Analiz:

Nicel veriler normal dağılıma uygun olmadığı için gruplarda Kruskal Wallis testi kullanılarak analizler gerçekleştirildi ve grupların çoklu karşılaştırmaları yapıldı. Tanımlayıcı istatistikler medyan (25-75 persantil) biçiminde gösterildi. Nitel verilerin analizinde ise Fisher kesin ki-kare testi ve T-test kullanıldı ve tanımlayıcı istatistikler frekans (yüzde) biçiminde gösterildi. $p<0,05$ olduğu durumda istatistiksel olarak anlamlı kabul edildi.

4. BULGULAR

İntraperitoneal kemoterapi uygulanan deneklerde, postoperatif dönemde mortalite görülmedi. Hipertermik kemoterapi verilen grupta dört hayvanda hafif yan etkiler(anoreksi ve laterji) gözlendi ve iki gün içerisinde kayboldu. Dokuz hayvanda insizyon hattında minimal ayrışmalar görülse de, sakrifikasyon sürecine kadar mortalite yaratacak enfeksiyon ve yara ayrışması izlenmedi.

Makroskopik Bulgular: Peritoneal kanser indeksi gruplar arası karşılaştırıldığında Hipertermik intraperitoneal MMC verilen grup(grup III) ortalama en düşük değer sahipti[6.42(±1.71)]. Bu değer istatistiksel olarak anlamlıydı($p=0.034$). Tümör çapları ve

asit miktarları gruplar arasında karşılaştırıldığında grup III yine en düşük değerlere sahip idi[5.28(±2.28)mm, 3(±2.16)ml]. Bu değerlerde istatistiksel olarak anlamlıydı(p=0.011, p=0.046). Ancak grup III dışındaki, gruplar arasında bu üç parametre açısından çalışmamız da anlamlı bir fark saptanmamıştır(Tablo-2).

Tablo 3 Grup -III' ün ortalama PKI, tümör çapı ve asit miktarı diğer gruplara göre anlamlı olarak daha azdı(Kruskal-Wallis test , T-test).

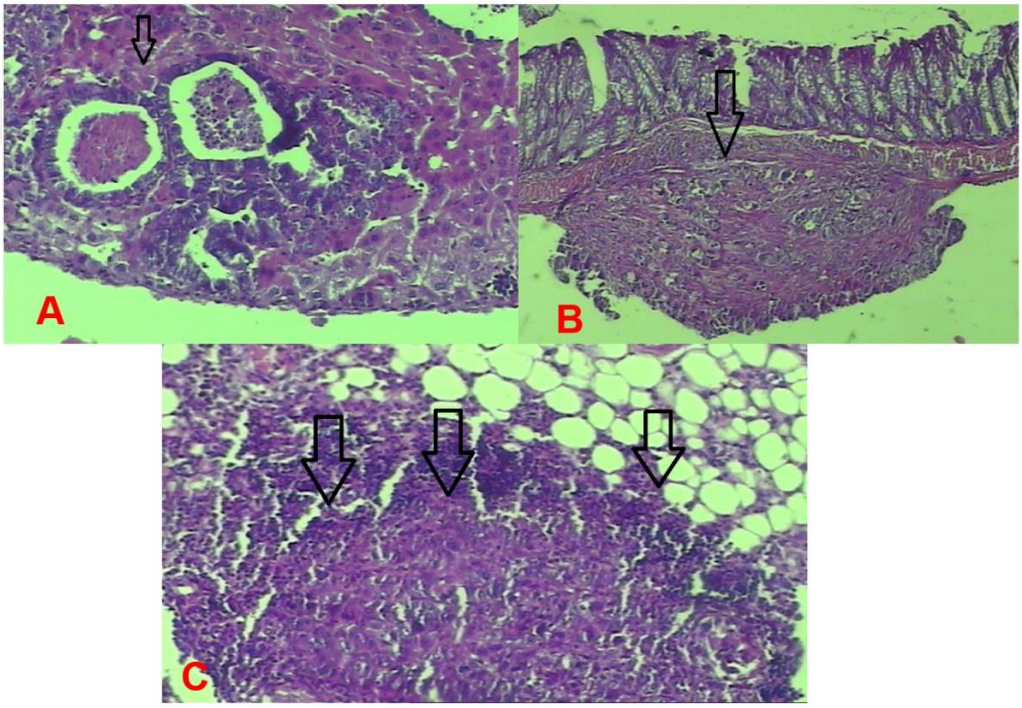
Mean(std±)	**G-I**	**G-II**	**G-III**	**G-IV**	***p value***
PKI	6.71(±1.38)	6.42(±1.71)	4.42(±0.53)	6.42(±1.39)	*.034*
Tümör çapı(mm)	5.85(±3.28)	5.28(±2.28)	2.42(±0.53)	5.42(±1.90)	*.011*
Asit(ml)	4(±1.93)	3(±2.16)	1.28(±1.77)	4.21(±0.63)	*.046*

PKI: peritoneal kanser indeks, std: standard deviasyon.

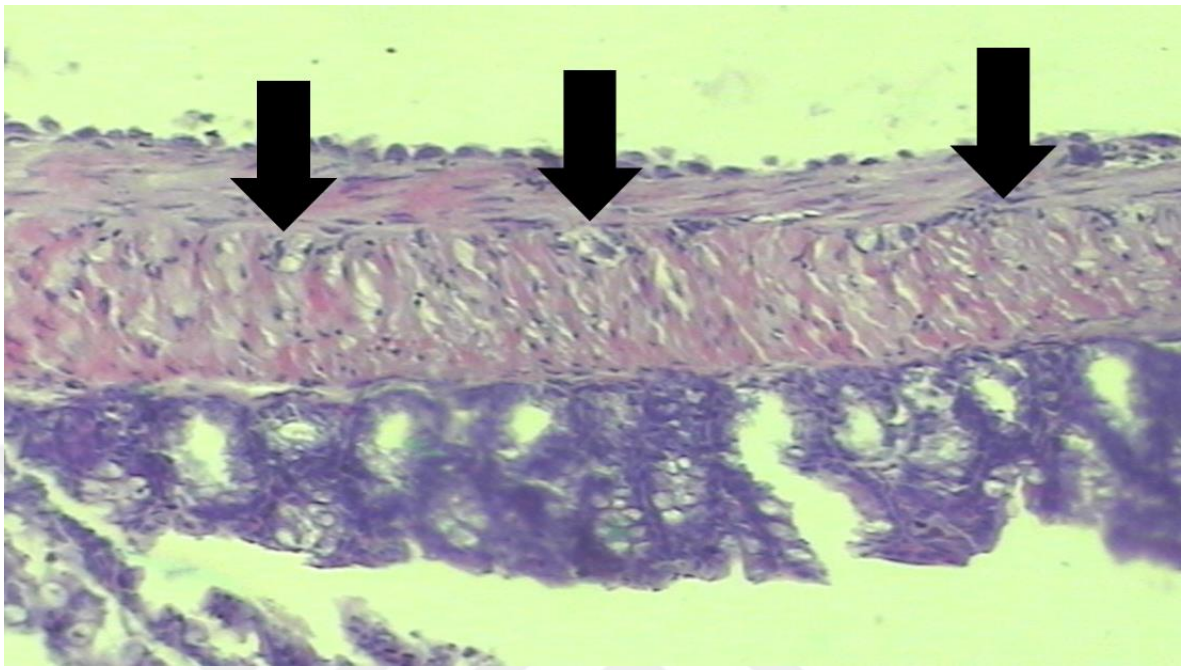
Mikroskobik Bulgular: Sakrifikasyon sonrası alınan doku örnekleri(intestinal sistem, periton, karaciğer) mikroskop altında değerlendirildiğinde, tüm dokularda tümör hücre infiltrasyonu görüldü. Tümörün nodüler, indiferansiye yapıda olduğu saptandı. Gruplar mitoz sayısı, apoptoz sayısı ve tümör nekrozu açısından karşılaştırıldığında, istatistiksel anlamlı farklar saptanmıştır($p<0.01$). Hipertermik intraperitoneal MMC(grup III) uygulanan grupta apoptoz sayısı ve tümör nekrozunun diğer gruplara göre istatistiksel anlamlı daha fazla olduğu saptandı($p<0.001$,$p=0.009$). Mitoz sayısı ise G I ve G IV' e göre G III' de daha düşük olduğu saptandı($p<0.001$). Normotermik intraperitoneal MMC(grup II) uygulanan gruptaki mitoz sayısı kontrol grubu(G I) ve normotermik 5 FU grubuna(G IV) göre istatistiksel olarak anlamlı daha düşük olduğu izlendi($p<0.001$). Hipertermik MMC grubuyla(G III), normotermik MMC grubu(G II) arasında mitoz sayısı açısından anlamlı bir farklılık saptanmamıştır.(Tablo-3)(Şekil 9-10-11).

Tablo 4 Gruplardaki tümör dokularında ortalama; mitoz sayıları, apoptoz sayıları ve tümör nekrozu oranları(Kruskal-Wallis Test, T-Test, p<0.001, p=0.009).

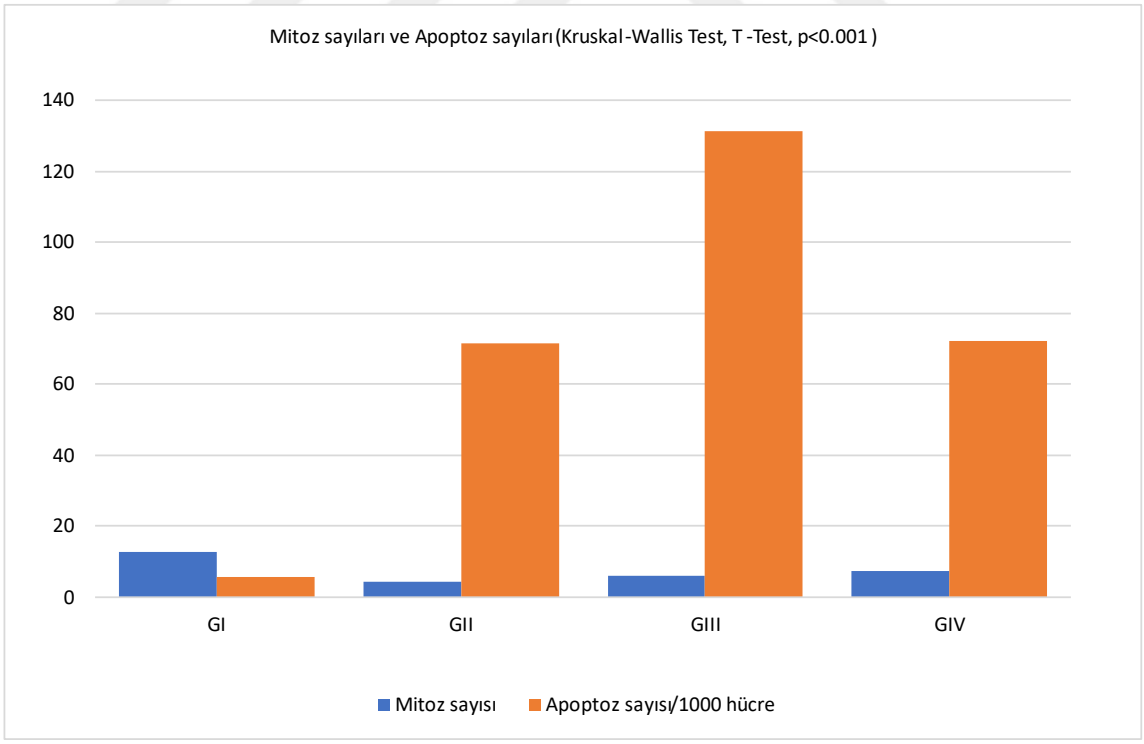
	Tümör Hücrelerindeki Mitoz Sayısı (10 büyük büyütme)	**Apoptoz Sayısı/1000 Hücre**	**Gruplardaki Tümör Nekroz(+) Denek Oranı(%)**
G I*(Kontrol)*	12.714(std 1.79)	5.42(std 2.29)	14.2
GII*(Normotermik MMC)*	4.285(std 1.97)	71.42(std 37.16)	28.5
GIII*(Hipertermik MMC)*	5.857(std1.34)	131.42(std 48.79)	100
GIV*(Normotermik 5FU)*	7.285(std 2.49)	72.14(std 29.98)	28.5
***p** (Kruskal-Wallis Test)*	***<.001***	***<.001***	***.009***



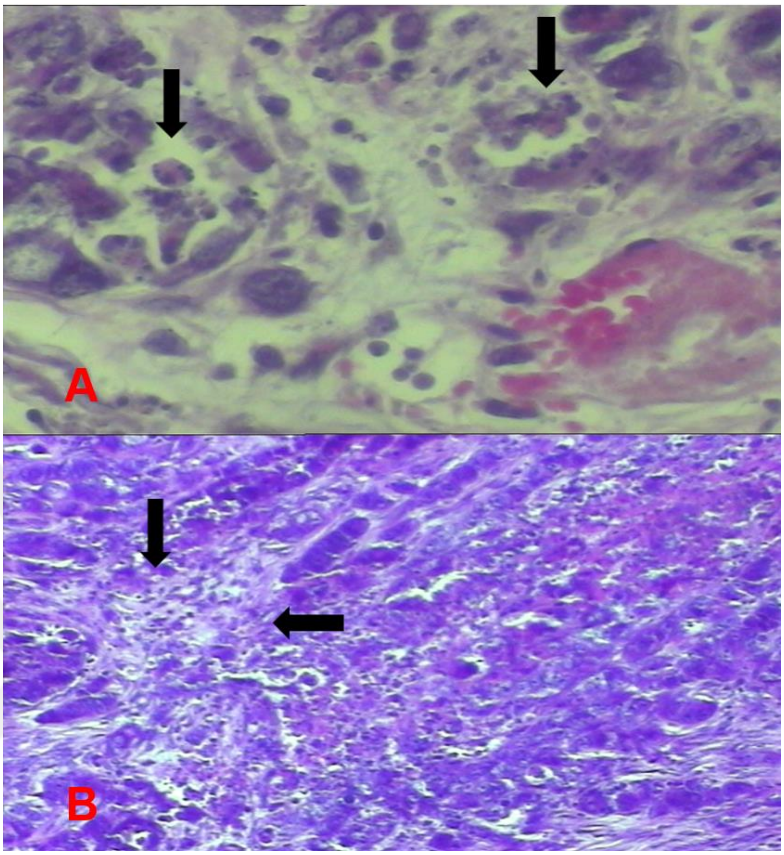
Şekil 9 Grup I(Kontrol) tümör görüntüleri; **A:** Karaciğere implante olmuş nodüler tümör, **B:** Barsak duvarına tümör implantasyonu, **C:** Peritoneal yağ dokusuna infiltre tümör.



Şekil 10 Barsak duvarı mezotel hücreleri(Tümör yok).

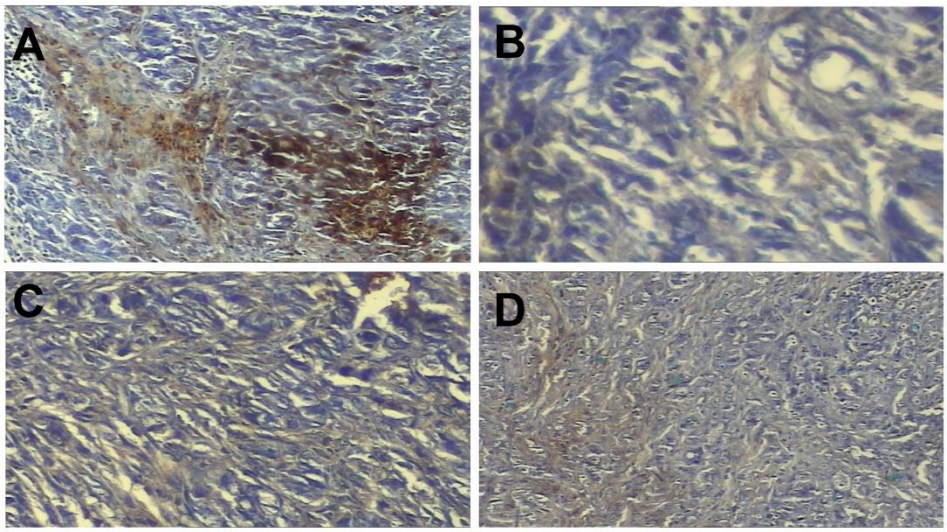


Şekil 11 Mitoz ve apoptoz sayısı



Şekil 12 Grup III(Hipertermik MMC) tümör görüntüleri; **A:** Tümör hücrelerinde apoptoz artışı, **B:** Tümör nekroz alanları.

İmmünohistokimyasal Bulgular: Tüm deneklerden elde edilen tümörlerde LYVE-1 pozitifliği vardı. Kontrol grubunda(grup I), güçlü pozitiflik oranı intraperitoneal mitomisin verilen gruplara(grup II-III) göre istatistiksel anlamlı yüksek olduğu saptandı($p=0.004$). Ang-1 boyanma şiddetleri arasında gruplar arasında anlamlı bir fark saptanmamıştır. Kontrol grubunda Ang-2'nin intraperitoneal kemoterapi uygulanan gruplara göre anlamlı olarak güçlü pozitif olduğu saptanmıştır($p=0.002$).



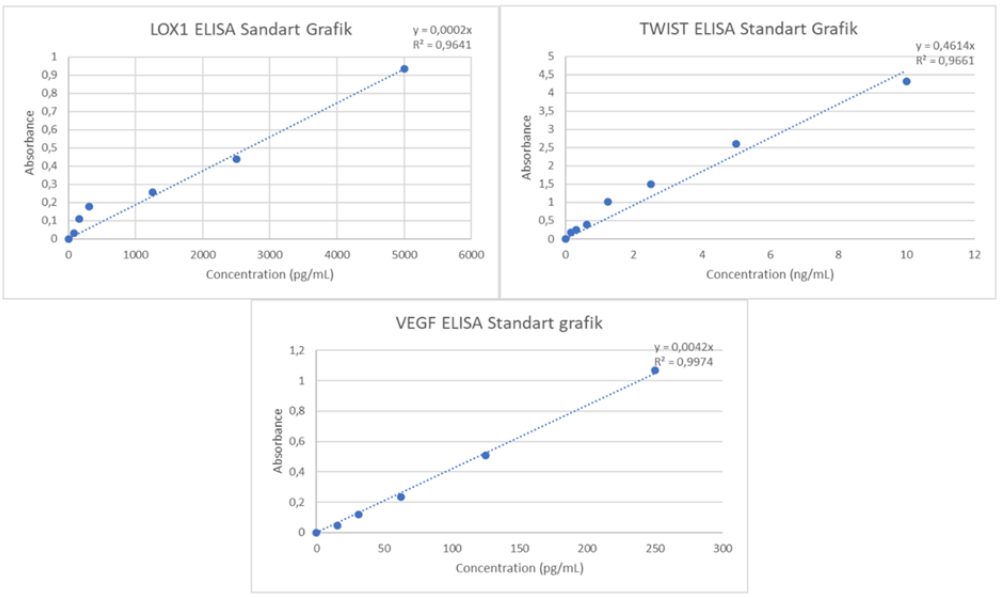
Şekil 13 A-C: Grup I(Kontrol) LYVE-1 ve Ang-2 şiddetli boyanma, B-D: Grup III(Hipertermik MMC) zayıf boyanma.

Biyokimyasal Bulgular: Gruplar arasında karın içi asit sıvısındaki VEGF, LOX1 ve TWIST ortalama değerleri GIII' de diğer gruplara göre istatistiksel olarak anlamlı düşük saptanmıştır[VEGF; 17.960(std±24.728)pg/mL, LOX1; 225.000(std±308.801)pg/mL, TWIST; 0.254(std±0.407)ng/mL (p=0.011, 0.042, 0.044)]. Diğer gruplar arası anlamlı bir fark saptanmamıştır(Tablo-4).

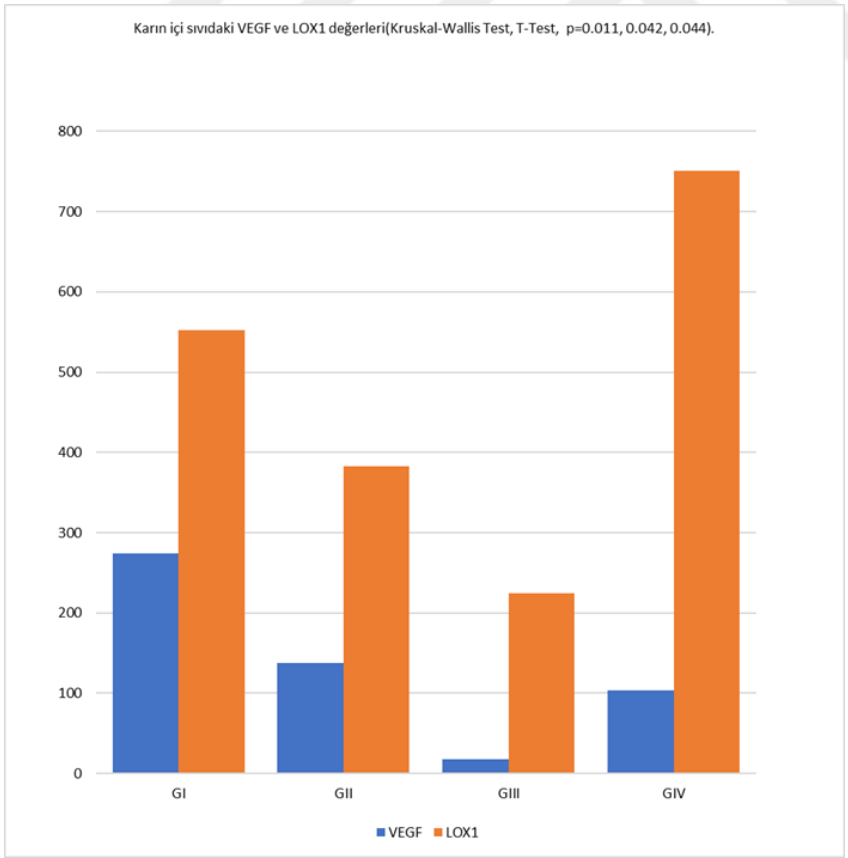
Tablo 5 Gruplar arasında karın içi asit sıvısında VEGF, LOX1 VE TWIST değerleri (Kruskal-Wallis Test, T-Test, p=0.011, 0.042, 0.044).

	VEGF	**LOX1**	**TWIST**
GI	274.625(std±192.498)	552.142(std±326.622)	1.416(std±1.164)
GII	137.687(std±113.335)	382.857(std±303.422)	1.565(std±1.258)
GIII	17.960(std±24.728)	225.000(std±308.801)	0.254(std±0.407)
GIV	103.640(std±62.946)	750.714(std±362.254)	2.176(std±1.498)
p	***.011***	***.042***	***.044***

VEGF:Vasküler Endotelyal Büyüme Faktör, LOX1: *Lizil Oksidaz Benzeri Protein-1, TWIST: Twist Transkripsiyon Faktör.*



Şekil 14 LOX1, TWIST, VEGF ELISA Standart Grafikleri



Şekil 15 Karın içi sıvıdaki VEGF ve LOX1 değerleri

5. TARTIŞMA

Çalışmamız da atimik farelerde peritoneal karsinomatoz modeli oluşturularak, bu modelde kendi geliştirdiğimiz peritoneal infüzyon pompasıyla intraperitoneal kemoterapi verilerek farklı ısı ve ilaçların etkinliklerinin karşılaştırılması amaçlanmıştır.

Litaretürde ilk olarak psödomiksoma peritonei tanısı olan bir hastada Spratt ve arkadaşları HİPEK uyguladılar. Ardından mitomisin C ile HİPEK, çeşitli peritoneal yüzey maligniteleri için sitoredüktif cerrahiyi takiben uygulanmıştır[51]. Yapılan çalışmalar da tek başına sistemik kemoterapi ile karşılaştırıldığında HİPEK için önemli bir sağkalım yararı gösterilmiştir[52-54]. Teknik olarak tam yapılan sitoredüktif cerrahi en önemli prognostik faktördür. Eksik sitoredüksiyon, sınırlı sağkalıma neden olur[55,56].

HİPEK prosedüründe kullanılan ilaçların sınırlı bir penetrasyon derinliği vardır. Bu nedenle HİPEK kapsamlı sitoredüktif cerrahi uygulanarak makroskopik tümörün ortadan kaldırıldığı veya minimal tümör kalan hastalarda uygulanır[57]. Bu nedenle Veenhuizen ve arkadaşları tarafından oluşturulan bir PK modelinde, sitoredüktif cerrahiyi simüle etmek için tümör hücreleri intraperitoneal bir yağ yastığına implante edilmiştir[58]. Bu teknik kullanılarak tümör implantlarının yayılımı sınırlandırılmaktadır. Bu da sitoredüktif bir cerrahi yapılmış, tümör yükü azaltılmış bir karını simüle eder. Ancak tümör yükünün az olması, ilaç etkinliklerinin karşılaitırılmasını zorlaştırmaktadır. Bu nedenle genellikle çalışmalar da intraperitoneal injeksiyon yoluyla tümör oluşturulmaktadır[59,60]. Bu da daha fazla tümör yükü olan modeler oluşmasını sağlamaktadır. Biz çalışmamızda tümör hücrelerini intraperitoneal boşluğu vererek yaygın tümöral implant oluşumu sağladık. 7-10 gün içerisinde tüm deneklerde yaygın peritoneal implantlar oluştu. Yaygın peritoneal implantların oluşturulması makroskopik PKİ skorunu belirlememizi kolaylaştırdı. Bunun dışında gruplarlara uygulanan farklı ilaçlar arasındaki etkinlik farkını daha iyi tespit etmemizi sağladığını düşünmekteyiz. Bazı çalışmalarda intraperitoneal tümör ekimi sonrası tümör oluşum oranı %80 olarak bildirilirken[61,62], intraperitoneal yağ yastığına implante edilen bir çalışma da %100 olarak bildirilmiştir[58]. Bizim çalışmamıza baktığımızda bu oran %75 olarak belirlenmiştir.

Geliştirdiğimiz İPİP sistemiyle HİPEK' in atimik fare PK modelinde etkin olarak yapılabileceğini gördük. Perfüzyon sırasında ve sonrasında deneklerde kayıp olmadı. İntraperitoneal kemoterapi verilmesinden sonra hayvanlar 7 gün gözlendi. Ciddi komplikasyon izlenmedi. Sadece hipertermik kemoterapi verilen grupta dört hayvanda hafif yan etkiler(anoreksi ve laterji) gözlendi. Tüm bu yan etkiler iki gün içerisinde kayboldu. Geç dönem etkileri, morbiditeler 7. Günde sakrifikasyon olması nedeniyle tam olarak değerlendirilemedi. Temelde HİPEK sitoredüktif cerrahiyle birlikte etkinliği kanıtlanmış bir prosedürdür. Ancak çalışmamızda model üzerinde sitoredüktif cerrahi yapmak uygun olmadığı için sadece HİPEK uygulanmıştır. Bu durumda, uygulananan kemoterapötik ilaçların etkinliğinin sınırlı kalmasına neden olmuştur.

Sitotoksik ilacın ve sıcaklığın homojen dağılımını sağlamak zordur, ancak bu prosedürün tümörosidal etkinliği için çok önemlidir. Bu nedenle homojen sıcaklık ve ilaç dağılımını sağlamak için karın açık olarak yapılan yaklaşım seçilebilir[63]. Bu yöntemin en büyük dezavantajı sistotksik ilaçlara maruz kalmamızdır. Çalışmamız da perfüzyon kateterleri yerleştirildikten sonra karın duvarı kapatıldı ve sonra peritoneal infüzyon başlatılmıştır. Sıvı gidiş ve geliş kateterlerinde sürekli yapılan ısı kontrolü ve infüzyon hızının ayarlanmasıyla optimal intraperitoneal sirkülasyon sağlanmış, istenilen ısı ve homojen ilaç dağılımı korunmuştur. Karının kapalı olması ilaç ısısnın kontrolünü ve sürerliğini kolaylaştırdı. Tedavi süresi tamamlandıktan sonra kanüller çekilerek işlem sonlandırıldı.

Kolorektal kanser orjinli peritoneal karsinomatozda Mitomisin C, HİPEK için kullanılan en yaygın kemoterapötik ajandır. Diğer bir intraperitoneal kemoterapi modalitesi de erken postoperatif intraperitoneal kemoterapidir(EPİK). 5-Florourasil esas olarak EPİK için kullanılır[64-65]. 5-FU hipertermik uygulamalarda kullanılmamaktadır. Bizim çalışmamız da MMC grup II' ye normotermik olarak uygulandı, grup III' e hipertermik olarak uygulandı. Grup IV' e ise 5-FU normotermik olarak uygulandı. Bu üç gruptaki ilaç etkinlikleri karşılaştırıldı. Tümörosidal etkinliğin en fazla olduğu grup III idi. Hayvan modellerinde, yapılan deneysel çalışmalarda MMC'nin 20 mg/m² intraperitoneal maksimum tolere edilen dozda oldukça güçlü olduğu ve tümör büyümesini önlediği

gösterilmiştir[66]. Çalışmamızda uyguladığımız teropötik MMC(20mg/m²) ve 5-FU(400mg/m²) konsantrasyonları, literatürdeki çalışmalara uygun olarak yapıldı[65-69].

Çalışmamızda ki sonuçlara bakıldığında, peritoneal karsinomatoz hayvan modellerinde, intraperitoneal kemoterapi uygulanan çalışmalarda toplanan klinik verileri desteklemektedir[70]. Makroskopik verilerle gruplar karşılaştırıldığında, en fazla tümörosidal etkinliğin görüldüğü grup hipertermik MMC uygulanan grup olmuştur(G-III). Diğer gruplar arasında istatistiksel olarak anlamlı bir fark saptanmamıştır. Mikroskopik incelemelerde; hipertermik MMC uygulunan grupta dokulardan elde edilen kesitlerde tümör hücrelerinde apoptoz sayısının ve tümör nekroz oranının diğer gruplara göre yüksek olduğu, mitoz sayısının düşük olduğu görülmüştür. Bu da verilen hipertermik tedavinin tümörisidal etkinliğinin diğer gruplara göre daha üstün olduğunu göstermektedir. Diğer tedavi gruplarında da kontrol grubuna göre apoptoz sayısının ve tümör nekrozunun fazla olduğu, mitoz sayısının düşük olduğu saptanmıştır. Lenfatik damar endotelyal hyaluronan reseptörü 1(LYVE-1) lenfatik endotele özgü, hücre yüzey reseptörüdür. Hyaluronan'ın extrasellüler matriksten lenf düğümüne taşınmasında görev alır. LYVE-1 güvenilir bir lenfatik damar belirtecidir ve immunohistokimyasal olarak kullanıldığında lenfatik damar yoğunluğu saptamakta yararlanılmaktadır. Koçdor ve arkadaşlarının[71] yaptığı çalışma da lenfanjiogenetik bir belirteç olarak LYVE-1 araştırılmış, meme kanserli hastalarda bölgesel lenfatik metastazı belirlemede etkinliği olduğu saptanmıştır. Yapılan çalışmalarda, bu belirtecin çeşitli solid kanser türlerinde lenfatik metastazı öngörebileceğini ve prognostik önemi olduğunu ortaya koymaktadır [72,73,74]. Çalışmamızda İntraperitoneal mitimosin verilen gruplarda LYVE-1 boyanma şiddetinin zayıf olması, tümörosidal etkinliğin olduğunu göstermektedir. Ang-1 ve Ang-2/Tie-2 ailesinin çeşitli kanser türlerinin patogenezinde yer aldığı bildirilmiştir. Ang-1'in Tie-2'ye bağlanması, endotelyal hücreleri ve çevreleyen hücre dışı matriks arasındaki etkileşim sağlayarak olgun damarları korur ve stabilize eder. Ang-2 ise anjiyojenik remodeling için gereklidir ve neovaskülarizasyonda rol oynadığı gösterilmiştir[75,76]. Çalışmamız da intraperitoneal kemoterapi verilen gruplarda kontrol grubuna göre anlamlı zayıf pozitiflik saptanmıştır. Bu bulgu da verilen kemoteropötik ajanın etkinliğini göstermektedir. Biyokimyasal parametrelere baktığımızda VEGF neaovaskülarizasyonda

görev alan temel aracıdır. Tümörlerin peritoneal yayılmasında rol oynar ve bunun sonucunda assit gelişir. Peritoneal tümörler assit sıvısına geçebilen yüksek seviyede VEGF eksprese ederler[77,78]. Epitelyal mezenkimal geçiş ve onkogenezde önemli rolü olan LOX ve TWIST belirteçleridir. LOX ekspresyonu ile az diferansiye hücre kümeleri arasında anlamlı ilişki tespit edilmiştir. Tümörün epitelyal komponentinde LOX ekspresyonu arttıkça stromadaki LOX ekspresyonun da arttığı gözlenmiştir. Stromadaki LOX ekspresyonu ile tümör tomurcuklanması arasında anlamlı ilişki saptanmış olup yüksek LOX ekspresyonunda yüksek tomurcuklanma dereceleri tespit edilmiştir. LOX'un hem tümör epitelyal hem stromal ekspresyonu ile maspin ekspresyonu arasında anlamlı ilişki izlenmiştir. Stromada kuvvetli LOX ekspresyonu saptanan vakalarda mikst ve nükleer maspin ekspresyonunda artış dikkati çekmiştir[79-81]. Çalışmamız da biyokimyasal değerlendirmelerin sonucunda da hipertermik MMC uygulanan grupta asit sıvısında VEGF, LOX1 ve TWIST değerlerinin anlamlı olarak diğer gruplara göre düşük olduğu görülmüştür ve bunun kemoterapötik etkinliğe bağlı olduğu düşünülmüştür. Tüm bulguları değerlendirdiğimizde makroskopik, mikroskopik ve biyokimyasal inceleme sonuçları ortak olarak en güçlü tümörosidal etkinliğin hipertermik MMC grubunda olduğunu göstermektedir.

6. SONUÇ VE ÖNERİLER

Oluşturulan peritoneal karsinomatoz modelinde HİPEK prosedürü uygulanabilir, sonuçlar niteliksel ve niceliksel olarak değerlendirilebilir. HİPEK'in etkisi makroskopik olarak kaydedilebildi. Kabul edilebilir morbi-mortalite oranlarıyla atimik farelerde postoperatif beş günlük gözlemler yapılabilmektedir. Geliştirdiğimiz peritoneal infüzyon pompasıyla efektif olarak intraperitoneal kemoterapi uygulaması gerçekleştirilebilmiştir. Bundan sonraki çalışmalarda İPİP rahatlıkla modeller üzerinde kullanılabilir. İlaç etkinliklerini gruplar arasında karşılaştırdığımız da tümörosidal etkinliğinin, hipertermik MMC uygulanan grupta istatistiksel olarak anlamlı yüksek olduğu saptanmıştır. Bundan sonraki çalışmalarda farklı ilaç etkinliklerinin farklı ıslarda oluşturduğumuz bu model ve geliştirdiğimiz İPİP sistemiyle denenmesi planlanmaktadır. Bununla birlikte, daha ileri

deneysel in vitro ve in vivo çalışmalar yaparak HİPEK prosedürünün etkinliğinin daha da arttırılabilmesi ve yan etkilerinin daha da azaltıması amaçlanmaktadır.

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EKLER

EK-1: TEZ İLE İLİŞKİLİ YAYINLAR

1) Manoğlu B, Sökmen S, Bişgin T, Yıldırım Y, Çevlik AD, Aksu Erdost H, Obuz F. Urgent re laparotomies in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ulus Travma Acil Cerrahi Derg. 2022 Oct;28(10):1389-1396. doi: 10.14744/tjtes.2022.62121.(SCI-E kabul edildi)

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Urgent re-laparotomies in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Affiliations + expand

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Inflammation-based prognostic scores in geriatric patients with rectal cancer

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Neglected prognostic importance of ileal resection in patients with peritoneal metastasis

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Submitted Manuscripts

STATUS	ID	TITLE	CREATED	SUBMITTED
AME: Solass, Wiebke • With Editor Contact Journal	PAP.2023.0002	Investigation of The Effectıveness of Hyperthermic Intraperitoneal Chemotheraphy In Experimental Colorectal Peritoneal Carcinomatosis Model View Submission Cover Letter	15-Jan-2023	15-Jan-2023

Investigation of The Effectıveness of Hyperthermic Intraperitoneal Chemotheraphy In Experimental Colorectal Peritoneal Carcinomatosis Model

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ABSTRACT

Background: In our study, it is aimed to (1) create a peritoneal carcinomatosis (PK) model in nude mice, administer intraperitoneal chemotherapy with the peritoneal infusion pump we developed in this model, and (2) compare the intraperitoneal chemotherapy efficacy at different temperatures and drugs.

Materials and Methods: The peritoneal carcinomatosis model was established in nude mice using the CC531 colon carcinoma cell line. Models with PK were randomized into four groups of seven animals each: group I, control group (n=7), group II normothermic intraperitoneal chemotherapy(NIPEC) with mitomycin C(MMC)(n=7), group III hyperthermic intraperitoneal chemotherapy(HIPEC) with mitomycin C (n=7), group IV NIPEC with 5-Fluorouracil (5-FU) were applied.

Results: Tumor development was achieved in all animals. While the tumor burden decreased significantly in treatment group III(p=0.034), no significant difference was found in the other groups. In the PK mouse model, hyperthermic intraperitoneal administration of MMC had the highest tumoricidal effect.

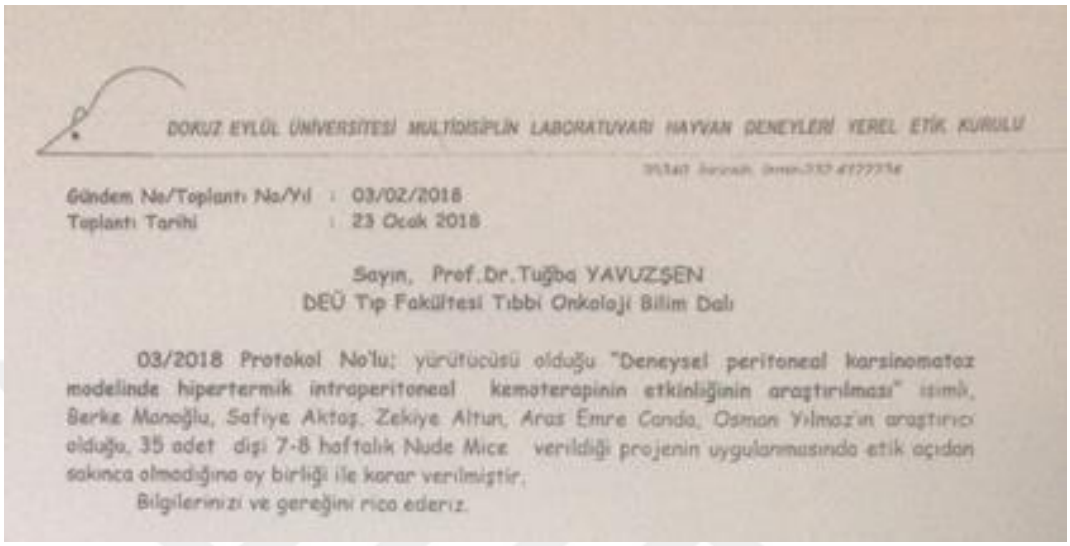
Conclusion: Our PK model provided a good opportunity to examine the efficacy of HIPEC and IPIP. In future studies, it is planned to evaluate different drug efficacy in the PK models we have created.

Key words: peritoneal carcinomatosis model, colorectal cancer, HIPEC

Dergi İndeksi



EK-2: ETİK KURUL ONAYI



DOKUZ EYLÜL ÜNİVERSİTESİ MULTİDİSİPLİN LABORATUVARI HAYVAN DENEYLERİ YEREL ETİK KURULU

Gündem No/Toplantı No/Yıl : 03/02/2018
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Sayın, Prof.Dr.Tuğba YAVUZŞEN
DEÜ Tıp Fakültesi Tıbbi Onkoloji Bilim Dalı

03/2018 Protokol No'lu; yürütücüsü olduğu "Deneysel peritoneal karsinomatoz modelinde hipertermik intraperitoneal kemoterapinin etkinliğinin araştırılması" isimli, Berke Manoğlu, Safiye Aktaş, Zekiye Altun, Aras Emre Canda, Osman Yılmaz'ın araştırıcı olduğu, 35 adet dişi 7-8 haftalık Nude Mice verildiği projenin uygulanmasında etik açıdan sakınca olmadığına oy birliği ile karar verilmiştir.

Bilgilerinizi ve gereğini rica ederiz.

KATKI

Tezin deneysel çalışmaları için gerekli bütçe **Dokuz Eylül Üniversitesi Bilimsel Araştırma Projeleri Müdürlüğü** tarafından 2021/72 numaralı proje ile sağlanmıştır.

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Tez Konusu: Meme Cerrahisi Sonrasında Seroma Gelişmesi Üzerine Nutrisyonun Etkisi Araştırılmışı
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Ağırlıklı Genel Not Ortalaması: 76.0 / 100.0

Deneyim / İşyeri Bilgileri

28 Ocak 2021 - Şu Anda (1 yıl 11 ay) (Tam Zamanlı)
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Yabancı Dil Bilgileri	İNGİLİZCE (Okuma: İyi, Yazma: İyi, Konuşma: Orta)

Bilimsel Teknolojik Faaliyet Alanları

Anahtar Kelimeler	Genel Cerrahi Cerrahi Onkoloji Kolorektal Cerrahi

Ar-Ge Yetkinlik

Makaleler

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TÜBİTAK Burs ve Destekleri

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Akut Apandisit

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Mekanik Barsak Obstruksiyonları

Cerrahi İnfeksiyonlar

ORIGINAL ARTICLE

Urgent re-laparotomies in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Berke Manoğlu, M.D.,[1] Selman Sökmen, M.D.,[1] Tayfun Bişgin, M.D.,[1] Yasemin Yıldırım, M.D.,[1] Ali Durubey Çevlik, M.D.,[1] Hale Aksu Erdost, M.D.,[2] Funda Obuz, M.D.[3]

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ABSTRACT

BACKGROUND: The objective of the study was to evaluate the morbidity-mortality results in terms of immunscore factors and to predict the outcomes of urgent re-laparotomized patients treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

METHODS: Prospectively maintained database of 661 patients treated with potentially curative intent of CRS and HIPEC through the years of 2007 and 2020 was evaluated. URL was done for 28 (4.2%) patients as unplanned re-explorative surgery; 22 (78.6%) of them was female. The median age was 57 year (ranging, 24–76 years). There were 22 (78.6%) elderly patients over 65 years old. All standard clinico-pathological characteristics, re-operative findings, and the morbidity-mortality results were analyzed. The well-known immunoscores such as neutrophil-lymphocyte ratio (NLR), neutrophil-thrombocyte ratio (NTR), and CRP-albumin ratio (CAR) were determined.

RESULTS: The main indication for URL was small bowel anastomotic leak (n=13, 46.4%). The abdominal wall disruption (n=5, 17.9%) was the second indication. The frequent localization of injured organ was again small bowel. The 28.6% of patients (n=8) were re-operated in early postoperative period (in 7 days), while as the rest of them (n=20, 71.4%) in 90 days. There was only one repeat-URL patient in this series. Many of the URL patients (n=16, 57.1%) had more than one co-morbidities. Delving into the overall group, there were Clavien-Dindo (C-D) Grade I-II complications in 104 (16.4%) patients and C-D Grade III-IV in 88 (13.9%) patients, whereas in URL patient group, C-D Grade III-IV complications were seen in 22 (78.6%). In this prospective cohort, the overall mortality rate was 3.2% (n=20) in patients who were not re-explored. Six (21.4%) patients were lost in URL patients, which the main reason for failure-to-rescue was sepsis due to entero-enteral anastomotic leak. In four of them, multiple co-morbidities were affected the post-URL period of complex cancer care. Pre-URL median NLR, NTR, and CAR values were 9.12 (ranging, 1.72–37.5), 0.03 (ranging, 0.01–0.12), and 41.4 (ranging, 4.2–181.3), respectively. NLR and CAR values (4.71 and 28.8) estimated before pre-CRS were also significantly high ($p=0.01$ and $p<0.01$) in patients who were going to be operated for URL. These immunoscores values did not show any association in between pre-CRS and pre-URL mortal patients.

CONCLUSION: The crucial decision-making factors at work were complex and complicated in "unplanned" URL. The overall morbidity-mortality results seemingly depends on the severity and extent of peritoneal metastatic disease. Medically-unfit URL patients with high-risk factors should be selected to a vigilant monitoring and clinical care. Timely surgical intervention and intense management strategy are utmost important issues to lower morbi-mortality results in patients treated with URL.

Keywords: Cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; immunscore; urgent relaparotomy.

INTRODUCTION

Surgeons enjoy to discuss, analyze, and present their successes, but there is an understandable reluctance to publish personal reoperative experiences. Surgical literature about URL is thus really lacking, reticence, and poorly structured.

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Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have become a preferred treatment option for patients with resectable peritoneal metastasis to improve their survival. This treatment option is applied in metastaticaly diseased peritoneum, which is usually caused by carcinomas of ovarium, colon and rectum, appendix, peritoneal mesothelium, gastric and primary peritoneum.[1–6] Sugarbaker[7] pioneered the procedure of CRS and HIPEC, because only systemic chemotherapy was not sufficient for long-term and durable survival in patients with peritoneal metastases (PM).[8,9] CRS is a maraton and complex combination of extended abdomino-pelvic surgical techniques including peritonectomies and/or multiorgan resections and intraoperative HIPEC is particularly attractive for treatment of PM that are amenable to complete Cytoreduction (CC-0).[7,8] Difficulties in critical decision making to operate or not and in URL surgical technique, particularly in a battlefield of CRS and HIPEC is a complex surgical situation.

Complications developed after extended surgical procedures usually cause poor oncologic results, decreased survival, and high costs.[8–10] Maximum efforts must be put in multidisciplinary board to properly select the right patient to minimize the possibility of life-threatening complications. However, relatively high rate of complications can occur in this difficult field of surgical oncology and prompt diagnosis of severe complications and timely management with urgent reoperation can lower the morbidity-mortality rates and even save lives.[11] Despite technical advances in early diagnosis and improvements in surgical care, the mortality rates are still high in URL patients having multi-comorbidities and chemo (-radio)therapy.[11,12]

In recent years, the "failure-to-rescue (FTR)" concept was studied as an important evaluation criterion after surgery.[13] and it was accepted in 2010 by the American National Quality Forum as a quality measure for surgical care.[14] Specific care with standardized management should be dedicated to significantly reduce postoperative complications, mortality, and FTR rate. We analyzed the reasons of the FTR rate in our patients who underwent URL in the clinical setting of CRS and HIPEC.

Human immune system has a complex and multi-faceted role in the development and treatment of cancer. It affects all aspects of the disease process, from tumorigenesis to treatment[15] as well as the results of surgical treatment and postoperative outcomes. Immune cells can act both as suppressors of tumor initiation and progression, and as accelerators of proliferation and metastasis ("stochastic").[16] Several studies had confirmed that clinical immunoscoring predicts outcome in a patient with early[17] or advanced[18] stage cancer. There is a growing body of evidence that chronic inflammation plays a significant role in the development of malignancy tissue.[19] The biochemical parameters such as C-reactive protein (CRP), albumin (ALB), neutrophil, lymphocyte, thrombocyte counts, and the ratios between these values were used in various oncologic studies to assess immunstatus.[18,19] It is thought that by evaluating the immunoscores of URL patients preoperatively can provide logical predictions about morbidity-mortality results.

The aims of our study were (i) to determine the morbidity-mortality results of URL patients operated with CRS and HIPEC treatment and (ii) to search the impact of immunscore evaluation on the outcomes of these patients.

MATERIALS AND METHODS

Prospectively maintained database of 661 patients treated with potentially curative intent of CRS and HIPEC through the years of 2007 and 2020 was evaluated. Approval was obtained from the ethics committee of Dokuz Eylul University Faculty of Medicine for the retrospective analysis of patient data (Reference No: 2022/16-20). The data of the routine pre- and post-operative practices performed by the Colorectal Surgery Unit of Dokuz Eylul University General Surgery Medicine Department were used. No special test, intervention, or examination was performed for the study.

These patients were first evaluated in the multidisciplinary tumor board and carefully selected surgical candidates were allocated for prehabilitation. In this study, we reviewed the postoperative results of patients who underwent an URL in the post-operative period after CRS and HIPEC procedures performed at our center. Urgent reoperation was defined as any unplanned surgery after the initial surgery within 90 days of surgery. These URL patients were compared with the pre-and post-operative results of non-reoperated CRS and HIPEC patients. URL was done for 28 patients as unplanned re-exploration (4.2%); 22 (78.6%) of them was female. Relaparotomy was performed in 28.6% (n=8) of the patients within the first 7 days, and 71.4% (n=20) between 7 and 90 days. All clinico-pathological characteristics, re-operative findings, and final outcomes were analyzed. The well-known immunoscores such as neutrophil-lymphocyte ratio (NLR), neutrophil-thrombocyte ratio (NTR), and CRP-ALB ratio (CAR) were determined.

Patients with URL (Group I) and patients without URL (Group II) were first compared statistically in terms of age and gender, and it was determined that they were homogeneous (Chi-square and t-test). These two groups were then compared in terms of neoadjuvant therapy, co-morbidity, smoking, peritoneal cancer index (PCI) score, completeness of cytoreduction (CC) score, length of hospital (LoH) stay, high grade complication (C-D III-IV), and mortality by univariate analyses. NLR, NTR, and CAR values were initially estimated and compared between the two groups before CRS (Mann–Whitney U test). ROC analyses were performed for NLR and CAR. Cutoff values, sensitivity, and specificity ratios were determined.

RESULTS

The median age was 57 year (ranging, 24–76 years). There were 22 (78.6%) patients over 65 years old. The 28.6% (n=8) of patients were re-operated in early postoperative period (in 7 days), while as the rest of them (n=20; 71.4%) in 90 days. There was only one re-URL patient in this series. 25% (n=7) of the patients in group I were smokers and many of them (n=16; 57.1%) had more than one co-morbidities such as diabetes mellitus and atherosclerotic heart disease. 64% (n=18) of the URL patients were received neoadjuvant chemotherapy and 28% (n=8) had pelvic radiotherapy. The median LoH stay (LoHS) after CRS and URL were 15 days (ranging, 3–94) and 22 days (ranging, 8–130), respectively. After URL, 71% (n=20) of the patients were admitted to the intensive care unit. The average duration of treatment in the intensive care unit was 8 days. When Groups I and II were compared in terms of age, gender, smoking, comorbidities, LoHS, and neoadjuvant treatment, no statistically significant differences were found (Table 1).

Table 1. Demographic and therapeutic characteristics of patients who underwent urgent

Variable	n	%
Sex		
Male	6	21.4
Female	22	78.6
Age, yr		
Median age (range)	57.50 (24 to 76)	
<65 yr	21	75
≥65 yr	7	25
Smoking		
Yes	7	25
No	21	75
Co-morbidities (>1)	16	57.1
Neoadjuvan chemotherapy		
Yes	18	64.3
No	10	35.7
HIPEC in CRS		
Yes	28	100
No	–	–
CC score		
0	23	82
1–3	5	18
Peritoneal Carcinomatosis Index (PCI)		
PCI ≤10	12	42.8
PCI 10–20	8	28.6
PCI ≥20	8	28.6
High grade complication (C-D III-IV)		
Yes	22	78.6
No	6	21.4
Postoperative mortality		
Yes	6	21.4
No	22	78.6

Re-laparotomy (URL); C-D: Clavien-Dindo; CC: Completeness of cytoreduction score; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

The cutoff PCI scores of URL, saved-URL, and lost-URL patients were 13, 12, and 14, respectively. During the first operation, the CC-0 score was determined in 23 patients who underwent relaparotomy and CC-1 in 5 patients. The CC score was calculated as 1 in two patients and 0 in four patients who died in the perioperative period after relaparotomy. When Groups I and II were compared in terms of PCI scores and CC scores, no significant differences were found (Table 1).

Delving into the overall cohort group, there were Clavien-Dindo (C-D) Grade I-II complications in 104 (16.4%) patients and C-D Grade III-IV in 88 (14%) patients, whereas in URL patient group, C-D Grade III-IV complications were seen in 22 (78.6%). In this prospective cohort, the mortality rate was 3.2% (n=20) without any re-exploration. However, six (21.4%) patients were dead in URL patients (Table 1). The cardinal reason for FTR was sepsis due to entero-enteral anastomotic leak in URL group (Fig. 1). In four of URL patients, pluri-co-morbidities affected the post-URL intensive care. Fifty percent of mortal patients in URL-treated had neoadjuvant chemotherapy.

The primary indication for URL was small bowel anastomotic leak (n=13; 46.4%). The secondary was the abdominal wall disruption (n=5; 17.9%) (Fig. 2). The frequent site of injured organ was again small bowel (Fig. 3).

For URL-patients, pre-URL median NLR, NTR, and CAR values were 9.12 (ranging, 1.72–37.5), 0.03 (ranging, 0.01–0.12), and 41.4 (ranging, 4.2–181.3), respectively. Interestingly, NLR

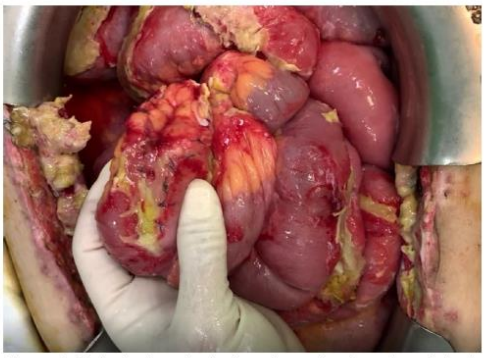


Figure 1. Abdominal sepsis due to entero-enteral anastomotic leak.

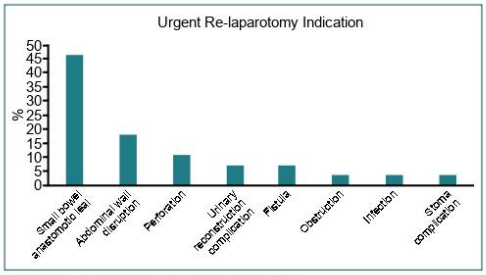


Figure 2. Urgent re-laparotomy Indication.

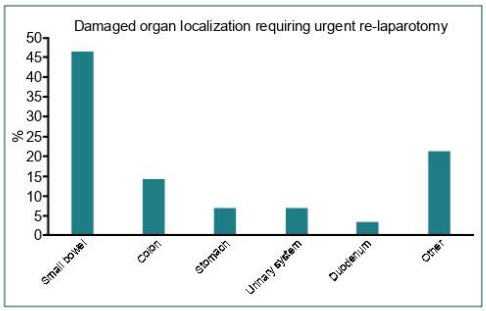


Figure 3. Damaged organ localization requiring urgent re-laparotomy.

and CAR values (4.71 and 28.8) estimated before pre-CRS were also significantly higher (p=0.01 and p<0.01) in patients who were going to be treated with URL (Table 2). The cut-off values of urgent NLR and CAR values before CRS were determined as 4.02 and 17.87, respectively (Table 3). The sensitivity and specificity of the NLR and CAR indices were 82% and 18% and 86% and 16%, respectively. There was no significant difference between the two groups in terms of NTR values. By determining the NLR and CAR values in pre-CRS patients, the potential risk of complications necessitating URL can be foreseen preoperatively. These immunoscore values did not show any association between two groups in terms of mortality.

DISCUSSION

The key prognostic factors to achieve complete CRS of peritoneal metastatic disease followed by HIPEC are the extent of the disease and radical eradication of tumor burden, however, the trade-off will be the increased morbidity, reoperation(s), and mortality. Even though the cytoreductive surgical team did their best for the indications with consummate skill, and judicious care, "unexpected" complications still arise which require urgent relaparotomy. The ability to know when and how to perform URL always brings greater technical difficulty than a first index operation, because anastomic planes are destroyed, dense fibrous-scarring and ceramized adhesions are present. The exhausted patient due to more advanced disease, pluri-cycles of chemotherapy, and malnutrition, the magnitude, and impact of the surgery becomes frequently greater.

URL was defined as surgery performed for a complication after primary surgical condition.[20] In the present study, patients who underwent URL after CRS were analyzed. The patients were divided into two groups as operated on in the early postoperative period (0–7 days) or operated on in the late postoperative period (7–90 days). Published studies of URL for different surgical operations had reported rates between 2% and 21%. It was stated that this variability in incidences stems from the different populations, types of operation, histopathology, immune status of the host, and co-existing diseases.[21–23] On the other hand, the incidence of complications requiring URL has been reported as 1–5.1% in patients undergoing major abdominal surgery.[24,25] The rates

Table 2. Neutrophile-lymphocyte ratio (NLR) and CRP-albumin ratio (CAR)

	NLR	CAR
Pre-CRS median ratio of non-URL group	2.28 (0.13 to 39.37)	2.13 (0.04 to 228.3)
Pre-CRS median ratio of URL group	9.12 (1.72 to 37.5)	41.4 (4.2 to 181.3)

CRS: Cytoreductive surgery; URL: Urgent re-laparotomy; CRP: C-reactive protein.

Table 3. ROC Analyzed NLR and CAR

Risk Factor	AUC (95%)	Cut-off	p	Sensitivity (%)	Specificity (%)
CAR	0.923 (0.886–0.959)	17.87	0.000	85.7	15.8
NLR	0.900 (0.843–0.958)	4.02	0.000	82.1	17.6

ROC: Receiver operating characteristic; NLR: Neutrophile-lymphocyte ratio; CAR: C-reactive protein-albumin ratio; AUC: Area under curve.

of urgent reoperation in vascular, obstetric and gynecology, pancreatic, and colorectal surgery has been reported as 12%,[21] 2.6%,[26] 11%,[27] and 10.4%[28] respectively. This URL rate was 4.2% in the current study. It can be thought to be a quite low rate for such an extensive radical surgery inherently when compared to other "conventional standard surgeries." The multidisciplinary working intelligence and experience resulted with good clinical outcomes.

Significant relationship has been established between URL and male gender.[12,22,29] In contrast, the female gender ratio was high in this study. The reason for this high rate is possibly due to the high incidence of female patients in the ovarian-CRS. No significant difference was found when the patients who underwent URL were compared with those who did not URL in terms of age and gender.

The cardinal causes of URL in the relevant literature were mainly septic complications due to anastomotic leak, intestinal perforation, and/or intestinal ischemic necrosis (32–51.3%), mechanical ileus (25–62.8%), eventration/evisceration (7.2–22%), bleeding (3.3–19%), and others (2–3%), respectively.[11,30] In our study, the main indications for URL were small bowel anastomotic leak (n=13; 46.4%) and the abdominal wall disruption (n=5; 17.9%). The frequent localization of injured organ was again small bowel. Regardless of the incidence, these complications mandated URL with vital indications.

Early detection of complications, vigorous resuscitation, and prompt intervention can save many lives.[24] At present, there is no ideal score system for the prediction of ongoing infection in complicated patients with possible abdominal sepsis after their initial index laparotomy. As in Van Ruler et al.[31] reported, available well-known scoring systems were out of clinical value in this group of patients. However, Pusajo et al.[32] described the score of Abdominal Reoperation Predictive Index (ARPI) and studied the usefulness of ARPI to predict whether to perform URL in case of septic complications. They found that usage of ARPI scoring system was resulted in a reduction in mortality against a control group mainly due to earlier relaparotomy. Studying Pusajo's ARPI criteria to our data of URL series the management would not have been differed. It must be over stressed that the small numbers in the study preclude any firm conclusion about the reliability and effectiveness of ARPI improving our patients' survival.[31–35] However, a scoring system can help in adequate and timely identification of patients for URL, none of the existing and widely used severity-of-disease scores have high performance to identify the patients with ongoing septic complications needing a URL. Even an Artificial Neural Network (ANN) investigations to aid algorithmic diagnostic ITER resulted in controversial findings and APACHE II and expert intensivists' experience were found to be superior in the prediction of patients outcome to the ANN and other tested scoring system.[36–39]

Morbidity rates varied between 30% and 68% and perioperative mortality rates between 3% and 8% in centers where CRS and HIPEC are performed.[40] In this prospective cohort, morbidity and mortality rates were found to be 30% and 3.2%, respectively. Our data were found to be consistent with the literature. Specific to our URL group, the high grade complication (C-D III-IV) rate was 78.6%. Despite early diagnostic work-up and therapeutic progress, mortality following URL is still high, ranging from 15.4% to 61.5%. This high mortality of URL has been reported due to the advanced age, medical unfitness, the aggressiveness of the primary surgery ("impaired wound healing and immune defense, disturbed physiologic reserves") and the severity of complications.[11,12,41] The URL mortality rate in our patients was 21.4% (n=6). In URL patients the overriding factors responsible for high mortality rate were proved to be (1) re-operation and (2) the organ in which the complication was occurred.[21,26,28] The adverse domino effect of primary operation-complication-urgent reoperation sequence on the multiorgan systems of the elderly, essentiality the impending abdominal sepsis, altered consciousness, respiratory, or renal failure, co-morbidities such as diabetes mellitus, and ischemic heart disease, may explain the high rate of mortality in this complex group of patients.[42–44] In this study, many of the patients who underwent URL had at least one of the co-morbidities mentioned above (57.1%, n=16). The general 'first 30-day' mortality rates after URL were ranged from 5.5% to 48%.[10,29,45] Our all complicated 6 URL patients died in exactly the first 30 days.

The FTR concept has gained acceptance as an interesting metric evaluation of quality after surgery.[46] The FTR rate can be associated with overall mortality rates and the other potential variables (surgical experiences, hospital technology, and increasing nurse-to-patient ratio). However, when FTR is evaluated for urgent surgery patients, it is estimated that complications gain much importance.[46,47] When we probed the FTR concept in our study, the overall complications were denominator as in the literature. Since 2007, a standardized perioperative clinical pathway was established at our peritoneal surface cancer center, which focused on patient selection, nutrition, renal protection, pain management, prevention, and early detection of complications to improve morbidity-mortality and oncologic outcomes. Although we assumed that the URLs were done in a timely fashion with proper surgical technique as a result of clinical and radiological evaluations, we lost a significant group of patients (21.4%) in the post-operative period. URLs were performed in four patients for small bowel anastomotic leakage, one patient for gastric perforation, and one patient for small bowel perforation. We failed to rescue our five patients due to abdominal sepsis: These losses depend on the decline of physiologic reserve, progressive multiorgan dysfunction, the prolonged need of ventilatory support, and clinical deterioration in patients' medical condition despite the optimum surgical intensive care support. Sepsis was the single most important prognostic determinant for death in this series. The other pa-

tient was failed to be rescued because of massive pulmonary thromboembolism.

Interest in measuring surgical quality is growing rapidly. Reoperation rate has gained increasing attention as a potential indicator of surgical quality in recent years. Surgical complication that resulted in reoperation is possibly plays a role in worsened outcomes, including postoperative death. In our high volume and complexity academic CRS and HIPEC practice, URL occurred 4.2%. This URL rate was relatively rare and most commonly associated with anastomotic leak. However, there are a lot of mutable risk factors for proper prediction model in the setting of complicated CRS and HIPEC. Unplanned reoperations are often the result of major complications (14%), mostly abdominal sepsis and can be tightly linked to worse patient outcomes as in our study (increased morbidity rate, 78.6%; and mortality rate, 21.4%). Thus, URL carry significant clinical outcome implications. The septic complications, particularly anastomotic leak rate may be a better marker of surgical quality to monitor for quality improvement targets in education and research program at peritoneal surface cancer center.[48]

The median PCI values of the patients who underwent URL and lost after URL were 13 (ranging, 3–29) and 14 (ranging, 5–24). There was no statistically significant difference in terms of PCI scores. When the CC scores were also compared in between alive-URL and dead-URL patients, no significant difference was found.

In the last decade, many biomarkers used to describe the systemic inflammatory response have been subjected to research for detecting clinical progression of solid tumors in the lung and gastrointestinal tract. There are two methods of assessing the systemic inflammatory response: Composite ratios (R) and cumulative scores (S). One approach is to take the ratio of different white blood cells and then set a prognostic threshold for the ratio. The most widely used of these is the ratio of circulating neutrophil-lymphocyte counts (NLR). Other confirmed examples are circulating platelet-lymphocyte (PLR) count and lymphocyte-monocyte (LMR) count ratios. In addition, many studies reported by Glasgow researchers proved that the ratio of acute phase proteins to CRP and ALB (CAR) had an important clinical prognostic significant.[49,50] A disadvantage of this ratio approach is that, depending on the threshold used, an abnormal ratio can be identified with one or two markers with a normal value. A simpler approach is the cumulative prognostic score. A widely used example of this approach is the modified Glasgow Prognostic Score based on two acute phase proteins, namely, CRP and ALB. In addition, neutrophil-platelet score (NPS) has recently been reported using neutrophils and platelets. Apart from these, there are other score systems that used in prognostic evaluation such as neutrophil-lymphocyte score, platelet-lymphocyte score, and lymphocyte-monocyte score. [50] In our study, we evaluated whether the immune scores measured pre-CRS and pre-URL can predict morbidity-mortality in the postoperative period. The immune prognostic ratios measured in our study revealed that NLR and CAR before CRS could significantly distinguish patients who underwent URL from patients who did not undergo URL ($p<0.001$). The NLR and CAR values of these patients who underwent URL before the first surgery were significantly higher than the other patients. Systemic inflammatory status of the host seems to affect the postoperative complicatory course. The immunscores as simple and consistent markers can be reliable predictive factors in the clinical use for CRS&HIPEC patients. They can be used to guide clinical pathways to optimize patients' immune status intensely.

The limitations of this study include its retrospective and case-mixed nature. Peritoneal tumor burden and the extent of tumor and the host factors and management could not be standardized. Being a single center study with small number of URL patients is also another drawback. The strengths of our database are prospective maintenance in the certified peritoneal surface cancer center and the well-controlled the data acquisition. Senior surgeons' experience highlighted many aspects of this type of extensive radical surgery and high-risk urgent relaparotomy.

It has always been our belief that patients undergoing CRS and HIPEC have somewhat limited reserve and capacity to withstand as a "second hit" such as septic or pleuropulmoner complication. Thus, whenever a complicated patient was stable, we always prefer to conservative measures. Nonetheless, URL becomes mandatory for source control, be it anastomotic leak or bleed. URL may really carry a major risk, as reflected in our study results and we cannot tell that URL for complication is not responsible for at least part of the high mortality in the reoperated cohort.

Conclusion

The judgmental factors at work are complex in unplanned URL. Patients with high risk factors and increased inflammatory status could be selected to an intense care pre- and post-operatively. Immune scoring before CRS can help us to predict the risks of urgent relaparotomy. Timely intervention and proper management strategy are utmost important to lower further morbidity-mortality in patients treated with URL. URL requires specialized surgeon who is willing to deal with a broad range of complications and complex problems after a "seemingly routine" standard extensive surgery.

Ethics Committee Approval: This study was approved by the Dokuz Eylul University Non-interventional Clinical Research Ethics Committee (Date: 27.04.2022, Decision No: 2022/16-20).

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source: S.S., B.M., T.B., Y.Y.; Materials: S.S., B.M., T.B., A.D.Ç.; Data: S.S., B.M., T.B.; Analysis: S.S., B.M., T.B., H.A.E., F.O.; Literature search: S.S., B.M., T.B., H.A.E., F.O.; Writing: S.S., B.M., T.B.; Critical revision: S.S., B.M., T.B.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi sonrası acil relaparatomiler

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AMAÇ: Sitoredüktif cerrahi (SRC) ve hipertermik intraperitoneal kemoterapi (HİPEK) sonrası komplikasyonlara bağlı acil relaparotomi yapılan hastaların immün skorlamalarla tahmin edilip, edilemeyeceğinin değerlendirilmesi amaçlanmıştır.
GEREÇ VE YÖNTEM: Kliniğimizde 2007–2020 yılları arasında SRC&HİPEK prosedürü uygulanan 661 hasta analiz edildi. Bu hastaların 28'ine (%4.2) acil relaparotomi (URL) yapılması gerekmiştir. Hastaların 22'si (%78.6) kadın, median yaş 57 (76–24) idi. Hastaların 22'si (%78.6) 65 yaş altındaydı. Tüm standart klinikopatolojik özellikler, ameliyat bulguları ve morbid-mortalite sonuçları analiz edildi. Nötrofil-lenfosit oranı (NLR), nötrofil-trombosit oranı (NTR) ve CRP (C-reaktif protein)-albümin oranı (CAR) gibi iyi bilinen immünoskorlar belirlendi.
BULGULAR: URL için ana endikasyon ince bağırsak anastomoz kaçağıydı (n=13, %46.4). İkinci en sık endikasyon ise karın duvarı defektleriydi (evisserasyon-evantrasyon) (n=5, %17.9). Hastalarda patoloji en sık ince bağırsak kaynaklıydı. Hastaların %28.6'sına (n=8) erken ameliyat sonrası dönemde (ilk 7 gün), geri kalanına (n=20, %71.4) 7–90 gün aralığında URL yapıldı. URL hastalarının çoğu (n=16, %57.1) birden fazla komorbiditeye sahipti. Genel gruba bakıldığında, 104 (%16.4) hastada Clavien-Dindo (C-D) evre I-II ve 88 (%13.9) hastada C-D evre III-IV komplikasyon görülürken, URL hasta grubunda 22 (%78.6) hastada C-D evre III-IV komplikasyon görüldü. Bu ileriye yönelik kohortta, URL yapılmayan hastalarda genel mortalite oranı %3.2 (n=20) idi. URL hastalarında altı (%21.4) hasta ameliyat sonrası dönemde kaybedildi ve kurtarılamamanın ana nedeni entero-enteral anastomoz kaçağına bağlı sepsisti. Bu hastaların dördünde çok sayıda komorbidite vardı. URL öncesi medyan NLR, NTR ve CAR değerleri sırasıyla 9.12 (1.72–37.5), 0.03 (0.01–0.12) ve 41.4 (4.2–181.3) idi. SRC öncesi tahmin edilen NLR ve CAR değerleri (4.71 ve 28.8), ameliyat sonrası dönemde çeşitli komplikasyonlara bağlı URL yapılan hastalarda anlamlı olarak yüksekti (p=.01 ve p<.01). Bu immün skor değerleri, SRC ve URL sonrası kaybedilen hastalar arasında herhangi bir ilişki göstermedi.
TARTIŞMA: SRC sonrası URL gerektiren ciddi komplikasyonlar genellikle artan mortalite oranı, kısa sağkalım, primer tümörün erken rekürrensi, merkezin kaynaklarının tükenmesi ve yüksek maliyetlerle ilişkilidir. URL, SRC&HİPEK prosedürü için önemli bir kalite göstergesi olarak kabul edilebilir. URL ile tedavi edilen hastalarda morbi-mortalite sonuçlarını azaltmak için zamanında cerrahi müdahale ve yoğun yönetim stratejisi son derece önemli konulardır.

Anahtar sözcükler: Acil relaparotomi; hipertermik intraperitoneal kemoterapi; immün skor; sitoredüktif cerrahi.

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ORIGINAL ARTICLE

Inflammation-based prognostic scores in geriatric patients with rectal cancer

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Abstract

Background Morbidity/mortality and oncologic outcomes can be worsened in geriatric rectal cancer patients due to comorbidities and frailty. The aim of this study was to compare surgical and oncological results of geriatric rectal cancer patients using inflammation-based prognostic scores.

Methods The prospectively maintained database of 991 rectal cancer patients treated at our center between 2007 and 2020 were analyzed. All conventional clinicopathologic features, and oncologic outcomes are compared between patients ≥ 65 years old (geriatric patients: Group I) and < 65 years old (non-geriatric patients: Group II). The modified Glasgow Prognostic Score (mGPS) and the C-reactive protein-albumin ratio (CAR), were determined. The prognostic value of mGPS and CAR as well as the well-known clinico-pathologic factors to predict surgical morbidity, mortality, local and/or distant recurrence, and overall survival was assessed.

Results There were 567 (57.2%) patients who were ≥ 65 years old (Group I; 349 males, median age 74 [range 65–9]) years) and 424 (42.8%) who were < 65 years old (Group II; 252 males, median age 58 [range 20–64] years). The high-grade [Clavien–Dindo III–IV] complications rates of Group I and Group II patients sere 20% ($n = 113$), and 9% ($n = 37$), respectively. High-grade complications were related to mGPS ($p < 0.001$) and CAR ($p < 0.001$) values. The high-grade complication rate was found to be higher in Group I than in Group II, and this was statistically significant ($p < 0.001$). High preoperative mGPS and CAR values were significantly associated with postoperative mortality ($p < 0.001$). In Cox multivariate analysis, mGPS ($p = 0.003$) and CAR ($p = 0.001$) were significantly in correlation with lowered overall survival. The mGPS and CAR were found to be independent prognostic factors for overall survival.

Conclusions The mGPS and CAR can predict severe postoperative complications and early mortality. mGPS, and CAR have a powerful prognostic value and the potential clinical usefulness to predict decreased overall survival in both geriatric and non-geriatric rectal cancer patients.

Keywords Rectal cancer · Oncologic surgery · Prognostic score · Geriatric patient

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Introduction

According to the data of the World Health Organization, colorectal cancer is the third most common cancer in both sexes in Turkey. As with many cancers, its incidence increases with age, and the mean age at diagnosis is 68 for men and 72 for women [1].With the aging population, the number of older people suffering from rectal cancer is expected to increase. It is thought that these patients may encounter increased complication rates and worse prognostic outcomes due to the higher rate of comorbidities. Current guidelines do not include optimal treatment recommendations for the elderly and only partially address the challenges faced in this population [2].

After colorectal cancer surgery, the incidence of postoperative complications varying between 20 and 60% is used as an indicator of quality in surgical care [3, 4]. This difference is possibly due to the heterogeneous population of elderly patients which includes a wide range of fit to frail patients. Hence the management strategy of multistep treatment becomes difficult and the development of personalized cancer care for each patient is required [5]. It has been shown that many elderly patients with rectal cancer receive inappropriate care, either undertreated due to their chronological age or overtreated in contrast to their degree of frailty [6, 7]. As elderly patients are typically excluded from clinical trials, treatment guidelines do not fully cover this age group. Only a few studies discussing morbi-mortality results and oncologic outcomes in geriatric patients with rectal cancer have been published [8–11]. It is thought that well-established treatments can also be applied to elderly frail patients after appropriate prehabilitation. As a result of this increasing awareness, the necessity of geriatric evaluation during multidisciplinary evaluation before surgery has come to the fore. A geriatrician may provide a valuable contribution to the treatment team both preoperatively and postoperatively [12–14].

Comprehensive geriatric assessments(CGA) make it possible to categorize patients according to their life expectancy and functional status [15]. Patients can be divided into three different categories through making this grouping before surgery. The first group of "fit patients", are candidates for standard cancer treatment, can receive the same treatments as younger patients, are functionally independent and do not have comorbidities [16]. The second group, "vulnerable patients", are those who need personalized treatment strategies with special pharmacological schemes. The third group, "frail patients", are those who are dependent in their daily life activities, have three or more comorbidities, and are candidates for palliative treatment [17–20]. Frailty is defined as a condition which leads to increasing dependency and/or mortality, when an individual experiences a physiological or psychological stressor [21–23]. In addition, it is crucial to evaluate whether the patient has cognitive impairment, because this will influence all the steps of the treatment trajectory, starting with decision-making capacity [21–23]. Frailty has a greater importance than chronological age in predicting postoperative complications [22, 23].

In the last decade, many biomarkers used to describe the systemic inflammatory response have been subjected to research for detecting clinical progression of solid tumors in the lung and gastrointestinal tract. Many studies reported by Glasgow researchers proved that the ratio of C-reactive protein to albumin (CAR) had an important clinical prognostic significance [24–27]. A disadvantage of this ratio approach is that, depending on the threshold used, an abnormal ratio can be identified with one or two markers with a normal value. A simpler approach is the cumulative prognostic score. A widely used example of this approach in various solid cancers is the modified Glasgow Prognostic Score (mGPS) based on two acute phase proteins, namely C-reactive protein and albumin.

It has been proven that activation of the systemic inflammatory response has an unfavorable impact on the outcome of patients with solid cancer. However, the data for the morbi-mortality results and the prognostic value of these inflammatory markers, particularly in geriatric rectal cancer patients, are limited and controversial [28–30]. Thus, the aim of current study was (1) to compare the morbi-mortality results and oncologic outcomes between geriatric and non-geriatric rectal cancer patients and (2) to assess the prognostic value of modified Glasgow Prognostic Score (mGPS) and CRP-albumin ratio (CAR).

Materials and methods

A prospectively maintained database of 991 patients treated for rectal cancer at our center between 2007 and 2020 was analyzed. Approval was obtained from the ethics committee of Dokuz Eylul University Faculty of Medicine for the retrospective analysis of patient data *(Reference No: 2022/20–18)*. The data of the routine pre- and postoperative practices of the Colorectal & Pelvic Surgery Unit of Dokuz Eylul University Medical Faculty, Dept. of Surgery were used. This was single-center allocated data. It was furnitured by one head-surgeon (SS) and two tenure-track staff surgeons (BM, TB). The departmental database of these patients is routinely maintained and monitored by surgeons and hospital administration. No special diagnostic test, intervention or examination was performed for the study.

These patients were initially evaluated in the multidisciplinary tumor board. Thoraco-abdominal computed tomography (CT) scan, magnetic resonance imaging

(MRI), and/or positron emission tomography-CT scan, if needed, were used for preoperative radiologic evaluation. A comprehensive geriatric assessment (CGA) was carried out in order to categorize patients according to life expectancy. Carefully selected surgical candidates were allocated for prehabilitation. Pluri-metastatic patients and patients requiring emergency rectal surgery were excluded. Due to the increased incidence of rectal cancer in the geriatric age group, we divided the patients into two groups to compare the oncological and surgical outcomes of different age groups. The two groups included rectal cancer patients ≥ 65 (Group I) and < 65 (Group II) years of age. All clinico-pathological characteristics, operative findings, and final outcomes were analyzed. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is shown in Fig. 1.

Group I and Group II were compared and it was determined that they were homogeneous (Chi-square and *t* test). These two groups were then compared in terms of neoadjuvant therapy, comorbidity, smoking, tumor localization, pathological data (pathological tumor-lymph node staging, vascular, lymphatic, neural invasion, and extramural venous spread),local recurrence/distant metastasis, length of hospital stay(LoS), Clavien–Dindo III–IV(C–D III–IV) (high-grade complication), and mortality by univariate analyses.

Blood tests done the day before surgery were used to determine the patients' C-reactive protein to albumin ratio (CAR) and the modified Glasgow Prognostic Score (mGPS). The values were compared between the two groups (Mann–Whitney *U* test). ROC analyses were performed for CAR and mGPS. Cut-off values, sensitivity and specificity ratios were determined. We evaluated whether CAR and mGPS could predict postoperative morbi-mortality, locally recurrent/distant metastatic disease, and overall survival in the two groups or not.

Statistical analysis

Statistical analysis was performed using SPSS 24.0. Categorical variables were compared among groups using Pearson's Chi-square test. Continuous variables were compared by independent samples *t* test. Continuous variables were expressed as means and ranges, and categorical variables as frequencies and percentages. Univariate analysis was performed using the chi-square test, and multivariate analysis was performed using a binary logistic regression model. Survival rates were calculated using the Kaplan–Meier method and were compared with the long-rank test. Multivariate

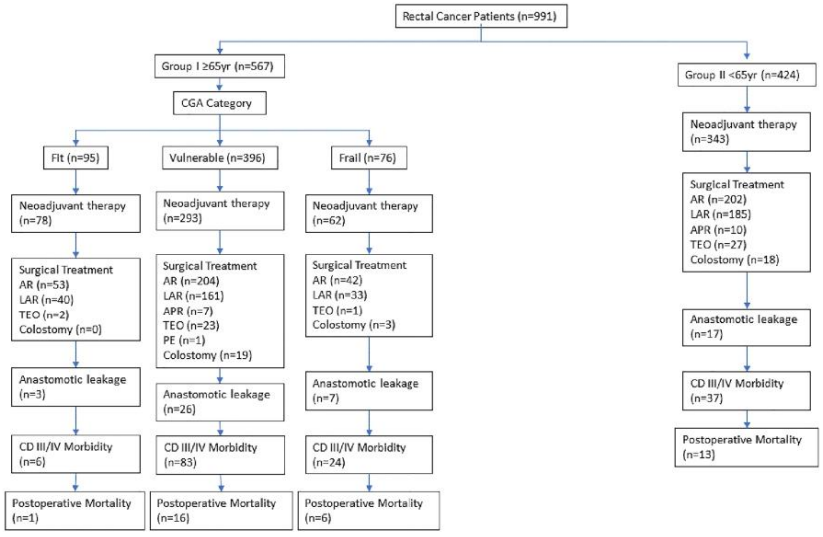


Fig. 1 CONSORT flow diagram. *CONSORT* Consolidated Standards of Reporting Trials, *CGA* Comprehensive geriatric assessment, *CD III/IV* Clavien–Dindo grade III-IV, *AR* Anterior Resection, *LAR* Low anterior resection, *APR* Abdominoperineal resection, *TEO* Transanal endoscopic operation, *PE*: Pelvic exenteration

analysis to identify predictors of survival was performed by constructing stepwise Cox proportional hazard models incorporating variables selected on the basis of the results of univariate analysis. p values < 0.05 were considered statistically significant.

Results

There were 567 (57.2%) patients who were ≥ 65 years old (Group I) and 424 (42.8%) who were < 65 years old (Group II), The median age of patients in Group I and Group II was 74 (range 65–99) years and 58 (range 20–64) years respectively. Three hundred forty-nine (61.6%) of patients in group I and 252 (59.4%) of patients in group II were male. The clinico-demographic characteristics are shown in Table 1. Four hundred thirty-one (76%)] Group I patients and 343 (81%) Group II patients had received neoadjuvant chemo/radiotherapy. Laparoscopic surgery was performed in 86 (15%) of Group I patients and 76 (18%) of Group II patients. A diverting loop ileostomy was constructed in all irradiated patients. All the pathological stages were well-matched in both groups. The mean duration of treatment for patients admitted to the postoperative intensive care unit was 2.8 (±1.69) days in Group I and 1.4 (±0.98) days in Group II. When the two groups were compared in terms of sex, smoking, comorbidities, LoS, neoadjuvant treatment, pathological stage and local and/or distant recurrence, no statistically significant differences were found (Table 1).

High-grade complication (C-D grade III-IV) rates in groups I and II were 20% ($n = 113$), 9% ($n = 37$), respectively. Perioperative mortality rates were 4% ($n = 23$) in Group I and 3% ($n = 13$) in Group II. The most important reason for failure-to-rescue in both groups were multiple organ failure due to pleuro-pulmonary complications. The high-grade complication rate was found to be higher in Group I than in Group II, and this was statistically

Table 1 Demographic and clinical characteristics of patients treated for rectal cancer

	Group I (≥ 65 years)	%	Group II (< 65 years)	%	*P* values
N patients	567	57	424	43	
Sex					
Male	349	61	252	59	0.482
Female	218	39	172	41	
Age (years), median (range)	74 (65–99)		58 (20–64)		
Comorbidity					
1 <	470	83	280	66	0.061
1 ≥	97	17	144	34	
Smoking status					
Yes	170		127	30	0.924
No	397	30	297		
Neoadjuvant chemo/radiotherapy					
Yes	431	76	343	81	
No	136	24	81	19	0.081
Tumor location					
Proximal rectum	312	55	215	51	0.077
Mid-rectum	160	28	112	26	
Distal rectum	95	17	97	23	
Local and/or distant recurrence					
Yes	149	26	126	30	0.203
No	418	74	298	70	
Length of hospital stay, days, median (range)	12 (3–54)		10 (3–50)		0.745
High-grade complication (CD III/IV)					
Yes	113	20	37	9	**< 0.001**
No	454	80	387	91	
Postoperative mortality (day 0–14)					
Yes	23	4	13	3	0.416
No	544	96	411	97	

CD III/IV Clavien–Dindo grade III-IV, *p* chi-square test

Table 2 Comprehensive geriatric assessment category

Comprehensive geriatric assessment category	Fit (*n*)	%	Vulnerable (*n*)	%	Frail (*n*)	%
Group I (≥ 65 years)	95	17	396	70	76	14
Neoadjuvant therapy	78	82	293	74	62	81
Surgical treatment						
Anterior resection	53	56	204	51	42	55
Low anterior resection	40		161	40.7	33	
Abdominoperineal resection	–	42	7	2	–	43
Transanal endoscopic operation	2		23	6	1	1
Pelvic exenteration	–	2	1	0.3	–	
Colostomy	–	–	19	5	3	4
Anastomotic leakage	3	3	26	6.5	7	9
High-grade complication (CD III/IV)	6	6	83	21	24	32
Postoperative mortality (day 0–14)	1	1	16	4	6	8

CD III/IV Clavien–Dindo grade III–IV

Table 3 Overall survival results (Kaplan–Meier, $p = 0.023$)

Group	Mean[a]			
	Estimate	Std. error	95% Confidence interval	
			Lower bound	Upper bound
G-I	117.305	4.508	108.470	126.140
G-II	115.118	3.728	107.811	122.425
Overall	123.689	3.911	116.025	131.354

G Group I, *G-II* Group II

[a]Estimation is limited to the largest survival time(month) if it is censored

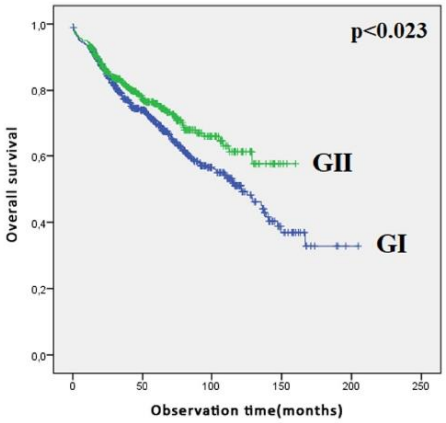


Fig. 2 Overall survival results in group I vs. group II patients [Log Rank (Mantel–Cox) $p = 0.023$, chi-square], *G-I* Group I, *G-II* Group II

significant($p < 0.001$).There was no statistically significant difference between the two groups in terms of mortality (Table 1).

The patients in Group I were categorized by comprehensive geriatric assessment (CGA):17% ($n = 95$) of the patients were fit, 70% ($n = 396$) were vulnerable, and 14% ($n = 76$) were frail. Other essential factors are shown in Table 2. Synchronous additional organ resections were performed in 4% ($n = 24$) of the patients. The most common extra-pelvic organ resection was synchronous segmental liver resection due to oligo-metastasis ($n = 15$). Curative surgery was performed in frail patients after adequate prehabilitation. high-grade complication (C–D grade III–IV) were observed in, 32% of frail patients, 21% of vulnerable patients, and 6% of fit patients. Perioperative mortality was observed in 8% off-rail patients, 4% of vulnerable patients, and 1% of fit patients (Table 2).

The estimated 3, 5, and 10-year survival rates of G-I and G-II patients were 77 and 82.3%, 69 and 76.2%, and 49 and 61.2%, respectively (Table 3) (Fig. 2).

When the preoperative CAR values of the patients were compared, a statistically significant difference was found

Table 4 Preoperative CAR values (Chi-square $p = 0.018$)

Group	Preoperative CAR median value
G I	1.38 (0.08–112.9)
G II	1.04 (0.05–228.4)

CAR C-reactive protein-albumin ratio, *G* Group I, *G-II* Group II

($p = 0.018$). However, the mGPS results showed no significant difference between the two groups (Table 4).

The preoperative CAR and mGPS values were significantly higher in those who developed postoperative

Table 5 ROC Analyzed CAR and mGPS with postoperative mortality

Risk factor	AUC (95%)	Cut-off	Sensivity %	Specificity %
CAR	0.914 (0.870–0.958)	4.33	80	83
mGPS	0.866 (0.802–0.930)	1	91.4	66.6

mGPS modified Glasgow Prognostic Score, *CAR* C-reactive protein-albumin ratio, *AUC* Area under the curve

Table 6 Cox regression analysis: CAR and mGPS independent prognostic factors for overall survival

	p	HR	95, % CI	
			Lower	Upper
CAR	0.001	1.901	1.280	2.824
mGPS	0.003	1.778	1.221	2.589

mGPS modified Glasgow Prognostic Score, *CAR* C-reactive protein -albumin ratio, *HR* Hazard ratio, *CI* Confidence interval

high-grade complications (C–D grade III/IV) ($p < 0.001$) and those who died perioperatively ($p < 0.001$) (Table 5).

In Cox multivariate analysis, the mGPS and CAR were found to be independent prognostic factors for overall survival (Table 6).

There were no significant associations between CAR and mGPS values and local/metastatic recurrence.

Discussion

In this cohort, we evaluated whether preoperative CAR and mGPS immune scores can predict surgical morbi-mortality and final oncologic outcomes in geriatric rectal cancer patients compared with a non-geriatric patient group. Geriatric patients had significantly higher CAR values ($p = 0.018$). However, there was no significant difference between the two groups when mGPS values were compared. It is essential to note that CAR and mGPS values measured in the preoperative phase could distinguish patients who developed high-grade complications (C–D grade III-IV) and mortality from patients who did not ($p < 0.001$). Hence, the systemic inflammatory status of the host seems to affect the postoperative complicatory course. Preoperative CAR and mGPS values were shown to be robust prognostic factors that predicted overall survival in both groups(CAR: $p = 0.001$ and mGPS: $p = 0.003$). These scores are simple, cheap, and consistent markers that can be reliable predictive factors for geriatric rectal cancer patients. They can be used to guide preoperative critical decision-making process and clinical pathways to optimize patients' immune status to decrease domino complications and to improve oncologic outcomes.

Geriatric patients undergoing visceral surgery are more likely to benefit significantly from prehabilitation and Enhanced Recovery After Surgery (ERAS) programmes. ERAS is a guiding guide throughout a patient's journey that starts before surgery and ends at home. It accelerates postoperative recovery, shortens hospital stay, morbidity, and recovery time. In recent meta-analyses, it has been emphasized that by applying ERAS protocols in major surgeries, the LoHS is shortened by 2–3 days and complications are reduced by 30–50% [31, 32]. In addition, specific studies in colorectal surgery have also shown that the rate of postoperative complications and length of hospital stay are also reduced in patients who have undergone prehabilitation. There are solid data showing that adequate prehabilitation in elderly patients in the preoperative period reduces postoperative abdominal complications by 50% [32, 33]. Hence, a preoperative CGA-directed ERAS programme is likely to have a positive impact on postoperative oncologic outcomes in older patients undergoing elective surgery. Diagnosing complications is often not straightforward in geriatric patients, particularly in frail patients. The difficulty in early diagnosis of the complications stems from diffuse symptoms of acute illness, usually referred to as geriatric syndromes.

The clinical studies discussing surgical morbi-mortality results and final oncologic outcomes in geriatric rectal cancer patients are limited and inconclusive. It has been determined that the results of sphincter-sparing surgery for lower rectal tumors in elderly patients are not different from younger patients in terms of sphincter control and functional results. Anastomosis can be performed in appropriate patients after explaining the risks. While presenting this option, it is necessary to consider multidisciplinary and patient-specific factors and develop an optimal treatment plan for elderly patients with rectal cancer [34–36]. In the present study, postoperative morbidity rate(C–D grade III–IV) was 20% ($n = 113$) in Group I patients. The morbidity rate increased in the geriatric patient group (C–D grade III–IV, 20 vs 9%). In patients divided into subgroups by CGA, the highest rate of morbidity (C–D grade III–IV, 32%) was observed particularly in frail rectal cancer patients. In the study by Suhool et al. [35], the postoperative morbidity rate was found to be 37%. Although the morbidity rate was not statistically significant, it increased with age (< 85 years, 40.6%; ≥ 85 years, 57.1%). Postoperative mortality was not detected due to the small number of patients ($n = 57$). Focusing on perioperative mortality rates, our mortality rate was higher in the geriatric patient group ($n = 23$; 4%), and it was also higher in the subgroup of frail patients ($n = 6$; 8%). However, no statistically significant difference was found between the two groups. In many studies, both the number of frail patients and the rate of postoperative complications and mortality increased in patients over 75 years of age [36, 37]. The mortality rates of frail patients who developed

postoperative complications and the LoS were increased. There was very strong evidence of a relationship between frailty and 30-day mortality according to Lin et al. [38]. We determined similar findings in our study: 14% ($n=76$) of our Group I patients consisted of frail patients. The major morbidity (C–D grade III–IV) and mortality rates of this group were 32 and 8%, respectively. Group I frail patients had the highest rates when compared to other CGA categories. Patients in a high-risk CGA category had increased morbidity and mortality, largely independent of age. This easy-to-use geriatric assessment system had a strong relationship with long-term outcome and morbidity. Almost half of high-risk patients died within the first 3 years after surgery [39].

Studies have shown that although more acute toxicity develops in vulnerable patients as a result of radiotherapy and chemotherapy than in fit patients, they can tolerate and complete the therapy with supportive treatment [39, 40]. In a study involving rectal cancer patients over the age of 85, it was reported that the 5-year overall survival rate without surgical treatment was 45% and the disease-free survival rate was 65% after primary chemoradiotherapy [41–46]. In our study, neoadjuvant chemoradiotherapy was given to the geriatric patient group after providing adequate prehabilitation. Seventy-six percent ($n=430$) of Group I patients received neoadjuvant therapy (radiotherapy or concomitant chemoradiotherapy). The standard total mesorectal excision (TME) and loop ileostomy procedure was done. We did not have any patients who were followed up without surgical treatment.

The anastomotic leak rate after TME for rectal cancer gas been shown to be 10% for patients aged 75 years and older versus 12% for patients younger than 75 years [41, 47]. In our study, overall anastomotic leakage rate in Group I patients was 6.3%. The distribution of anastomotic leak in frail, vulnerable, and fit Group I patients were found to be 9, 6.5, and 3, respectively. When the anastomotic leak rates were compared between CGA categories, it was determined that the leak rate was high in the frail patient group, but it did not reach a statistical significance. In Group II, the leak rate was 4%. Seventy percent of patients treated for anastomotic leak were treated conservatively without major pelvic sepsis. When we evaluated the Hartmann colostomy rate of rectal cancer patients, the geriatric patient group had the same rate as the non-geriatric group (Group I, $n=22$, [4%]; Group II $n=18$, [4%]). This remarkable data showed that anastomosis can be performed in carefully selected patients, regardless of age.

Methodologic limitations of this cohort include its retrospective nature which makes it difficult to control bias and confounders, and which also makes it difficult to establish cause and effect. It is a retrospective review from a single institution where patients were selected on the basis of clinical experience obtained over the past. There was also a little subset of patients that had to be excluded due to missing data. To omit potential confounders, we were careful not to include patients who may have had raised C-reactive protein levels due to obstructed and/or perforated rectal cancer. However, our colorectal cancer database is carefully, prospectively maintained and supervised by certified and experienced colorectal surgeons.

Conclusions

Geriatric rectal cancer patients are more likely to suffer from comorbidities, frailty and multimodal treatments. These sensitive and vulnerable patients are more prone to (domino-) complications. As a result, it is crucial that the patient is medically optimized in the perioperative setting by the use of prehabilitation to improve nutritional status and physical fitness in elderly patients undergoing rectal cancer surgery. Inflammation-based prognostic immunoscores can be used as a clinical niche to predict surgical morbi-mortality and overall survival.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approval was obtained from the ethics committee of Dokuz Eylul University Faculty of Medicine for the retrospective analysis of patient data (Reference No: 2022/20–18).

Informed consent After obtaining the non-invasive ethics committee approval required for retrospective studies, formal constent is not required.

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Neglected prognostic importance of ileal resection in patients with peritoneal metastasis

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We aimed to determine the prognostic role of ileal resection on postoperative complications and the final oncological results of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) treatment in patients with peritoneal metastasis (PM). Patients with PM who underwent CRS and HIPEC between 2007 and 2020 were analyzed retrospectively. Ileal resection was defined as the resection of the ileum at 100 cm or below. Patients were divided into ileal-resection and non-ileal resection groups. Besides clinico-pathological variables, peritoneal cancer index (PCI), completeness of cytoreduction (CC-0-1-2), (neo)adjuvant chemotherapy, operative time, need for surgical intensive care unit, and usage of blood products were all evaluated. The data of 664 patients was analyzed. Ileal resection was performed in 346(52.1%) patients. The median follow-up period was 27 months. The ileal resection group had significantly lower 3-and 5-year survival rates (55% and 43% vs. 69% and 52, $p = .005$, respectively). High PCI score ($p < .001$), more CC-1-2 cytoreductions ($p < .001$), more anastomoses ($p < .001$), prolonged operative time ($p < .001$), more ostomy creation ($p = .001$), increased morbidity ($p < .001$), and more infectious complications ($p < .001$) were all significantly associated with ileal resection. The loss of ileal function has a potential prognostic role in increased post-operative complications and worsened overall survival in patients with PMs.

Peritoneal metastasis (PM) is often considered as an end-stage disease. Cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC) and perioperative chemotherapy have emerged as the only potentially curative treatment of PM in the last three decades. In appropriately selected patients, this triplet treatment modality can be undertaken with low morbi-mortality and is associated with better survival outcomes[1–4]. Intraperitoneal disease burden is the most important prognostic factor[5]. It is well-known that this intraperitoneally disseminated disease burden prefers to settle down in particular areas such as the pouch of Douglas, sigmoid colon, terminal ileum, right paracolic gutter, and right subphrenic space, presumably by the combined effect of respiratory movements, gravity, limited mobility, and continuous bowel peristalsis[6–8]. Resection of the terminal ileum is often a component of aggressive CRS/HIPEC procedures. On the other hand, the ileum is the only segment of the small bowel in which bile acids and vitamin B12 are absorbed. It also has special capabilities for enzymatic digestion of nutrients, passive absorbtion of water, electrolytes, cholesterol, bicarbonate/chloride exchange, and immuno-protective functions[9–13]. Considering these unique functions of the ileum, the ileal resection may have a worsened effect on the postoperative outcomes. To the best of our knowledge, there is no solid data in the literature discussing the prognostic impact of loss of terminal ileum in this patient group with complex cancer care.

The objective of this study was to determine the prognostic role of ileal resection on postoperative complications and final oncological outcomes of CRS/HIPEC treatment in PM.

Material and methods

A prospectively recorded database of consecutive CRS and HIPEC procedures performed in the Peritoneal Surface Malignancy Center between 2007 and 2020 was reviewed. Patients who had undergone ileal resection (< 100 cm) were included. The exclusion criteria for CRS and HIPEC were: (1) massive involvement of the retroperitoneum, (2) mesenteric pedicle invaion, (3) massive small bowel involvement (which would result in

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a short bowel after resection), (4) unresectable extra-abdominal metastasis, (5) major vascular invasion, and (6) low ECOG perfomance status. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee. Informed consents was received from all of the patients.

The demographic data, tumor characteristics, extent of PM, intraoperative findings, and postoperative results were gathered from the medical records. Patients were divided into ileal-resection and non-ileal resection groups, and postoperative overall morbidity, mortality, and oncologic outcomes were analyzed.

Preoperative assessment. All patients who were potentially candidates for CRS/HIPEC were discussed on the multidisciplinary tumor board. Thoraco-abdominal computed tomography (CT), and magnetic resonance imaging (MRI), and/or positron emission tomography-CT, if needed, were used for preoperative radiologic evaluation. The co-morbidities were recorded according to the Charlson co-morbidity index (CCI)[14]. The interval between the last chemotherapy dose and surgery was at least 4 weeks in patients who received neoadjuvant treatment.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Mechanical bowel preparation and venous thromboembolism prophylaxis were given to all of the patients. Intravenous antibiotics (cefuroxime axetil and metronidazole) were administered 30 min before the incision and repeated every 3 h. Cytoreductive surgery was performed by the same surgical team as described by Sugarbaker, allowing the eradication of all macroscopic tumors[15]. The extent of the disease was assessed by the peritoneal carcinomatosis index (PCI)[16]. In the intraoperative evaluation, ileal resection was performed if the ileum was involved with disease that would not allow complete cytoreduction. Residual disease was recorded according to the "Completeness of cytoreduction" score: no residual tumor, CC-0; residual tumor ≤ 2.5 mm, CC-1; residual tumor > 2.5 mm, CC-2[17].

After CRS, two inflow (one in the pevis, one in the subhepatic area) and two outflow drains and two thermal probes were positioned in the abdominal cavity, and HIPEC was delivered by a perfusion system (The Belmont® Rapid Infuser RI-2, MA, USA) with the closed abdominal technique. The chemotherapeutic agents were decided by our oncologist individually for every patient. At a constant temperature of 42.5 °C, oxaliplatin (400 mg/m^2, 30 min), mitomycin-C (10 mg/m^2) and/or cisplatin (75 mg/m^2, 90 min) were administered. Patients did not receive concurrent intravenous chemotherapy. Gastrointestinal or urinary anastomoses were performed before HIPEC.

Early postoperative care and follow-up. "Common Terminology Criteria for Adverse Events" was used to record postoperative morbidity and HIPEC toxicity (minor morbidity-grade I/II, major morbidity-grade III/IV, or mortality-grade V[18]. Postoperative complications were classified according to the Clavien-Dindo system[19]. Death within 30 days after surgery and in-hospital mortality were recorded as mortality.

For the first year, physical examination and CEA measurements were performed every three months, and thoraco-abdominal computed tomography every six months. For the second year, physical examination and CEA measurements were performed twice a year and computed tomography once a year. Patients underwent colonoscopy at the end of the first year.

Statistical analysis. Statistical analysis was performed using SPSS 22.0. Categorical variables were compared among groups using the Pearson Chi-Square test. Continuous variables were compared by independent samples *t*-test. Continuous variables were expressed as means and ranges, and categorical variables as frequencies and percentages. Univariate analysis was performed using the Chi-Square test, and multivariate analysis was performed using a binary logistic regression model. Survival rates were calculated using the Kaplan–Meier method and were compared with the log-rank test. Multivariate analysis to identify predictors of survival was performed by constructing stepwise Cox proportional hazard models incorporating variables selected on the basis of the results of univariate analysis. P values < 0.05 were defined as statistically significant.

Results

Patients characteristics. There were 664 consecutive CRS/HIPEC patients between 2007 and 2020, among whom 346 (52.1%) were in the ileal resection group and 318 (47.9%) were in the non-ileal resection group. The mean age was 54.5 (±17.3) years. Median follow-up and survival were 27 (1–190) and 55 (44–67) months, respectively. The origin of PM was ovarian in 280 (40.3%), colorectal in 212 (30.9%), appendix in 74 (11.2%), peritoneal mesothelioma in 37 (5.6%), stomach in 26 (3.9%), and other tumors in 35 (5.3%). Ovarian cancer-PM was similarly distributed between groups; colorectal cancer and appendicieal cancer-PM were more common in the ileal-resection group ($p = 0.005$). The clinico-demographic findings of patients are given in Table 1.

Univariate analysis showed that high PCI (PCI ≥ 15) ($p < 0.001$), CC 1–2 cytoreduction ($p < 0.001$), 5 or more organ resections ($p < 0.001$), 1 or more anastomoses ($p < 0.001$), prolonged operative time ($p < 0.001$), and ostomy creation ($p = 0.001$) were significantly associated with ileal resection. The ileal resection group had higher rates of both grade I–II and grade III–IV morbidity ($p < 0.001$) and perioperative mortality ($p < 0.001$). Ileal resection was associated with more infectious complications ($p < 0.001$) (Table 2). Male gender (OR, 1.81; 95% CI 1.22–2.68; $p = 0.003$), high PCI score (OR, 4.10; 95% CI 2.86–5.89; $p < 0.001$), and neoadjuvant chemotherapy (OR, 1.51; 95% CI 1.07–2.14; $p = 0.020$) were found to be significant risk factors in the ileal resection group in multivariate analysis (Table 3).

	Ileal resection, n (%) 346 (52.1)	Non-ileal resection, n (%) 318 (47.9)	p^*
Gender			**<.001**
Male	110 (16.6)	63 (9.5)	
Female	236 (35.5)	255 (38.4)	
Age (year, mean ± SD)	55.3 ± 20.8	53.7 ± 12.3	*.218*
BMI (mean ± SD)	27.7 ± 11.1	29.9 ± 20.3	*.279*
Smoking (+)	74 (11.2)	59 (9.0)	*.324*
Co-morbity	150 (22.6)	134 (20.2)	*.752*
Tumoral origin			**.005**
Ovarian	128 (19.3)	152 (22.9)	
Colorectal	123 (18.5)	89(12.4)	
Appendiceal	51 (7.7)	23 (3.5)	
Peritoneal mesothelioma	18 (2.7)	19 (2.9)	
Gastric	10 (1.5)	16 (2.4)	
Others	16 (2.4)	19 (2.9)	
Onset			**.001**
Synchronous	185 (29.6)	131 (20.9)	
Metachronous	141 (22.5)	169 (27.0)	
Neoadjuvant chemotherapy (+)	200 (30.1)	219 (33.0)	**.003**

Table 1. Clinical and demographic characteristics of the patients. Bold values indicated statistical significance ($p < 0.005$). *BMI* body mass index. *Pearson χ^2 test and independent samples *t*-test. Significant values are in italics.

The ileal resection group had significantly lower 3- and 5-year overall survival rates (55% and 69% vs. 43% and 52, $p = 0.005$, respectively) (Table 4). Significant factors such as ileal resection, PCI score, complete cytoreduction, the use of intraoperative blood products, HIPEC toxicity, and infection were modeled into Cox regression analysis to determine independent prognostic factors of survival. High PCI score (HR, 1.41; 95% CI 1.11–1.80; $p = 0.002$), complete cytoreduction (CC-0vsCC-1-2) (HR, 1.52; 95% CI 1.19–1.95; $p = 0.001$), intraoperative ES (HR, 1.63; 95% CI 1.30–2.07; $p < 0.001$), and infection (HR,1.52; 95% CI 1.19–1.95; $p = 0.001$) were independent prognostic factors in Cox-regression analysis (Table 5).

Discussion

For the last three decades, the prognosis of patients with PM has been improved by multimodal treatment, including complete cytoreduction and HIPEC. This combined therapy has prolonged overall survival rates in carefully selected patients. The prognosis of these patients primarily depends on the extent of the peritoneal disease (PCI), the completeness of cytoreduction, and the histopathologic types[1–5]. To achieve complete resection, an extended multivisceral and/or peritoneal resection is usually needed. On the other hand, the degree of small bowel involvement is insistently considered to be a limiting factor to radically eradicate macroscopic tumor burden[8,20–22]. The terminal ileum, as a special part of the small bowel with its own features of anatomical fixity and limited peristaltic movements, is frequently resected in cytoreductive procedures. Besides, the intraperitoneal fluid circulates in a well-defined manner (in the head-caudal-head direction and is controlled by gravity and respiratory movement sequence), which leads to the accumulation of influxing cells on some special anatomic sites such as the ileum[6–8]. In light of these findings, the terminal ileum can be affected by tumor nodules irrespective of the extent of the disease. The current study is particularly focused on the outcomes of ileal resection in patients with PM. High PCI, more CC-1 or CC-2 resection, more gastrointestinal anastomosis, more ostomy formation, more blood products, and albumin usage were strikingly in the ileal resection group. In addition, ileum-resected patients had prolonged operative time, high post-operative infection, increased nephrotoxicity, and prolonged hospital stay. C–D grade I–IV morbidity and perioperative mortality were significantly higher in the resection group.

The clinical consequences of functional loss of the terminal ileum and ileocecal valve have been well-documented in the literature: the ileocecal valve acts as a structural barrier for the passage of intestinal contents and provides the required time for efficient absorption of nutrients, electrolytes, and water by slowing intestinal transit time[13]. Bile acids, vitamin B12, and fat-soluble vitamins (vitamins A, D, E, and K) are significantly absorbed in the last 100 cm of ileum[9–13]. These vitamins are a prerequisite for normal cell division and growth. The loss of these important mechanisms may possibly result in a decline in the physiological reserve and immuncompetence of the patient and may contribute to more infections, more grade I–II and grade III–IV morbidity, and longer hospital stays in the ileal resection group in our series. The ileum is also the main site of bicarbonate and chloride exchange and has an important clinical role in the passive absorption of water and electrolytes. Only the ileum can absorb sodium chloride against steep electrochemical gradients. When the ileal mechanism that provides the exchange of bicarbonate with chloride ions is disrupted, excessive amounts of chloride and hydrogen ions pass into the colon, bicarbonate accumulates in the body and metabolic alkalosis develops. When the decrease

	Ileal resection, n (%) 346 (52.1)	Non-ileal resection, n (%) 318 (47.9)	*p**
Perioperative characteristics			
PCI			**<.001**
<15	177 (26.7)	258 (38.9)	
≥15	169 (25.5)	60 (9.0)	
Completeness of cytoreduction			**<.001**
CC-0	212 (33.9)	252 (40.3)	
CC-1,2	114 (18.2)	48 (7.7)	
Number of resected organs			**<.001**
<5	179 (27.0)	300 (45.2)	
≥5	167 (25.2)	18 (2.7)	
Number of resected anatomosis			**<.001**
0	111 (16.5)	178 (26.8)	
1	184 (22.7)	116 (17.5)	
≥2	51 (7.7)	24 (3.4)	
Ostomy (+)	154 (23.5)	50 (7.6)	**<.001**
Preoperative RBCs (+)	22 (3.3)	10 (1.5)	*.052*
Intraoperative RBCs (+)	175 (26.6)	99 (15.0)	**<.001**
Intraoperative albumin (+)	83 (12.7)	36 (5.5)	**<.001**
Intraoperative FFP (+)	139 (22.2)	69 (11.6)	**<.001**
Operative time (min, mean ± SD)	358.6 ± 114.1	320 ± 12.3	**<.001**
Postoperative characteristics			
ICU stay (+)	123 (18.9)	103 (15.5)	*.391*
Post-operative RBCs (+)	82 (12.6)	36 (5.5)	**<.001**
Length of hospital stay (days, mean ± SD)	21.2 ± 14.5	17.7 ± 13.8	**.004**
Morbidity			**<.001**
None	204 (30.7)	238 (35.8)	
Grade I–II	66 (9.9)	38 (5.7)	
Grade III–IV	52 (7.8)	37 (5.6)	
Postoperative mortality	24 (3.6)	5 (0.8)	**<.001**
HIPEC toxicity	38 (5.7)	25 (3.8)	*.167*
Infection (+)	100 (15.2)	43 (6.5)	**<.001**
Nephrotoxicity (+)	40 (11.6)	21 (6.6)	**.027**

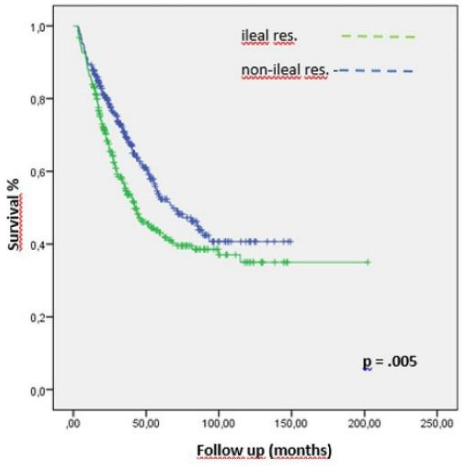
Table 2. Comparison of surgical characteristics between ileal resection and non-ileal resection groups. Bold values indicated statistical significance ($p < 0.005$). *PCI* peritoneal carcinomatosis index, *RBC* red blood cell, *FFP* fresh frozen plasma, *ICU* intensive care unit, *HIPEC* Hyperthermic intraperitoneal chemotherapy. *Pearson χ^2 test and independent samples *t* test. Significant values are in italics.

	OR	95% CI	*p*
Gender (male)	1.81	1.22–2.68	**.003**
PCI			
≥15	4.10	2.86–5.89	*<.001*
Neoadjuvant chemotherapy (+)	1.51	1.07–2.14	**.020**

Table 3. Preoperative factors independently associated with ileal resection in multivariate analysis. *PCI* peritoneal carcinomatosis index. Significant values are in bold and italics.

in bicarbonate/chloride exchange is accompanied by loss of fluid (diarrhea) and monovalent ions, the kidneys cannot maintain the acid–base balance and alkalosis deepens[13,23]. Considering these unique tasks of the ileum, nephrotoxicity was found to be a statistically significant factor in the ileal resection group in our series. It's sure that chemotherapeutic agents used during HIPEC also had an important role in nephrotoxicity, but 40 of the 61 (67%) patients who developed nephrotoxicity were patients with ileal resection ($p = 0.027$). In this nephrotoxicity group, cisplatin was used in 19 of these patients, cisplatin + mitomycin in 27, oxaloplatin in 8, and other chemotherapeutic agents in 5 patients.

Hence, resection of the ileum may adversely affect overall survival. In our study, the ileal resection group had significantly lower 1-, 3-, and 5-year survival rates ($p = 0.005$). Distal small bowel resections are less tolerated



Overall survival (year)	Ileal resection (%)	Non-ileal resection (%)
1	85	89
3	55	69
5	43	52

Table 4. Overall survival of the patients between two groups.

	HR	95% CI	*p*
PCI (≥ 15)	1.41	1.11–1.80	**.002**
Completeness of cytoreduction	1.52	1.19–1.95	**.001**
Intraoperative ES	1.63	1.30–2.07	**<.001**
Infection	1.52	1.19–1.95	**.001**

Table 5. Independent prognostic factors in Cox-regression analysis. Significant values are in bold.

than proximal small bowel resections. This important feature is because of the remarkable ability of the ileum to compansate the absorbtive functions of the proximal intestine. Fifty to sixty percent of the mid-jejunum can be resected with few long-term metabolic consequences, however, resection of more than 30% of the ileum is poorly tolerated[24–26]. It is well known that tumor burden (PCI) and complete cytoreduction are the most important prognostic factors in peritoneal metastasis. In our study, high PCI, complete cytoreduction, intraoperative ES replacement, and post-operative infection were independent prognostic factors for overall survival in Cox regression analysis whereas ileal resection could not stay in the Cox model. Higher PCI scores and incomplete cytoreduction rates in the ileal resection group may undoubtedly lead to lower survival rates. We are fully aware that it is pleonastic to underline that the assessment of terminal ileum involvement partly contributes to overall PCI assessment. However, in many studies, heterogeneous PCI cut-off scores have been accepted as a prognostic role in peritoneal metastasis. In addition, the involvement of some special areas (such as small bowel) negatively affects both the probability of a complete cytoreduction and the prognosis, regardless of the PCI score. Elias et al., clearly demonstrated that, independent of PCI, terminal ileal segment involvement in the small intestine has a negative effect on the prognosis. They revealed that lower ileal segment involvement, whether PCI < 15 or PCI ≥ 15, significantly worsened 5-year overall survival for peritoneal metastasis of colorectal origin[8]. Also, we are fully aware that the inclusion of tumors from different origins is one of the limitations of the study and they each have different survival rates. However, we aimed to show the effects of ileal resection on post-operative complications in a large case series. In the light of all this, it would be assertive to say that ileal resection alone is associated with poor survival. But the above-mentioned unique functions of the ileum, which are not replaceable

in the long-term period, may be one of the key factors that negatively affect post-operative morbi-mortality and overall survival in ileal resection group. In a global assessment, the involvement of terminal ileum should be added amongst the considered factors to precisely evaluate every patient's prognosis.

To the best of our knowledge, this is the first study reporting outcomes of ileal resection in patients with PM who underwent CRS and HIPEC. It has several inherent limitations. First, it was an observational, retro-pro mono-center study. Second, there were various histotypes of peritoneal surface malignancies. And also, potential confounding factors from uncontrollable variables may affected the analyses. We are fully aware that ileum-resected patients usually undergo more extensive cytoreductive procedures. Thus, it can be pleonastic to overstress the assessment of the ileum as a risk factor besides the well-known variables. But, we aimed to search for the clinical significance of ileal resection in high volume patient data to improve results to optimize patients' intensive care and oncologic outcomes.

Conclusion

In this study, the ileum was resected in 52% of cytoreduced patients. Ileal resection negatively affected morbi-mortality results and oncologic outcomes. These consequences of ileal resection are neglected in both clinical practice and the related literature. To optimize outcomes, prehabilitation, vigilant monitoring, intense care, and increased awareness must be instituted for these complex cancer patients.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by T.B., S.S. and H.E. The first draft of the manuscript was written by T.B. and S.S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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