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INVITED REVIEW

Experimental Modeling and Treatment Strategies for Peritoneal Carcinomatosis

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ABSTRACT

Peritoneal carcinomatosis (PC), associated with a range of gastrointestinal and gynecological malignancies, represents a significant condition characterized by the dissemination of cancer cells within the peritoneal cavity. The advancement of our comprehension of the pathophysiology and therapeutic strategies for PC hinges on utilizing experimental models. This comprehensive review provides an overview of the current experimental models employed in the examination of PC along with the current treatment strategies. The review comprehensively explores the merits and demerits of each model and their respective contributions to our understanding of peritoneal metastasis. This review will serve as a valuable resource for researchers and clinicians engaged in investigating and managing PC, offering direction for future endeavors to refine experimental modeling and clinical outcomes.

Keywords: Experimental models, peritoneal carcinomatosis, treatment

Introduction

Peritoneal carcinomatosis (PC) refers to the widespread dissemination of cancer cells in the peritoneal cavity, forming tumor nodules on the peritoneal surfaces. Since various types of cancer can spread to the peritoneum, PC is highly heterogeneous. The diversity observed in patients with cancer depends on various factors, such as differences in primary cancer treatment strategies, genetic background, age, sex, and epigenetic factors. These factors make it challenging to conduct unbiased clinical research studies.[1,2] However, experimental models can help overcome these limitations and provide insights into the molecular mechanisms implicated in cancer and the efficacy of new treatment options.

To enhance the accuracy of preclinical data, it is crucial to initiate a clear statement outlining the biological problem and provide a comprehensive description of the relevant model, incorporating its advantages and disadvantages.[3] Preclinical experimental models consist of three methods: *in vitro*, *in vivo*, and *in silico*.[4] While *in vitro* models offer some benefits, they are not fully comprehensive in accurately representing the complexity of a patient's condition. Therefore, it is crucial to consider the limitations of such models when studying diseases and developing new treatments. *Ex vivo* models are more complex and representative tools that are commonly used in the evaluation of intraperitoneal (IP) drug delivery and treatment efficacy. However, this type of model lacks several features, such as functional immunity and drug metabolism.[5] *In vivo* models, such as mice, rat, and pig models, closely mimic the patient's condition and are commonly used to study diseases.[6] Novel *in vivo* models, such as patient-derived xenograft (PDX) and transgenic mice models, are created to mimic patient tumors better.[7] To represent the molecular characteristics of tumors and to choose the best treatment option for patients with cancer, individualized preclinical, experimental models need to be generated. To this end, *in silico* methods, known as "dry labs", analyze retrospective and prospective data in computational platforms, such as genome, transcriptome, proteome, and metabolome platforms, to provide insights into the molecular phenomena of malignancies.[8]

This review provides valuable insights by outlining various experimental models used in cancer research. A comprehensive understanding of these models is crucial for developing more

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effective treatments and therapies to fight cancer. By thoroughly exploring the current research landscape, we aim to pave the way for significant advancements in cancer treatment.

Materials and Methods

This narrative review aims to provide a comprehensive overview of the experimental models and treatment strategies for PC. The review synthesizes findings from preclinical and clinical studies, focusing on *in vitro*, *ex vivo*, and *in vivo* models, as well as innovative therapeutic approaches. Given the complexity of PC and its challenging treatment landscape, a thorough examination of relevant literature was conducted using established databases, including PubMed, Scopus, and Web of Science.

Literature Search

A literature search was performed across multiple databases using a combination of relevant keywords, including "PC", "experimental models", "treatment strategies", "animal/*in vitro*/*in vivo* models", "photodynamic", "gene therapy", "IP chemotherapy", and "immunotherapy". The search covered articles published up to February 2024. Studies included preclinical models (*in vitro*, *ex vivo*, *in vivo*, and *in silico*), various treatment modalities, and emerging approaches such as targeted therapies and immunotherapy.

Inclusion and Exclusion Criteria

To ensure relevance to the topic, only articles focusing on the development and use of experimental models for PC and their application in assessing treatment efficacy were included. Both basic science and translational research articles were considered. Studies focusing on other forms of carcinomatosis or not addressing PC-specific treatments were excluded. Review articles, original research papers, and conference proceedings were evaluated for inclusion.

Synthesis of Evidence

The evidence was categorized according to model type (*in vitro*, *ex vivo*, and *in vivo*) and the treatment strategy used. Emphasis was placed on identifying the strengths, limitations, and translational relevance of each model in mimicking human PC. Therapeutic strategies were analyzed in terms of their preclinical efficacy, clinical applicability, and innovative potential.

Study Limitations

As a narrative review, this study does not involve a formal meta-analysis or systematic review process, and as such, does not employ strict quantitative data synthesis. The scope of this review is also limited to articles available in English and may not fully capture all international research.

In summary, this narrative review provides a synthesized understanding of the experimental models used to study PC and the evolving landscape of treatment strategies, with a focus on their translational potential.

Modeling for Peritoneal Carcinomatosis

In vitro Models

The conventional two-dimensional (2D) cell culture technique for cancer research remains the most widely used *in vitro* model. However, this model has several limitations in representations of the natural tumor microenvironment (TME) due to the absence of cellular communication (cell-cell) and interaction (cell-cell and cell-matrix).[9-11] An increasing amount of research indicates that tumor growth is influenced by cancer cells and the surrounding stroma, known as the TME.[12,13] The TME is crucial in enabling cancer cells to acquire key characteristics through reciprocal interaction between cancer cells and TME components, which include both cellular elements and the extracellular matrix (ECM).[14,15] The ECM within the tumor TME serves as a structural framework, composed primarily of collagens, fibronectins, proteoglycans, elastins, and laminin. Additionally, various other molecules are ensnared within this matrix. The cellular constituents of the TME consist of endothelial cells, infiltrating immune cells, pericytes, and fibroblasts.[16] The conventional *in vitro* models cannot replicate the oxygen, pH, and nutrient gradients found in *in vivo* tumors, thus leading to a lack of realistic representation.[11] There is a growing trend in research towards creating three-dimensional (3D) culture systems to address these constraints, which has become essential for advancing tumor studies.[17] In this approach, false results can be reduced, meaning the clinical translation of any novel anticancer drugs can be improved.[18] Several approaches exist to create more real-like PC models by including ECM components in the culture system. Differences between 2D and 3D models and their features are summarized in Figure 1.

Aiming at the significant effect of 3D formation on cancer cell behavior, a study by Chen et al.[19] created a 3D PC spheroid model using patient-derived cells and commercial cell lines. The results showed that the 3D spheroid model has different proliferation kinetics and anoikis resistance with various cancer lines, including YOU, PANC1, HEYA8, CHLA10, and TC71, compared with 2D culturing.[19] On the other hand, to prove the critical role of TME components, a published study by Loessner et al.[20] focused on creating an ovarian TME to replicate PC progression. The study involves ovarian cancer cell-loaded hydrogels with mesothelial cell-layered melt electrospun written scaffolds, with transcriptomic and proliferation analyses performed for the characterization. The results indicated elevated cancer cell proliferation in the co-culture system compared with single-cell type culture.[20]

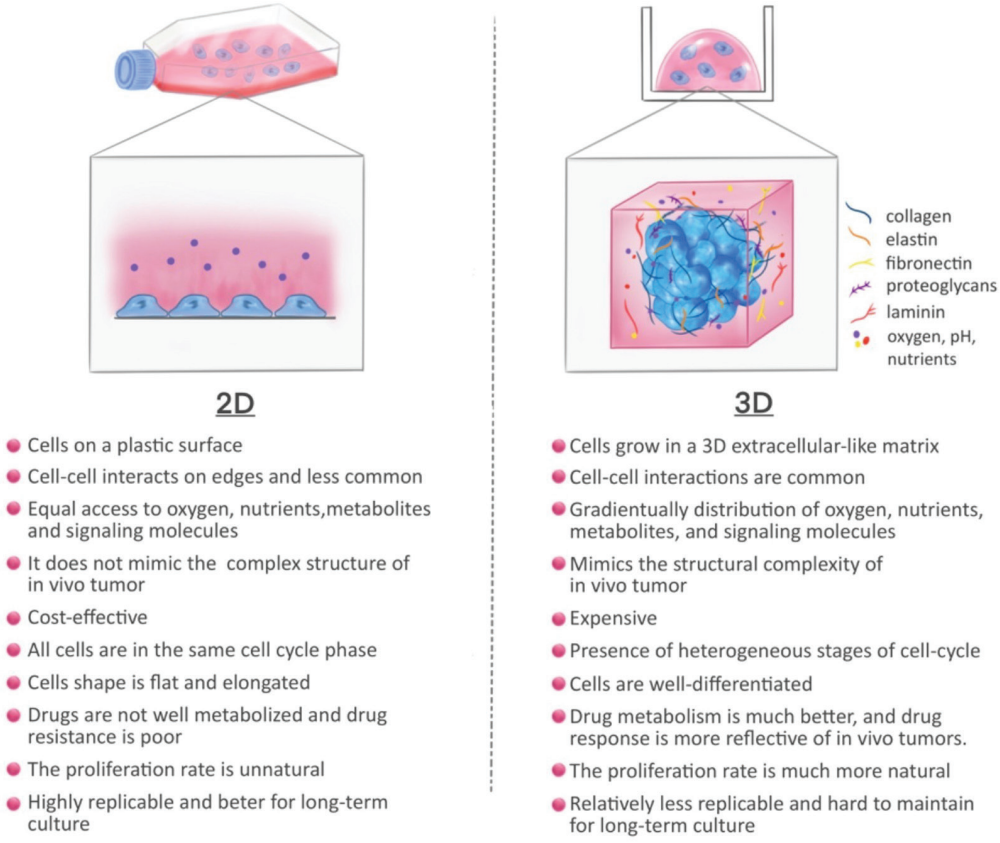

Figure 1. Identical features for 2D versus 3D culture systems
2D: Two-dimensional, 3D: Three-dimensional

Brooks et al.[21] devised an innovative approach utilizing 3D multicellular ovarian cancer spheroids within an omentum-mimicking hydrogel. The authors proposed incorporating patient-derived ascites in future studies to enhance the model's fidelity to the TME.[21] In similar vein, Malacrida et al.[22] generated a four-cell-culture model in plates to investigate the impact of platelets on omental metastases and to validate a robust, high-throughput model of ovarian cancer TME. However, despite these advancements, a 3D model capturing the complex ovarian TME and its relationship with ascites, including a functional vasculature, remains elusive. In a separate investigation, Ibrahim et al.[23] pioneered the creation of the initial vascularized model simulating the human peritoneum and ovarian cancer TME. The authors explored how the functions of mesothelial cells, endothelial cells, and adipocytes influenced tumor metastasis within this human 3D peritoneal model.[23]

Recently, a novel 3D disease modeling termed stem cell-based organoid modeling emerged.[24] The use of cancer organoids allows for the retention of the 3D structure of the TME, providing a physical context for molecular interactions.[25] Numerous studies on PC organoid modeling utilize hydrogels, Matrigel, and other materials to mimic the ECM in general.[26,27] The ECM has a unique structure and is a critical modulator of individual tumor behavior. Varinelli et al.[28] implemented a novel approach using decellularized ECM from the peritoneal cavity to support the cultivation of organoids originating from peritoneal metastasis (PM). This approach formed 3D nodules that closely resembled *in vivo* PC characteristics. The organoids preferred growing on ECM scaffolds obtained from neoplastic peritoneum, which were stiffer than standard scaffolds. Gene expression profiling of organoids cultured on various substrates faithfully mirrored clinical and biological characteristics. Moreover, the ECM appeared to influence the response to standard chemotherapy for PM. This 3D model, combining patient-derived decellularized ECM with organoids, provides a valuable platform for developing personalized therapeutic strategies in a biologically relevant context.[28]

All these models contributed novel insights into the molecular mechanism of PC and its treatment strategy. However, several limitations can be addressed using a tissue-based *in vitro* culture system known as an *ex vivo* model.

Ex vivo Models

Ex vivo models have become essential tools in cancer research, providing valuable insights into tumor biology, drug responses, and therapeutic advancements. These models, which involve cultivating and manipulating cancer cells or tissues outside the body, provide a controlled and reproducible environment for studying various cancer progression and treatment aspects. In addition to these advantages, the model offers several advantages for studying PC.[29]

Several studies focused on human tissue-based *ex vivo* models to mimic PM of different primary cancers, such as ovarian and colon cancer. A published article by Wong et al.[30] showed that utilizing human omentum to cultivate ovarian cancer cells in its adipose-rich environment allows for observing the factors influencing tumor growth and immune response regulation. The model is a valuable tool for studying the TME and offers a robust platform for developing and assessing new therapies targeting metastatic cancer cells within this niche. Importantly, this model is cost-effective, straightforward to generate, and applicable to translational research endeavors.[30] Mönch et al.[31] developed a human *ex vivo* peritoneal model using colorectal cancer (CRC) cell lines and patient-derived tumor organoids cultured with human peritoneum, maintaining peritoneal structures and revealing the presence of immune cells, fibroblasts, and ECM components. Co-culturing with CRC cells revealed cancer cell growth and migration into the peritoneum, mimicking CRC PM. This model provides a clinically relevant platform for studying PM mechanisms and exploring treatment options.[31] However, *ex vivo* modeling with human tissue has limitations, including variability between samples, challenges in reproducing experiments reliably, and limited ability to replicate therapeutic outcomes observed *in vivo* due to the absence of systemic factors and spatial constraints. The lack of a functional immune system in *ex vivo* models also limits their utility in studying the peritoneal immune response in carcinomatosis. Given the limitation of collecting human tissue samples for the PC *ex vivo* model, Schnell et al.[32] conducted unique research in which they created an *ex vivo* peritoneal model for evaluation of the efficacy of IP chemotherapy that is easy to use, reproducible, and cost-effective. The model resembles the human abdominal cavity in volume and shape, with an inner surface lined with serosa, allowing for pharmacological and biological analysis. The model uses a fresh urinary bladder from an adult bovine, which is inverted through an incision to expose the serosa on its inner side. It is regarded as an innovative and versatile *ex vivo* model for optimizing drug delivery of IP treatment strategies such as pressurized intraperitoneal aerosol chemotherapy (PIPAC), replacing the need for live animal experiments.[32]

To overcome the aforementioned limitations, novel approaches are needed to create *ex vivo* PC models.

In vivo Models

Cancer investigations have massively evolved through enlightening the complexities of the disease, and *ex vivo* models have played a crucial role in improving our knowledge. Although this model has many significant advantages, as with all experimental models, it also has several disadvantages. With regard to the advantages, *ex vivo* models mimic human cancers more realistically in terms of tumor structure, microenvironment, and physiology.[33] These advantages help scientists to comprehensively understand how carcinogenesis occurs and responds to treatments in living organisms. The most essential parameters for novel chemotherapeutic agents are efficacy and safety. Additionally, for the metastasis process, researchers can clarify the mechanism of spreading the cancer cells and create a potential treatment option to stop it. In addition, *ex vivo* models are convenient for investigating the interactions between immune and cancer cells.[34]

The literature identifies three primary *ex vivo* models: syngeneic, xenograft, and genetically engineered mouse models (GEMMs), with their unique characteristics shown in Figure 2.[35]

Syngeneic models utilize cells or tissue from donors with the same genetic background. This results in a more authentic TME, as the recipient animals have normal immunity. In studies involving immunocompetent mice, the CT26 cell line (syngeneic to BALB/c mice) and the MC38 cell line (syngeneic to C57BL/6 mice) are commonly used. While CT26 is a fast-growing grade IV carcinoma with similarities to aggressive, undifferentiated human CRC cells, MC-38 is a grade III adenocarcinoma. Both cell lines cause PC within 2-3 weeks of IP injection.[36,37]

In immunocompetent rats, the CC531 cell line (syngeneic to WAG or WAG/Rij rats) is commonly used. Widely used in metastasis research, CC531 is a 1, 2-dimethylhydrazine-induced adenocarcinoma with low immunogenicity. IP injection of CC531 causes widespread carcinomatosis and hemorrhagic ascites after 3 weeks.[38,39] However, the colon tumors in these models are chemically induced and do not fully mirror the genetic and molecular diversity seen in human cancers. Despite this limitation, syngeneic models are the preferred choice for studying cancer immunotherapy.[40,41]
Xenograft model generation using commercially available cell lines provides expedited tumor development, heightened engraftment rates, and reduced study durations, resulting in productive time and cost management. These cell lines boast comprehensive published data, well-defined genetic profiles, and established responsiveness to therapeutic interventions. Their proliferative capacity affords an inexhaustible cell reservoir for initiating xenografts, with facile integration of genetic modifications for diverse applications, including quantitative imaging methodologies.[42] PC xenograft models

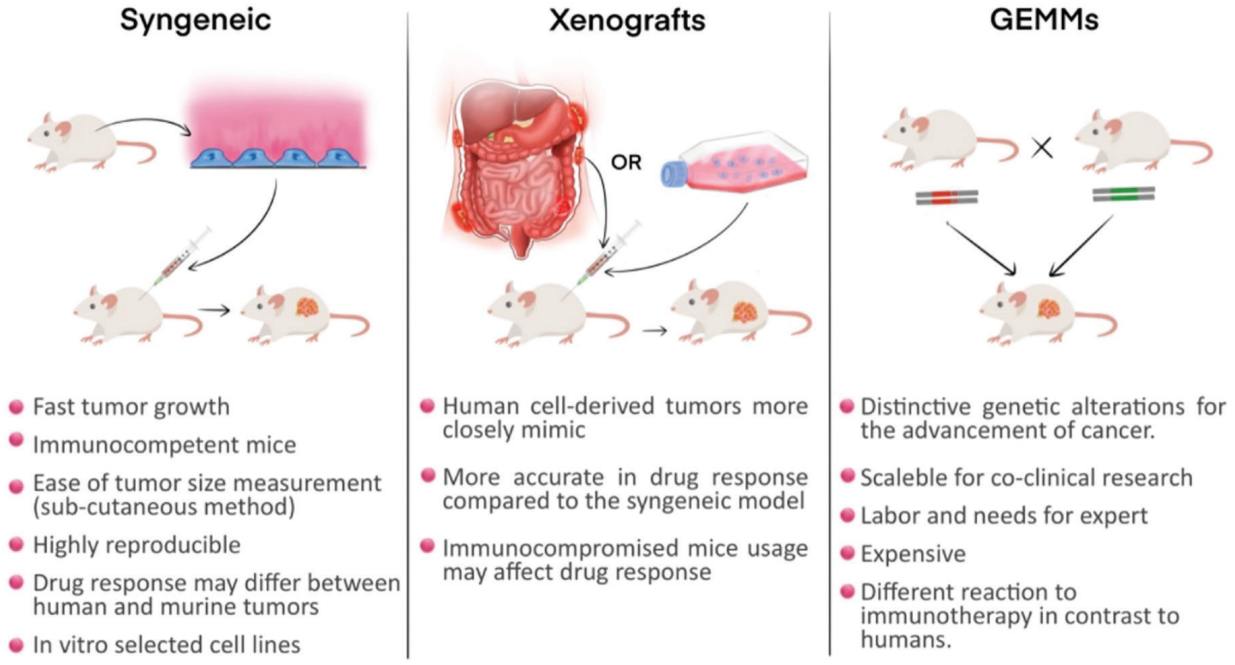

Figure 2. Main characteristics of different *in vivo* models
GEMMs: Genetically engineered mouse models

involve transplanting human cancer cells or tissue into the peritoneal cavity of immunodeficient mice, such as severe combined immunodeficiency (SCID), athymic nude, non-obese diabetic (NOD), or NOD SCID gamma mice; however, these models lack the ability to mount an immune response against human cells, which contributes to the promotion of tumor growth in the peritoneal cavity. Furthermore, the homogeneous nature of the source material raises concerns regarding the faithful representation of the original human cancer, and the absence of intratumoral heterogeneity in patient tumors during *in vitro* culture further underscores potential limitations.[43] PDXs may offer a more intricate portrayal of human cancers, albeit at the expense of prolonged latency periods and elevated financial commitments.

Although PDX models have been used to determine the efficacy and safety of chemotherapeutics, the main hindrance is the lack of an immunocompetent environment. To address this constraint, researchers employed GEMMs to study PC. This type of model has been used to study PM, including transgenic, knock-out, and knock-in mice, and can replicate various human cancers at a genetic level and demonstrate comparable phenotypes in the TME.[44,45] Numerous mouse models, including those expressing human tumor endogenous antigens such as carcinoembryonic antigen (CEA) as a transgene, have shown improved engraftment of tumor cells expressing this antigen.[46] However, more authentic and intricate models that closely mimic PM in humans have been developed by genetically modifying primary aggressive peritoneal tumors, such as those originating from the ovary, colon, stomach, or pancreas, to investigate early PM. In this regard, some studies have utilized triple-mutant mice ($p53^{LSL\text{-}R172H/+}$ $Dicer1^{flox/flox}$ $Pten^{flox/flox}$ $Amhr2^{cre/+}$).[47-49] This mouse model with $p53^{R172H}$ mutation, equivalent to human $p53^{R175H}$, common in ovarian high-grade serous carcinoma, develops tumors in the fallopian tube 1-2 months after birth, with all mice ultimately developing PC and severe hemorrhagic ascites causing mortality.

Tseng et al.[50] described a PC model where the histological morphology and immune microenvironment closely resemble PM high-grade serous carcinoma in humans. In immunocompetent mice, the combination of shRNA-p53 with overexpression of AKT and c-Myc oncogenes in the peritoneum led to the development of aggressive PC with visible implants within 21 days. This approach bypassed immunosurveillance and induced the formation of peritoneal tumors in the mice. Similarly, Iyer S et al.[51] developed cell lines combining loss of Trp53 and overexpression of CCNE1, AKT2, and Trp53R172H, driven by $Kras^{G12V}$ or Brd4 or Smarca4 overexpression. This model serves as a valuable platform for preclinical and translational research on PC, including testing immunotherapeutic agents, studying PC initiation and progression, identifying biomarkers, and predicting the origin of peritoneal cancer spreading.

Moreover, the xenograft model could be generated by patient-derived PC organoid engraftment in the mice that provide personalized PM modeling. A study by Fang et al.[52] successfully

established human malignant pleural mesothelioma organoids (MPMOs), providing a detailed description of the medium components necessary for MPMO culture. Examination and genomic analysis showed that MPMOs accurately represented the original tumors' histological characteristics and genomic diversity. These MPMOs effectively created subcutaneous and orthotopic xenograft models with high success rates. Drug sensitivity tests revealed varying medication responses among MPMOs, which correlated well with the clinical situations of the patients.[52]

Interpreting research results from animal models can be challenging due to differences in peritoneum physiology and function between rodents and humans. The highly vascularized omentum, which plays a key role in PC development in humans, has significantly lower vascularity in rodents. These differences highlight the importance of considering limitations in translating findings from rodents to humans.[53] The disadvantages of *in vivo* models are largely related to ethical problems. The ethical issues for animal models are highly critical. Scientists must adhere to strict ethical guidelines and reduce harm to the animal during the experimental process. A further disadvantage is the diversity of genetics and physiology of animals and humans, and a major hindrance to *in vivo* studies is that they are time-consuming and expensive.[54]

To conclude, experimental animals mimic the human PC model. Furthermore, due to the heterogeneity of cancer cell characteristics among patients, translating any treatment strategy to clinical practice has proven challenging. Therefore, it is imperative to develop personalized *in vivo* peritoneal cancer models to investigate individual cancer characteristics and predict the most effective treatment strategy for patients.

In silico Models

Improving our comprehension of cancer and other intricate diseases necessitates the integration of diverse datasets and algorithms. Combining *in vitro* and *in vivo* data with *in silico* models is crucial for addressing the inherent complexities of data. This integrated approach not only helps reveal underlying molecular mechanisms but also enhances our understanding of uncontrolled cell growth. Over time, a variety of biochemical and computational methods have been developed for studying diseases, with many initially relying on animal experiments. However, comparing cellular processes in both eukaryotic and prokaryotic organisms has proven valuable in elucidating specific aspects of disease progression, thereby enhancing the planning of future experiments. Adhering to principles of humane experimentation, advancements in alternative animal testing have focused on *in vitro* methods such as cell-based models and microfluidic chips, as well as clinical approaches such as microdosing and imaging.[55] The range of alternative methods has expanded to include computational approaches that draw on information from previous *in vitro* and *in vivo* experiments. *In silico* techniques, often overlooked, can play a critical role in understanding fundamental cancer processes, offering accuracy comparable to biological assays and providing crucial focus and direction to reduce experimental costs. Precision medicine aims to provide more personalized treatments, with digital twins representing a novel approach to achieving this goal. A clinical digital twin serves as a digital representation of an individual, offering tailored treatment recommendations, as illustrated in Figure 3. However, the centralized data gathering required to develop and enhance digital twin models is facing challenges related to patient privacy constraints.[56]

At present, no digital twin technique model design exists for any cancer type, including PC. Such a model could be beneficial in assessing personalized treatment strategies.

Treatment Strategies for Peritoneal Carcinomatosis

Intraperitoneal Treatment Approaches

The goal of therapy is to control the tumor for as long as possible and avoid or delay tumor-associated symptoms for most of the patients with PC. Quality of life (QoL) and survival time become determining factors in the therapy decision.[57]

In addition to "best-supportive care" and systemic treatment as standard therapy, locoregional therapy methods such as hyperthermic intraperitoneal chemotherapy (HIPEC) and PIPAC have also become established in recent years. Although HIPEC and PIPAC are procedures for the IP application of chemotherapy, fundamental differences must be considered when determining the indication.[58]

There are significant variations between protocols within the HIPEC framework. The diversities are based on chemotherapeutic drugs, temperature, carrier solution, volume, and duration of the treatment. The most frequently utilized drugs in preclinical animal studies are mitomycin C (MMC), cisplatin, oxaliplatin, paclitaxel, and doxorubicin. The temperatures applied varied widely for all these drugs, ranging from 39 °C to 44 °C.[59]

The carrier solution used in HIPEC significantly affects its pharmacokinetics. Park et al.[60] demonstrated this by combining oxaliplatin or MMC with different carrier solutions: a 1.5% Dianeal peritoneal dialysis solution, 5% dextrose solution, or 20% lipid solution. The choice of carrier solution in HIPEC affects drug pharmacokinetics. While peritoneal drug concentrations remain consistent across carriers, plasma concentrations vary significantly. Using a lipid carrier solution with MMC resulted in a threefold higher area under the curve ratio between peritoneum and plasma compared with a Dianeal solution. Oxaliplatin plasma concentrations were similar with lipid and Dianeal solutions but significantly higher with dextrose, potentially increasing systemic toxicity due to differences in membrane permeability.[60]

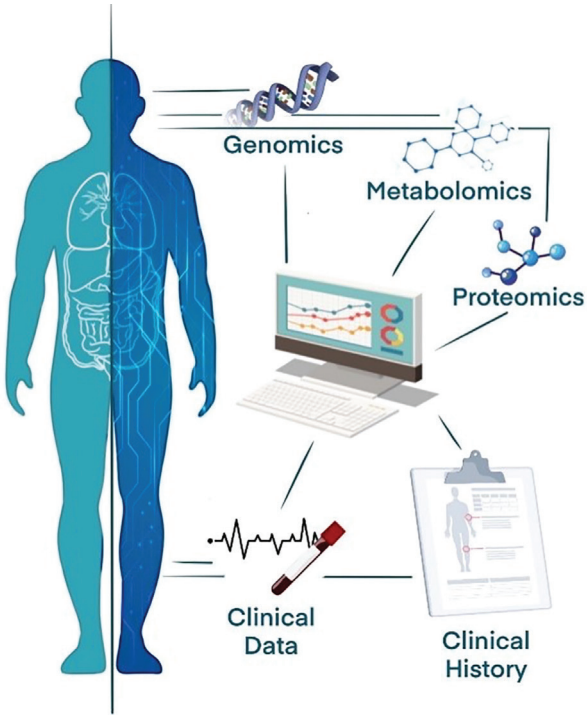

Figure 3. Digital twins for individualized treatments

The temperature is another critical factor in HIPEC treatment. Heat has been shown to have a positive impact on the 5-year survival rates of patients with PC.[61] The effectiveness of chemotherapy administered during HIPEC is boosted by a temperature-dependent factor called the thermal enhancement ratio.[62] Generally, three hyperthermic scales are recognized: mild (39 °C-41 °C), moderate (41 °C-43 °C), and severe (>43 °C) hyperthermia (34298644). Severe hyperthermia carries the risk of damaging healthy tissues and is not employed in HIPEC clinical practice. On the other hand, mild and moderate hyperthermia both increase tissue blood flow, stimulate the immune response, and enhance the cytotoxicity of chemotherapy in a temperature-dependent manner. Among the studies reviewed, moderate hyperthermia was the most commonly used type (71% vs. 29% for mild hyperthermia).[63] A study by Manoğlu et al.[64] successfully created an *in vivo* PM model by injecting a CC531 colon carcinoma cell line into the peritoneum to evaluate MMC and 5-fluorouracil efficacy in a HIPEC treatment system. The authors proved that HIPEC treatment is significantly more effective than normothermic MMC administrations.[64]

In vitro studies indicate that there is an ideal treatment duration where hyperthermia coupled with chemotherapy exhibits maximum efficacy. A recently published study by our team focused on improving the HIPEC treatment of PM originating from CRC. Due to the challenges in conducting randomized trials, the study proposes a novel *in vitro* 3D microfluidic PC model to test different HIPEC treatment parameters. The effects of current HIPEC protocols with oxaliplatin were tested on the developed 3D microfluidic PC model. The results showed that epithelial-mesenchymal transition-induced HCT116 colon carcinoma cells were less sensitive to oxaliplatin treatment and that increasing the temperature and duration of the treatment increased cytotoxicity. The study suggests that 200 mg/m^2 of oxaliplatin applied for 120 min is the more effective HIPEC treatment compared with 460 mg/m^2 for 30 and 60 min.[65] Studies highlight the importance of treatment duration in enhancing the efficacy of chemotherapy. Kirstein et al.[66] demonstrated that combining heat (42 °C) with oxaliplatin for 2 hours was more effective than using 30 min. Löffler et al.[67] found that a 30 min exposure to clinical oxaliplatin concentrations often fails to induce sufficient cell death, suggesting that longer application times are needed. Murata et al.[68] observed similar growth-inhibitory effects between 30 and 60 min treatments for most cell lines and chemotherapy combinations under hyperthermic conditions, but longer durations were more effective for specific cell lines, indicating a cell-line-dependent response to chemotherapeutics. These studies emphasize the significance of prolonging treatment duration to enhance drug efficacy.

Moreover, HIPEC treatment can be administered using either the conventional open abdominal technique (open HIPEC) or the closed technique. A novel approach, the Peritoneal Recirculation System [(PRS)-1.0 Combat] with CO_2 recirculation technology (PRS closed HIPEC), has been developed for closed HIPEC. Studies have shown that the

closed technique offers a superior homogeneous distribution of heat and anticancer agents. In a study by Diaz et al.,[69] 84 patients with curative CRC were treated using different HIPEC techniques. The closed HIPEC group demonstrated a significantly improved median overall survival of 67 months, compared with 43 months in the open HIPEC group (p<0.001). Median disease-free survival was also longer in the PRS closed HIPEC group (40 months) compared with the open HIPEC group (15 months, p<0.001). These results suggest that PRS closed HIPEC is a reliable and safe technique, offering a viable alternative for administering HIPEC.[69]

On the other hand, PIPAC exploits gas and pressure to overcome the limitations of IP chemotherapy, enhancing drug exposure and diffusion into tumor nodes. Evidence from *in vitro*, *in vivo*, *ex vivo*, and clinical studies suggests that PIPAC offers superior pharmacological properties to traditional fluid-based IP chemotherapy, leading to enhanced local efficacy and reduced systemic toxicity. Initial retrospective analyses in ovarian, gastric, and CRCs demonstrate promising results in palliative settings, with ongoing prospective trials assessing effectiveness and safety. Additionally, electrostatic precipitation PIPAC (ePIPAC) has been proposed to enhance pharmacological properties further. Preclinical evaluations show that ePIPAC is technically feasible, achieving improved tissue drug delivery compared with standard PIPAC.[70] In a study by Reymond et al.,[71] the ePIPAC procedure was technically feasible, with no intraoperative complications, was well-tolerated by patients, and had no adverse events exceeding CTCAE grade 2. Patient 1, diagnosed with PC of unknown origin, exhibited an objective histological and radiological response and survived for 11 months. Patient 2, diagnosed with ductal pancreatic cancer, underwent secondary resection following ePIPAC, resulting in no residual PM, but experienced tumor recurrence after 5 months. Patient 3, diagnosed with gallbladder adenocarcinoma, exhibited radiological improvement in liver infiltration and survived for 22 months without histological signs of PM.[71]

Clinical trials are needed to further evaluate the efficacy and application of PIPAC, but recent data on PIPAC with low-dose cisplatin and doxorubicin or oxaliplatin shows promising results. Studies on PC from various cancers have demonstrated the safety and tolerability of PIPAC, with a median survival rate of 15.7 months. The PIPAC method has been shown to induce histological regression and improve QoL in patients, with no change in QoL stabilization over 3 months of treatment.[72] These treatments are presented in Figure 4.

However, PIPAC may not be suitable for patients with recurrent disease following cytoreductive surgery (CRS) due to adhesions hindering aerosol diffusion.[73] Combining PIPAC with systemic chemotherapy has shown significant improvements in tumor response, clinical response, and QoL.[74]

Immunotherapy

Immunotherapy has become a hopeful strategy for PC treatment. The peritoneal cavity contains a diverse array of immune cells, which recent research highlights as pivotal in regulating tumor growth in this region. Nonetheless, peritoneal

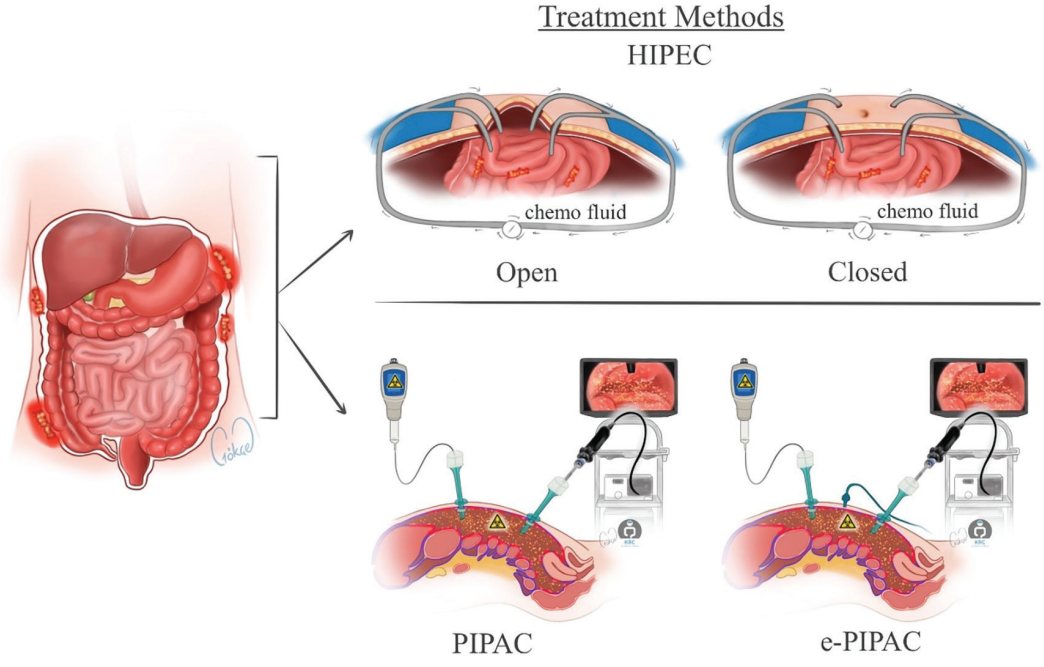

Figure 4. The open/closed HIPEC and PIPAC techniques
HIPEC: Hyperthermic intraperitoneal chemotherapy, PIPAC: Pressurized intraperitoneal aerosol chemotherapy, ePIPAC: Electrostatic precipitation PIPAC

tumors frequently evolve mechanisms to evade immune detection, resulting in disease advancement and unfavorable prognoses. To combat this challenge, substantial endeavors are underway to devise novel immunotherapeutic strategies that can augment immune cell migration into the peritoneum and enhance tumor immunogenicity.[75] Catumaxomab, a trifunctional antibody approved in Europe, is an example of IP immunotherapy that targets EpCAM, reducing malignant ascites. IP immunotherapy aims to break immunological tolerance to treat peritoneal diseases. Approaches such as boosting T-cell reactions and developing vaccines targeting tumor-specific antigens are under investigation. Potential therapies for PC encompass CAR-T cells, vaccines, dendritic cells with proinflammatory cytokines and natural killer cells, adoptive cell transfer, and immune checkpoint inhibitors. Here, CAR-T cells designed to target CEA-expressing tumors have demonstrated suppression, a response that was heightened with anti-PD-L1 or anti-Gr1 treatment. Additionally, CAR-T cells for folate receptor cancers, when paired with CD137 co-stimulatory signaling, facilitated T-cell infiltration and persistence within the body.[76] Studies such as Checkmate-649 have shown significantly improved overall survival in patients with advanced gastric cancer and PM with high PD-L1 expression (CPS ≥5) when treated with nivolumab and chemotherapy compared with chemotherapy alone.[77] Another study centered on individuals with solitary PC stemming from dMMR/MSI-H CRC reported a notable 46% response rate to immune checkpoint inhibitor therapy, a level of success challenging to attain with conventional chemotherapy.[78] Additionally, a study on claudin 18.2 targeting CAR-T therapy in patients with advanced gastric cancer showed promising responses.[79] Recent studies demonstrated that immune-enhanced patient tumor organoids (iPTOs) present a promising tool for predicting clinical outcomes in response to immunotherapies. A study by Votanopoulos et al.[80] reported an 85% agreement between iPTO models and actual patient responses, highlighting their potential for personalized treatment planning. These models facilitate the exploration of tumor-immune system interactions and can be utilized to screen the efficacy of immune checkpoint inhibitors.[80] Moreover, iPTOs can aid in the generation of tumor-reactive lymphocytes for use in adoptive cell transfer therapies.[81] Despite ongoing challenges in the standardization and scalability of these co-culture systems, they hold great promise in advancing precision oncology. By enabling patient-specific immunotherapy testing, iPTOs provide valuable insights into the TME. Their use could optimize the administration of expensive immunotherapies, leading to better patient outcomes and more efficient resource allocation.[82]

These studies suggest that immunotherapies could be effective and safe treatments for PC.

Intraperitoneal Photodynamic Diagnosis and Therapy

The CRS-HIPEC technique is recommended solely in cases where the peritoneal tumor burden is not extensive, as indicated by the Peritoneal Carcinomatosis Index (PCI) or other scoring systems.[83,84] The PCI is determined through intraoperative inspection and palpation, as conventional preoperative imaging methods such as computed tomography (CT) and 18F-positron emission tomography/CT often fail to accurately estimate the extent of the disease.[85,86] This leads to reported rates of futile laparotomy ranging from 5% to 15% in patients undergoing surgery for PC.[87-90] Although diagnostic laparoscopy may enhance PCI assessment, its additional predictive value is limited.[91] Thus, more precise imaging methods are necessary to identify suitable candidates for CRS-HIPEC among patients with low PCI and those with PM. Fluorescence labeling presents a novel approach for diagnosing and prognosing PC, with CEA being a prime target for CRC.[92,93] In fact, CEA is highly expressed in CRC cells, whereas its expression in healthy tissue is significantly lower.[94] Labetuzumab, a humanized monoclonal antibody targeting CEA, has been extensively studied as a radiotracer, therapeutic agent, and antibody-drug conjugate for various malignancies.[95,96] The dual-labeled form, [111In]In-DOTA-labetuzumab-IRDye800CW, has shown promise as a multimodal imaging agent for CRC in preclinical studies.[97,98] Clinical trials have evaluated the safety and feasibility of preoperative single-photon emission CT imaging, intraoperative radio detection, and near-infrared fluorescence-guided surgery following intravenous administration of different doses of [111In]In-DOTA-labetuzumab-800CW in patients with CRC PM. A conceptional image for IP photodynamic diagnosis/therapy is presented in Figure 5.

Moreover, IP photodynamic treatment (PDT) shows promise as a therapy for PC due to its superficial treatment effect. A Phase II trial using the photosensitizer, Photofrin®, demonstrated clinical tolerability but substantial toxicity, indicating a narrow therapeutic index. Despite this, responses were seen in heavily pre-treated patients, suggesting clinical effectiveness. However, Photofrin® showed little selectivity for tumors over normal tissues, contributing to its narrow therapeutic index. Newer, molecularly targeted photosensitizers and strategies to enhance PDT cytotoxicity offer the potential to improve the therapeutic index of the treatment. Nanotechnology and fractionated PDT administration are also being explored to enhance the treatment's effectiveness and tolerability. These advancements may lead to highly effective and well-tolerated IP PDT for treating carcinomatosis.[99]

Matts et al.[100] investigated whether fullerenes could enhance PDT efficacy against PC in a mouse model. Characterized by a thin layer of tumor nodules on abdominal organs, PC is known

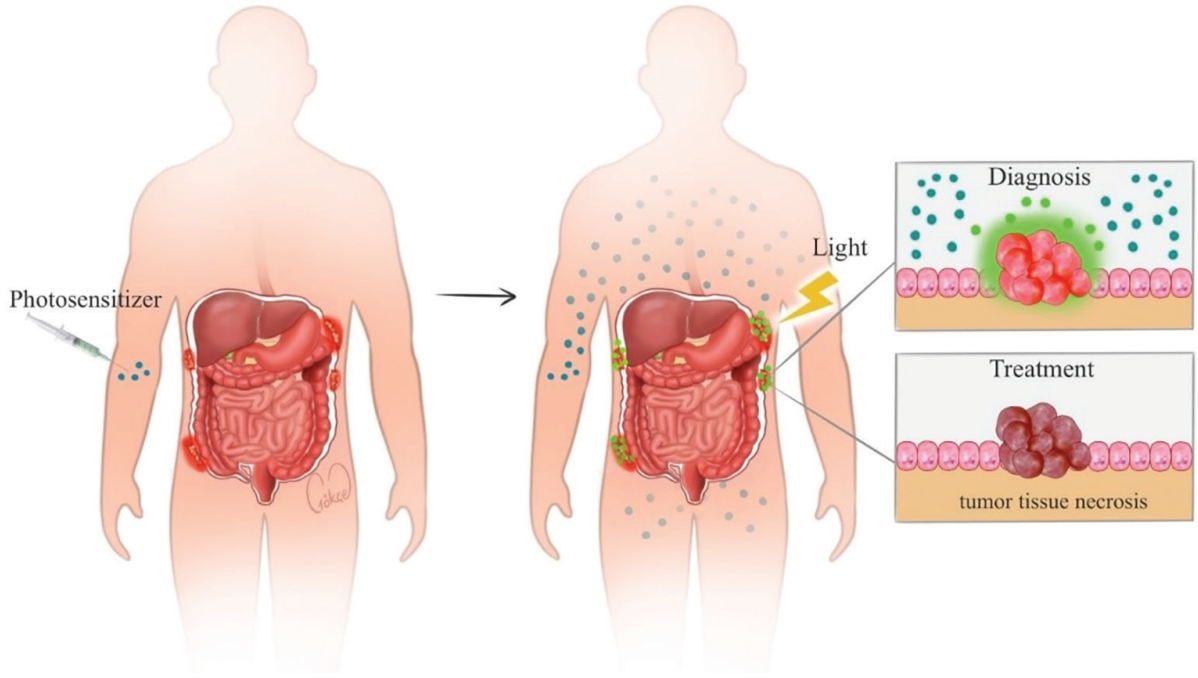

Figure 5. Photodynamic diagnosis and treatment for PC
PC: Peritoneal carcinomatosis

for its poor response to standard treatments in humans. The authors employed a colon adenocarcinoma cell line (CT26) modified to produce luciferase, allowing them to monitor IP tumor burden in BALB/c mice using real-time optical imaging with a sensitive low-light camera. After administering N-methylpyrrolidinium-fullerene in Cremophor®-EL micelles via IP injection, the mice were exposed to white-light illumination through a skin flap in the peritoneal wall. This treatment led to a notable decrease in bioluminescence and improved survival.[100]

Almerie et al.,[101] conducted a systematic review that included three human and 25 animal studies. Their analysis of phase I and II human trials using first-generation photosensitizers revealed the feasibility of applying PDT following surgical debulking in patients with PC, exhibiting some clinical benefits. However, the limited tumor selectivity of the photosensitizers resulted in notable toxicities, particularly capillary leak syndrome and bowel perforation. Animal studies indicated that PDT increased survival rates by 15-300% compared with control groups, with the treatment also leading to higher tumor necrosis values (PDT; 3.4±1.0 vs. control; 0.4±0.6, $p<0.05$) and reduced tumor size (residual tumor size =10% of untreated controls, $p<0.001$). Overall, the review indicates that PDT shows potential as a treatment option for PC.[101]

Samel et al.[102] focused on L293 cells that are genetically engineered to produce the CYP2B1 enzyme using a cytomegalovirus promoter, which activates ifosfamide, a cytotoxic drug. These modified cells were encapsulated in a cellulose sulfate formulation (Capcell). In an animal study involving BALB/c mice with green fluorescently labeled colon-26 cancer cells, early IP treatment combining ifosfamide with CYP2B1 cells led to complete tumor regression. In contrast, treatment beginning on day 5 or using ifosfamide alone resulted in partial responses. These findings highlight the potential of targeted IP chemotherapy, employing prodrug-enzyme combinations, as a practical approach for treating peritoneal spread from CRC.[102]

Recent advancements in tumor selectivity and light delivery systems show promise, but further refinement is needed before PDT can be widely used for PC.

Gene Therapy

Gene therapy delivers various types of genes to repair damaged genes causing disease. These gene therapy medicinal products are classified as advanced medicinal therapy products by the European Medicines Agency.[103] They repair tissue damage, replenish deficiencies, and prevent unwanted gene expression. Gene therapy can replace mutated genes with healthy copies, inhibit mutated gene expression, silence unwanted genes, replace deficient genes, or deliver therapeutic genes to target tissues for disease treatment.

Methods such as antisense RNA or nuclear phthalate can be employed to silence genes and inhibit oncogene expression, effectively slowing tumor cell proliferation. Suicide gene

therapy involves introducing a gene that converts an inactive prodrug into a toxic agent within the cells. This approach using inactive drugs is known as gene-directed enzyme prodrug therapy. Gene replacement therapy aims to correct specific gene mutations in cancer cells by introducing a functional gene copy using a vector. Vectors, which can be viral or non-viral, deliver genetic material for gene therapy. The goal of gene therapy is to deliver therapeutic genes to target cells using a reliable, safe, and effective carrier. Non-viral vectors are often favored over viral vectors due to their superior attributes.[104]

Gene therapy, categorized by cell type and treatment mode, modifies gene expression in living cells for therapeutic purposes. Its potential for fewer side effects sets it apart from traditional methods.[105]

Several studies focused on gene therapy for PC. In a study by Natatsuka et al.[106] the suppressor of cytokine signaling1 (SOCS1) was investigated for its potential as a therapeutic target in gastric cancer. Known for regulating cytokines, SOCS1 was found to suppress proliferation in four out of five gastric cancer cell lines by influencing cell cycle-associated molecules at the G2/M checkpoint. The study also showed promising results in a preclinical xenograft PC mouse model, suggesting that forced expression of SOCS1 could be a new therapeutic approach for treating PC in gastric cancer.[106] In another study by Wu et al.[107] antiangiogenic therapy targeting angiogenesis, a crucial process in tumor growth and metastasis, was investigated using pigment epithelium-derived factor (PEDF) as an angiogenesis inhibitor. Adeno-associated virus (AAV)-mediated human pigment epithelium-derived factor (hPEDF) was evaluated as a tumor suppressor for cancer gene therapy. Recombinant AAV2 encoding hPEDF (rAAV2-hPEDF) inhibited proliferation and tube formation of human umbilical vein endothelial cells *in vitro*. In a colorectal PC mouse model, rAAV2-hPEDF suppressed tumor growth and metastasis, prolonged survival, reduced microvessel density, and increased apoptosis in tumor tissues. Elevated hPEDF levels in the serum and ascites of treated mice indicate the potential of rAAV2-hPEDF as an antiangiogenic therapy agent. These investigations offer a novel treatment approach for PC.[107]

Conclusion

This review emphasizes the need for improved experimental models to accurately replicate the complexities of PC. Researchers can gain insights into the mechanisms of peritoneal dissemination by studying various animal models, cell cultures, and advanced technologies such as organoids and microfluidic platforms. While progress has been made, challenges remain, suggesting that future studies should integrate advanced imaging and molecular profiling to enhance translational relevance. Refinement of these models will advance our understanding of PC and aid in developing more effective therapies.

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Footnotes

Authorship Contributions

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RESEARCH ARTICLE

Comparison of Oncological Outcomes After Curative Resection for Right-side Colon Cancer and Left-side Colon Cancer: a Retrospective Observational Study

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ABSTRACT

Aim: This study aims to compare clinicopathological findings and oncological outcomes after curative resection between right-side colorectal carcinoma (RCC) and left-side colorectal carcinoma (LCC).

Method: A retrospective review of 209 patients who underwent elective surgery for right and left colon cancer between January 2013 and October 2022 was conducted. After applying the exclusion criteria, 182 patients were included. The patients were grouped based on embryological development: right side (cecum, ascending colon, hepatic flexure, and proximal transverse colon) and left side (distal transverse colon, splenic flexure, descending colon, and sigmoid colon). Clinicopathological features, lymph node removal, and oncological outcomes were compared. Statistical analyses were performed using the chi-squared test, Fisher's exact test, Mann-Whitney U test, the Kaplan-Meier method, and Cox regression analysis.

Results: Among the 182 patients, 108 (59.3%) had RCC, and 74 (40.7%) had LCC. No significant differences were found between the groups regarding age, gender, body mass index, carcinoembryonic antigen value, tumor size, T/N stage, lymphovascular/perineural invasion, positive lymph nodes, and hospital stay. However, more lymph nodes were removed in RCC cases ($p<0.0001$). Oncologically, 32.4% of the patients with RCC and 29.7% of the patients with LCC died during follow-up, with no difference in mean survival. Multivariate analysis identified age and tumor size as prognostic factors for 5-year survival.

Conclusion: Despite clinical and pathological differences between RCC and LCC, no significant difference was observed in 2- and 5-year survival. Early diagnosis and personalized treatment remain crucial for both cancer types. Further large-scale studies are recommended.

Keywords: Colon cancer, curative resection, prognosis

Introduction

Colorectal cancer (CRC) is the second most common cancer worldwide and has a high mortality rate, especially in more advanced stages.[1] According to the American Joint Committee on Cancer, radical surgical resection is the standard treatment for stages I-III CRC, with postoperative adjuvant chemotherapy also being applied to patients with high-risk stages II and III colon cancer.[2]

There are embryological origin, anatomical, histological, genetic, and immunological differences between right-side colorectal carcinoma (RCC) and left-side colorectal carcinoma (LCC). During embryological development, the right-side colon (cecum, ascending colon, and proximal two-thirds of the transverse colon) develops from the midgut, whereas the left-side colon (distal third of the transverse colon, descending colon, and sigmoid colon) develops from the hindgut.[3]

In recent years, there has been increasing interest in distinguishing between RCC and LCC because these two types have different presentations, treatments, and prognoses.[4] Studies have shown that RCC and LCC have different clinical and biological characteristics and are currently considered two separate entities.[5]

This study aims to analyze the clinicopathological findings and oncological outcomes between RCC and LCC after curative resection.

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Materials and Methods

A total of 209 patients who underwent elective surgery for RCC and LCC between January 2013 and October 2022 were included in this study. Patients with rectal cancer, RCC or LCC who underwent surgery despite having metastatic disease (9 patients), patients with T1 depth of invasion (1 right-sided, 10 left-sided) (the reason for excluding T1 tumors is their expected long survival, which would not impact this study), patients with fewer than 12 lymph nodes removed (3 right-sided, 4 left-sided), and those who underwent emergency or urgent operations were excluded from the study. The evaluation was conducted on a total of 182 patients (Figure 1).

Patients with colon tumors were divided into right-sided and left-sided groups according to their embryological development sites. Right-sided colon cancers included the cecum, ascending colon, hepatic flexure, and proximal transverse colon cancers, whereas left-sided colon cancers included distal transverse colon, splenic flexure, descending colon, and sigmoid colon cancers. Proximal transverse colon cancers were included with hepatic flexure cancers, and distal transverse colon and splenic flexure cancers were included with descending colon cancers.

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Koşuyolu Yüksek İhtisas Research and Training Hospital (approval number: 2020.4/23-325, dated: 08.05.2020), and it adhered to the ethical standards expected for medical research involving human participants.

Statistical Analysis

The normality of numerical data was assessed using the Kolmogorov-Smirnov test. Variables between the two groups (RCC and LCC) were analyzed using the chi-squared test, Fisher's exact test, and the Mann-Whitney U test. Kaplan-Meier analysis was used to evaluate differences between the groups in terms of 2-year, 5-year, and overall survival. Additionally, prognostic factors affecting 2-year, 5-year, and follow-up survival were assessed using Cox regression analysis with the stepwise procedure. SPSS 22 software was used for the statistical analysis, and the level of statistical significance was set at an alpha of 0.05.

Results

The average follow-up duration for the patients included in this study was 62.11±36.84 months for right-sided colon cancers and 66.45±31.95 months for left-sided colon cancers.

Clinical and Pathological Characteristics:

A total of 182 patients were included in the study, with 108 (59.3%) having RCC and 74 (40.7%) having LCC. The main clinicopathological characteristics of the patients are shown in Table 1. There were no statistical differences between the two groups in terms of age, gender, body mass index, initial carcinoembryonic antigen value, tumor size, T/N stage, lymphovascular invasion (LVI), perineural invasion (PNI), number of positive lymph nodes, Clavien-Dindo classification, and hospital stay duration. However, there was a statistical difference in the total number of lymph nodes removed ($p<0.0001$), with an average of 29±14 lymph nodes removed in right-sided colon cancers compared with 23±11 in left-sided colon cancers.

Oncological Outcomes

At the end of follow-up, 35 (32.4%) of the patients with RCC and 22 (29.7%) of the patients with LCC had died. The average survival time was 96.286±4.876 months for RCC and 99.479±5.703 months for LCC, with no difference in 2-year, 5-year, and overall survival between the groups (Table 2, Figure 2).

Univariate and Multivariate Analysis of Prognostic Factors

Potential prognostic factors for 2-year, 5-year, and overall survival, including gender, age, tumor size, tumor invasion depth, total number of lymph nodes removed, number of positive lymph nodes, PNI, and vascular invasion, were investigated using multivariate Cox regression analysis (Tables 3 and 4). Univariate and multivariate analyses did not identify any prognostic factors for 2-year follow-up. In the 5-year follow-up, univariate analysis identified age, tumor size, number of positive lymph nodes, and PNI ($p=0.001$, $p=0.028$, $p=0.030$, $p=0.034$) as prognostic factors, whereas multivariate analysis identified age and tumor size ($p=0.001$, $p=0.033$) as prognostic factors. For overall survival at the end of follow-up, univariate analysis identified age, number of positive lymph nodes, and PNI ($p=0.003$, $p=0.025$, $p=0.006$) as prognostic factors, whereas multivariate analysis identified only age ($p=0.005$) as a prognostic factor.

Discussion

CRC is one of the most common cancers worldwide. In 2018, deaths related to CRC accounted for 5.8% of all deaths.[6] It is now known that RCC and LCC differ by gender, age, and geographic region and should be considered as two distinct entities. Numerous studies have explored these differences, including pathophysiology and related genetic pathways, age and symptomatology at presentation, stage at presentation, prognosis, chemotherapy regimens, premalignant lesions, and risk factors.[7,8]

In the study by Saltzein and Behling[9] it was found that patients with RCC were more likely to be older women. Similarly, older studies also reported that RCC was more frequent in older adults and women.[10] However, in our study, men were more predominant, although this was not statistically significant.

Recent studies, in line with our findings, also report no significant difference in terms of age and gender between RCC and LCC.[11] In our cohort, the mean age for RCC was 62.14 years, whereas for LCC, it was 64.14 years.

One of the most notable distinctions between RCC and LCC is their difference in T stage at diagnosis. RCC is often diagnosed at more advanced stages, whereas LCC tends to be detected earlier. This may be due to the larger lumen of the right colon, which leads to a delayed onset of symptoms.[12] As the T stage advances, the prognosis worsens for both RCC and LCC; however, this progression tends to be more rapid in RCC. Several studies have shown that tumor penetration and peritoneal dissemination rates are higher in the T3 and T4 stages of RCC, which may contribute to higher postoperative recurrence rates.[13] These findings underscore the need for careful follow-up and tailored treatment strategies for patients with RCC.[14] In our study, however, no significant differences in the T stage between RCC and LCC were observed.

LVI and PNI serve as important prognostic markers in colon cancer.[15] LVI, which indicates the spread of tumor cells to the lymphatic and blood vessels, is reported to be more common in RCC, suggesting a higher potential for distant dissemination and metastasis in these tumors.[16] PNI, which refers to the invasion of tumor cells around nerve sheaths, usually occurs at more advanced stages and has been shown to be more frequent in RCC compared with LCC. Both LVI and PNI are associated with a poorer prognosis and should be considered when planning postoperative treatment strategies.[17] In our study, we evaluated these factors but found no statistically significant differences between RCC and LCC.

The total number of lymph nodes removed during surgery is a critical prognostic factor in CRC. Several studies from the

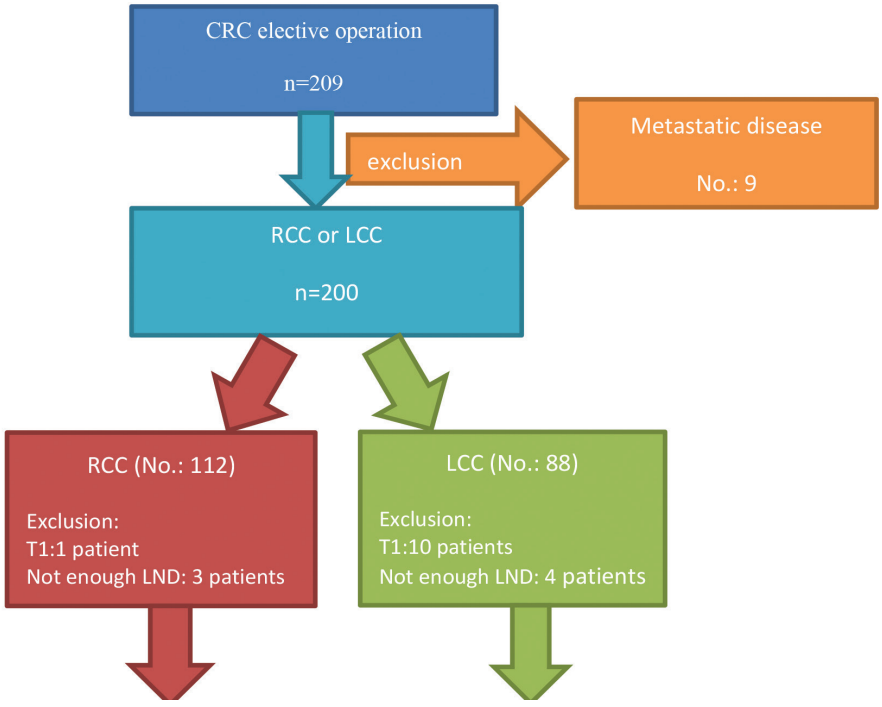

Figure 1. Flowchart of inclusion and exclusion criteria for study participants

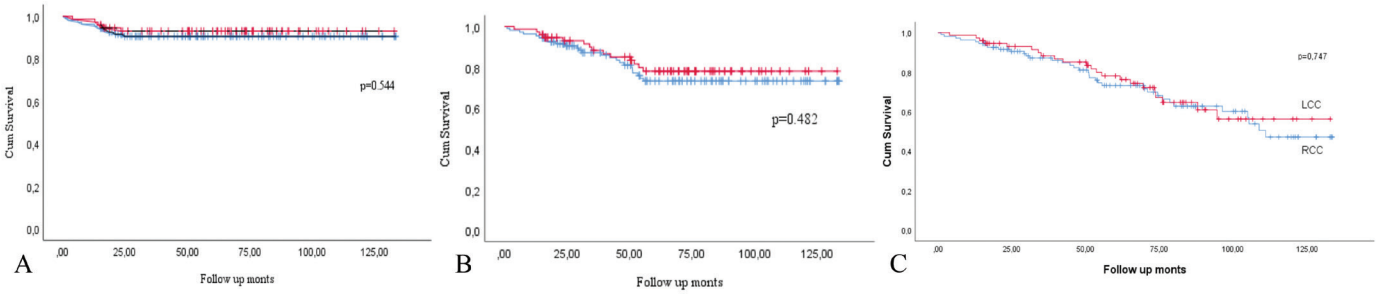

Figure 2. Comparison of survival in patients with right- or left-colon cancer. A) 2 years, B) 5 years, C) overall
RCC: Right-side colorectal carcinoma, LCC: Left-side colorectal carcinoma

Table 1. Dermographic and clinical features

	Right	Left	p
Cancer location (%)			
Ceacum			
Right colon			
Hepatic flexura	40 (37)		
Left colon	36 (33.3)	24 (67.6)	
Sigmoid colon	32 (29.6)	50 (32.4)	
Sex (%)			
Male	62 (57.4)	46 (62.2)	0.521
Female	46 (42.6)	28 (37.8)	
T stage (%)			
T2	7 (6.)	6 (8.1)	0.786
T3	85 (78.7)	55 (74.3)	
T4	16 (14.8)	13 (17.6)	
N stage (%)			
N0	65 (60.2)	47 (63.5)	0.843
N1	32 (29.6)	19 (25.7)	
N2	11 (10.2)	8 (10.8)	
Stage (%)			
I	5 (4.6)	4 (5.4)	0.972
II	66 (61.1)	45 (60.8)	
III	37 (34.3)	25 (33.8)	
Lymphovascular invasion			
No	71 (65.7)	47 (63.5)	0.757
Yes	37 (34.3)	28 (36.5)	
Perinoral invasion			
No	82 (75.9)	55 (74.3)	0.806
Yes	26 (24.1)	19 (25.7)	
Age (mean ± SD, range)	62±14 (24-88)	64±14 (31-83)	0.214
Tumor size (mean ± SD, range)	4.8±2.3 (1.8-12.5)	5±3.7 (1.1-31)	0.939
CEA	24.15±127.06 (0.2-1062)	7.94±15.93 (0.40-94)	0.861
BMI	26.92±4.46 (19-38.1)	27.06±4.36 (16.5-36.3)	0.733
Total number of lymph nodes removed	29±14 (12-90)	23±11 (12-58)	0.000
Number of positive lymph nodes	2±4 (0-21)	2±4 (0-17)	0.570
Clavian dindo			
I	21 (63.6)	12 (36.4)	0.983
II	33 (62.3)	20 (37.7)	
III	2 (66.7)	1 (33.3)	
Length of hospital stay	9±4 (4-41)	9±4 (5-22)	0.889

SD: Standard deviation, BMI: Body mass index, CEA: Carcinoembriogenic antigen

Table 2. Evaluation by Kaplan-Meier analysis according to right-sided colon cancer or left-sided colon cancer status

	2 years		5 years		Overall	
	SE	95% CI	SE	95% CI	SE	95% CI
RCC	122.094±3.467	(115.298-128.890)	106.811±4.748	(97.506-116.117)	96.286±4.876	(86.728-105.843)
LCC	124.597±3.572	(117.596-131.597)	111.347±5.138	(101.277-21.417)	99.479±5.703	(88.300-110.657)
Overall	123.382±2.528	(118.427-128.337)	108.906±3.519	(102.008-15.804)	97.274±3.744	(89.935-104.613)

RCC: Right-side colon cancer, LCC: Left-side colon cancer, SE: Estimate, CI: Confidence interval

Table 3. Univariate analysis for prognostic factor of 24 months, 60 months and overall survival after surgery for colon cancer

	Univarite analysis for 24 months overall survival		Univarite analysis for 60 months overall survival		Univarite analysis overall survival	
	OR (95.0% CI)	p	OR (95.0% CI)	p	OR (95.0% CI)	p
Age	1.047 (0999-1.096)	0.054	1.056 (1.024-1.089)	0.001*	1.036 (1.012-1.060)	0.003*
Gender	0.954 (0.340-2.681)	0.929	1.168 (0.616-2.214)	0.634	1.325 (0.787-2.230)	0.288
Tumor localization (right or left)	0.724 (0.247-2.118)	0.556	0.790 (0.408-1.527)	0.483	0.908 (0.532-1.552)	0.727
Tumor size	1.048 (0.930-1.180)	0.446	1.080 (1.008-1.157)	0.028*	1.064 (0.987-1.146)	0.106
T stage (over T2 stage T3 and T4)		0.070		0.046 0.675 0.131		0.072 0.202 0.053
			1.361 (0.322-5.747) 3.190 (0.707-14.403)		2.522 (0.609-10.454) 4.293 (0.981-18.781)	
Total number of lymph nodes	0.967 (0.914-1.023)	0.239	0.987 (0.954-1.020)	0.430	0.992 (0.965-1.019)	0.548
Pozitive lymph nodes	1.057 (0.962-1.161)	0.245	1.067 (1.006-1.131)	0.030*	1.061 (1.007-1.117)	0.025*
Lenfovaskuler invasion	1.175 (0.418-3.303)	0.759	1.414 (0.746-2.681)	0.288	1.033 (0.603-1.170)	0.905
Perinoral invasion	1.579 (0.540-4.622)	0.404	2.042 (1.056-3.951)	0.034*	2.199 (1.254-3.857)	0.006*

*p<0.05 indicates statistical significance, OR: Odds ratio, CI: Confidence interval

Table 4. Multivarite analysis for prognostic factor of 24 months. Sixty months and overall survival after surgery for colon cancer

	Multivarite analysis for 24 months overall survival		Multivarite analysis for 60 months overall survival		Multivarite analysis overall survival	
	OR (95.0% CI)	p	OR (95.0% CI)	p	OR (95.0% CI)	p
Age	1.048 (0.998-1.100)	0.062	1.053 (1.022-1.085)	0.001*	1.033 (1.010-1.056)	0.005*
Gender	0.826 (0.271-2.520)	0.737	1.133 (0.568-2.259)	0.723	1.212 (0.696-2.112)	0.497
Tumor lokalization (right or left)	0.422 (0.129-1.378)	0.422	0.488 (0.231-1.029)	0.060	0.709 (0.396-1.267)	0.246
Tumor size	1.045 (0.924-1.181)	0.483	1.086 (1.007-1.172)	0.033*	1.070 (0.992-1.155)	0.079
T stage (over T2, T3 and T4)		0.043		0.098 0.800 0.353		0.096 0.486 0.122
			0.825 (0.186-3.667) 2.179 (0.422-11.256)		1.674 (0.394-7.120) 3.375 (0.722-15.772)	
Total number of	0.946 (0.884-1.012)	0.104	0.975 (0.936-1.015)	0.215	0.983 (0.953-1.014)	0.277
Pozitive lymph nodes	1.049 (0.909-1.210)	0.515	1.054 (0.967-1.148)	0.231	1.061 (0.988-1.140)	0.105
Lenfovaskuler invasion	0.575 (0.147-2.250)	0.427	0.915 (0.413-2.026)	0.826	0.629 (0.321-1.231)	0.176
Perinoral invasion	1.149 (0.293-4.512)	0.842	1.740 (0.775-3.908)	0.180	1.905 (0.972-3.734)	0.060

OR: Odds ratio, CI: Confidence interval

past 5 years have shown that removing 12 or more lymph nodes leads to better survival outcomes by providing more accurate staging and better informing postoperative treatment decisions.[18] Removing 12 or more lymph nodes provides more accurate staging and allows for better determination of treatment strategies.[19]When comparing RCC and LCC, lymph node removal was found to be equally important in both groups. This finding emphasizes that meticulous lymph node dissection during surgery can improve long-term outcomes for patients.[20] In our review, the number of lymph nodes removed was significantly higher in RCC compared with LCC, which aligned with findings from other studies suggesting that this was due to differences in surgical approaches or more advanced disease stages in RCC.

Two- and 5-year overall survival rates are critical metrics in assessing the success of colon cancer treatment. Studies comparing survival rates between RCC and LCC have yielded

mixed results.[21] Some research suggests that patients with LCC have higher survival rates, with 2-year survival rates ranging from 70-75% in patients with RCC and up to 75-80% in patients with LCC. These differences can be attributed to the fact that RCC is generally diagnosed at more advanced stages and is associated with a worse prognosis.[3] However, in our study, no significant difference in 2-year survival rates between RCC and LCC was observed. Similarly, 5-year overall survival rates have been reported with variation in the literature. Some studies suggest that 5-year survival rates are approximately 55-60% for RCC and 60-65% for LCC.[22] The lower survival rates in RCC can be explained by its tendency to be diagnosed at later stages and its more aggressive biological behavior. However, in our study, no significant difference in 5-year survival rates between RCC and LCC was found. These findings suggest that despite the distinct clinical and pathological characteristics of right- and left-sided colon cancers, survival rates may be similar between the two.[23] This highlights the importance of early diagnosis and personalized treatment strategies in both cancer types.[16]

Some studies in the literature have proposed that RCC may have a more aggressive course and that patients with RCC may require closer monitoring and more aggressive treatment.[11] However, the lack of such a distinction in our study suggests that larger-scale prospective studies are necessary. Particularly in RCC, factors such as peritoneal dissemination and advanced tumor penetration may significantly impact survival outcomes. Therefore, follow-up and additional treatment strategies should be carefully planned for patients with advanced-stage RCC. In conclusion, despite the clinical and pathological differences between RCC and LCC, the similar survival outcomes observed in our study emphasize the importance of multidisciplinary approaches and individualized treatment for both cancer types.

Study Limitations

This study has several limitations. Its retrospective design and single-center nature may limit the generalizability of the findings. While the sample size is substantial, a larger cohort would allow for more robust analyses and stronger statistical power. Additionally, variability in follow-up duration and missing clinical and pathological data may influence the accuracy of the results. The study lacked molecular and genetic data, which are crucial for a more comprehensive understanding of CRC subtypes, particularly regarding microsatellite instability-high (MSI-H) and BRAF mutations. These mutations are known to have a negative impact on prognosis, and their absence from the analysis limits the study's ability to fully evaluate their roles in RCC and LCC outcomes. Treatment variability across patients and the absence of quality-of-life assessments also represent limitations. Furthermore, the evolving nature of treatment guidelines may affect the current applicability of the results. External validation through multicenter studies is necessary to strengthen the findings. Future research should aim to address these limitations by conducting prospective, multicenter studies with larger patient cohorts and incorporating comprehensive molecular profiling, including MSI-H and BRAF mutation analysis.

Conclusion

In conclusion, despite the well-documented clinical and pathological differences between RCC and LCC, our study found no significant difference in 2- and 5-year survival rates between the groups. This suggests that both RCC and LCC, though distinct entities in terms of presentation and pathophysiology, may have comparable oncological outcomes. These findings emphasize the importance of early diagnosis and individualized treatment strategies, regardless of tumor location. Additionally, the higher number of lymph nodes removed in RCC and its potential for more advanced tumor stages highlight the need for meticulous surgical techniques and close postoperative monitoring, particularly in patients with RCC. Future large-scale studies are warranted to further explore the role of factors such as peritoneal dissemination and tumor penetration in influencing survival outcomes in RCC, ensuring that tailored follow-up and treatment strategies are effectively implemented. Ultimately, a multidisciplinary approach remains crucial in optimizing care and improving long-term outcomes for all patients with CRC.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Koşuyolu Yüksek İhtisas Research and Training Hospital (approval number: 2020.4/23-325, dated: 08.05.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.U., M.D., S.G., A.O.S., Concept: M.T., E.P., A.S.S., A.O.S., Design: M.T., O.U., E.P., A.S.S., Ö.Ö., Data Collection or Processing: M.D., M.Di., Ö.Ö., Analysis or Interpretation: E.P., A.S.S., Literature Search: E.P., M.Di., A.O.S., Writing: M.T., S.G.

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RESEARCH ARTICLE

Prophylactic Sublay Mesh Placement During Stoma Closure to Prevent Incisional Hernias: a Pilot Study

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ABSTRACT

Introduction: There are many methods to prevent hernia following stoma closure; however, there is a lack of evidence of the efficacy of prophylactic sublay synthetic mesh placement. This study aimed to investigate the safety of sublay mesh placement during stoma closure.

Methods: Patients with rectal cancer who underwent stoma closure with prophylactic sublay mesh placement following low anterior resection at N.N. Blokhin Cancer Research Center between June and July 2023 were included in this pilot study. The inclusion criteria were age 18-75, TNM stage I-III, and written informed consent. The exclusion criteria included patients with synchronous and metachronous cancers, human immunodeficiency virus, an Eastern Cooperative Oncology Group score of >2, and those undergoing chemotherapy. The sublay mesh placement technique was used, with the endpoints being surgical site infection rate at 30 days, operative time, mesh placement time, and postoperative morbidity (Clavien-Dindo classification).

Results: Ten patients were included in the study. Among them, one patient (10%) had a postoperative surgical site infection, which did not require mesh removal. There was no other morbidity. The median operative time was 105.5 min, whereas the median mesh placement time was 25.5 min.

Conclusion: A low surgical site infection rate makes it possible to consider preventive sublay mesh placement during stoma closure. We initiated a prospective randomized clinical trial after this pilot study (ClinicalTrials.gov, NCT05939687).

Keywords: Hernia, stoma closure, sublay mesh, rectal cancer

Introduction

Up to 20-40% of patients suffer from incisional hernias following stoma closure.[1-3] Approximately 20% of patients require surgical repair of parastomal hernia.[4] There exist many methods to prevent this complication, but there is a lack of evidence of the efficacy of prophylactic sublay mesh placement. The main reasons for the reluctance to use synthetic meshes are increased risk of surgical site infection and the risk of mesh removal in this case.[5] Only one randomized controlled trial on prophylactic biological mesh stoma site reinforcement has been reported, in which the hernia rate at 2 years was 12% in the mesh group and 20% in the control group [odds ratio (OR): 0.62; 95% confidence interval: 0.43-0.90; p=0.012].[6] However, biological mesh is expensive and the inlay method used in the above study may be difficult to reproduce.

Synthetic meshes are more widely available, but no randomized clinical trials have been published on their efficacy in stoma site reinforcement. Not only is the choice of mesh a matter of debate but also the method of placement. The onlay method is considered to be associated with increased surgical site infection risk when used at the stoma site, whereas the sublay method is technically more challenging.[7]

A lack of evidence-based data on the efficacy of mesh placement in patients who underwent stoma closure makes further study of this topic important. The aim of the present research was thus to investigate the safety of sublay mesh placement during stoma closure.

Materials and Methods

In this pilot study, we recruited patients who underwent ileostomy or colostomy closure and prophylactic sublay mesh placement following low anterior resection (open or laparoscopic) for rectal cancer at N.N. Blokhin Cancer Research

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Center between June and July 2023. We included patients aged 18-75 years with stage I-III disease. Written informed consent was a prerequisite for patient inclusion in the study. The study was approved by the N.N. Blokhin Cancer Research Center Ethics Committee (approval number: 35981, date: 16.11.2023). Exclusion criteria were synchronous and metachronous cancers, human immunodeficiency virus, and an Eastern Cooperative Oncology Group score of >2. Patients undergoing chemotherapy were also excluded.

The mesh placement technique in all these cases was as follows. Following colostomy closure, the hernia sack was removed. The space between rectus abdominis muscle and posterior rectus sheath was then opened. Following this, the anterior and posterior rectus sheath were divided before the posterior rectus sheath was sutured. Prior to sublay mesh placement, the size was adjusted according to the available space, with the minimal margin =3 cm. Anterior rectus sheath and skin were also sutured (Figures 1-3).

The primary endpoint was surgical site infection rate at 30 days, whereas the secondary endpoints were operative time, mesh placement time, and postoperative complication rate (Clavien-Dindo classification).

We arbitrarily decided to include 10 patients in the pilot study and deemed that the method would be considered safe for further investigation if the surgical site infection rate was no more than 20% and there were no cases of mesh removal.

Statistical Analysis

Statistical analysis was performed using the SPSS program (IBM SPSS Statistics 26).

Results

Patient characteristics that could affect the prognosis are presented in Table 1. The median age was 61.5 years (range: 45-74). Only one patient had diabetes mellitus and one patient had an American Society of Anaesthesiologists classification of class II. Transrectal stoma placement was used in nine patients and lateral pararectal in one. The median body mass index was 25.05 kg/m^2 (range: 19.2-38.0 kg/m^2). The median mesh size was 63 cm^2 (range: 58-66 cm^2), the median operative time was 105.5 min (range: 69-148 min), and the median mesh placement time was 25.5 min (range: 18-33 min).

One patient (10%) had a postoperative surgical site infection (Clavien-Dindo grade II), which was successfully managed using bedside wound care. There was no other morbidity.

The median follow-up was 10.8 months. No cases of incisional hernias were observed.

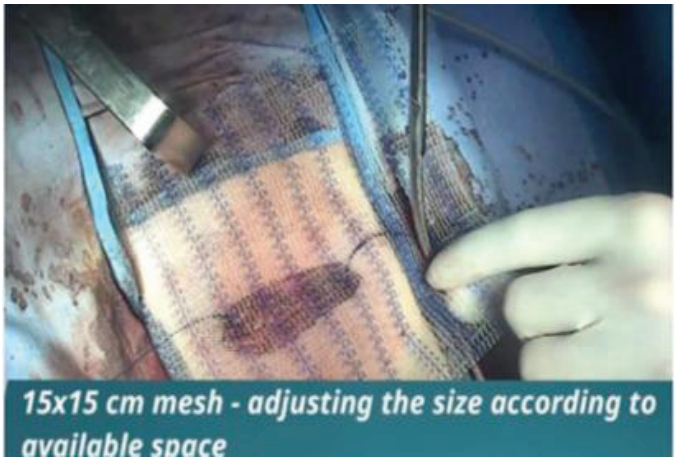

Figure 1. 15x15 cm mesh-adjusting the size according to avaliable space

Discussion

In this pilot study, no increased surgical site infection risk associated with synthetic mesh placement was observed. Mesh placement increased the operative time by 25.5 min. In a systematic review including six comparative studies, there was no significant difference in surgical site infection risk between groups with and without mesh placement (OR: 1.09, p=0.59).[1] The surgical technique was pre-peritoneal mesh

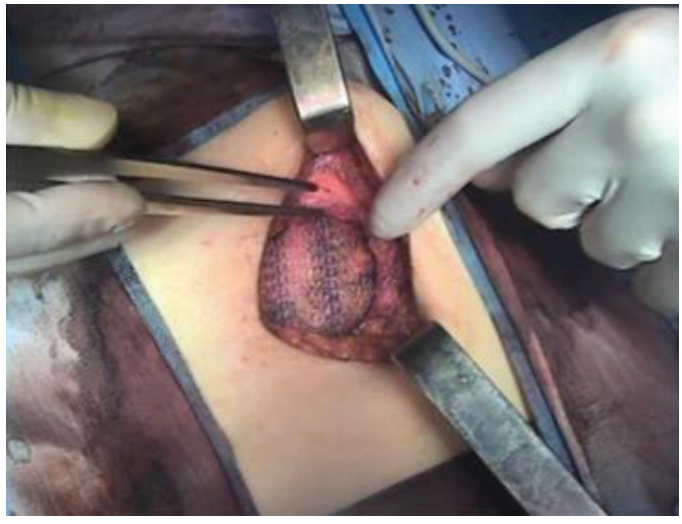

Figure 2. The sublay-installed mesh

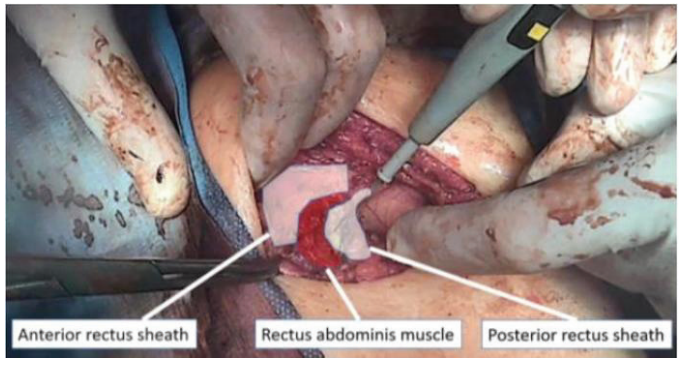

Figure 3. Opening of the space between rectus abdominis muscle and posterior rectus sheath

Table 1. Patient characteristics

Characteristic	Number of patients (n=10)	Percentage (%)
Gender		
•Women	5	50
•Men	5	50
Diabetes mellitus		
•Presence	1	10
•Absence	9	90
Eastern Cooperative Oncology Group score		
•0	7	70
•1	3	30
American Society of Anaesthesiologists classificaton		
•II	9	90
•III	1	10
Stoma type		
•Colostomy	6	60
•Ileostomy	4	40
Stoma placement		
•Transrectal	9	90
•Lateral pararectal	1	10
Surgical site infection		
•Presence	1	10
•Absence	10	100
Postoperative morbidity (Clavien-Dindo classification)		
•0	9	90
•I	0	0
•II	1	10

placement in 59.5% of patients, onlay placement in 23%, and sublay placement in 17.5%. In this review, mesh placement was associated with significantly increased operative time (mean difference: 47.78, p=0.02). In a blinded case-matched study conducted by Maggiori et al.,[8] there were no differences in the wound abscess rate between the sublay mesh placement group (30 patients) and the non-mesh group (64 patients) (7% vs. 5%; p=0.238).[8]

In a randomized clinical trial conducted by Bhangu et al.,[4] the authors observed an identical surgical site infection rate at 30 days in the mesh group (16%; 60/371 patients) and in the non-mesh group (13%; 49/369 patients) (p=0.32).[6]

A retrospective study conducted by Lee et al.[9] compared 15 (45.5%) patients who underwent mesh placement during ileostomy closure and 18 (54.5%) patients who underwent primary ileostomy closure. There were no cases of mesh removal due to mesh-related complications. Two patients (13.3%) in the mesh group and one patient (5.6%) in the primary closure group had a postoperative hernia (p=0.579).

In an unpaired case-control study involving 164 patients, hernia history of parastomal hernia was established as the main risk factor for future hernia development (OR: 5.90, 95% CI: 1.97-17.68).[10] Prophylactic mesh placement may need to be considered only in high-risk patients.

Study Limitations

The main strength of our research is that we used synthetic meshes, which are not well covered in the literature. The limitations of the study are the small sample size and the short follow-up; however, we believe that this was sufficient to determine the safety of the method in a pilot study.

In this pilot study, while we investigated the safety of synthetic mesh placement, the results should be confirmed through a prospective randomized clinical trial. Such a trial has been initiated based on the findings in this pilot study (ClinicalTrials.gov, NCT05939687).

Conclusion

In this pilot study, we obtained important data on the efficacy of sublay mesh placement in patients with rectal cancer who underwent stoma closure following low anterior resection. Prophylactic sublay mesh placement during stoma closure may reduce incisional hernia rates. The results of this research can be used for parastomal hernia prevention.

Ethics

Ethics Committee Approval: The study was approved by the N.N. Blokhin Cancer Research Center Ethics Committee (approval number: 35981, date: 16.11.2023).

Informed Consent: Written informed consent was a prerequisite for patient inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.G., N.M., Concept: S.G., Z.M., Design: S.G., Z.M., Data Collection or Processing: Y.B., Analysis or Interpretation: Y.B., Literature Search: Y.B., Writing: Y.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

The Relationship of Tumor-infiltrating Lymphocyte Ratio with Histopathological Parameters and Effect on Survival in Colorectal Cancers

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ABSTRACT

Introduction: Tumor lymphocyte infiltration demonstrates a positive effect on patient survival in breast cancer, melanoma, renal cell carcinoma, and lung cancer. This study aimed to elucidate the relationship between tumor-infiltrating lymphocyte (TIL) ratio and disease-free survival (DFS) and overall survival (OS) by considering localization, clinical and pathological features, microsatellite instability (MSI) status, mutation status, and demographic data.

Method: Patients (n=248) diagnosed with colorectal cancer stages 1, 2, and 3 were analyzed retrospectively. Patients with an Eastern Cooperative Oncology Group performance score of <2 were excluded. Clinical characteristics, age, gender, histopathologic features, TIL ratio, and carcinoembryonic antigen (CEA) level of the patients were recorded.

Results: Stage, CEA level, TIL ratio, N stage, T stage, and lymphovascular invasion were statistically significant. Early stage (p=0.019), low CEA level (p≤0.001), high TIL ratio (p=0.046), low N stage (p=0.004), low T stage (p=0.016), and absence of lymphovascular invasion (p=0.037 and p=0.046) were associated with longer DFS. Lymphovascular invasion, N stage, CEA levels, and TIL ratio were analyzed using multivariate analysis. According to the results, the hazard ratio (HR) for the TIL ratio was 1.68 (95% confidence interval (CI): 1.005-2.807; p=0.048), and the HR for the CEA level was 0.49 (95% CI: 0.293-0.846; p=0.01).

Conclusion: Regarding the outcomes of this research, the TIL ratio was found to be an effective indicator of DFS, confirmed via multivariate analysis to present a 32% reduction in the risk of recurrence/relapse. The TIL ratio was identified as a prognostic factor beyond the effects of stage, grade, lymphovascular invasion, CEA level, and MSI status. The current data provides substantial evidence to support the ratio's consideration in staging guidelines.

Keywords: Colorectal cancer, tumor-infiltrating lymphocytes, tumor immunology, immune response, prognostic factors

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the leading cause of mortality after lung cancer. Recent evidence indicates that the incidence of CRC, especially in the left colon and rectum, increases in the <50-years age group and decreases in older groups. Therefore, determining prognostic factors and developing new treatment modalities have gained importance, with the increasing use of individualized treatment. Although the etiopathogenesis is unknown, the disease is thought to develop secondary to genetic and environmental factors affecting the colonic mucosa.[1]

Modern immune surveillance theory emphasizes that the human immune system has the ability to detect and destroy tumor cells. In addition, this theory argues that tumor cells are not passive targets for the immune system; they can also escape and neutralize the person's immune system. This

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theory expresses the complexity of the interactions between tumor cells and immune system cells or their products.[2] It is estimated that the immune system cell, not the tumor cell, often dies due to these interactions. Many years ago, it was noted that lymphocytes-immune system cells-exist in varying numbers in malignant tumors. These lymphocytes were later defined as tumor-infiltrating lymphocytes (TILs).

These lymphocytes include antigen-specific B cells, natural killer cells, adaptive immune effector cells, and immune suppressor cells. These are the cells responsible for tumor cell killing and regression.[3] It was initially thought that these TILs indicated chronic inflammation in cancer. It was then later discussed whether TILs create a facilitating environment for cancer growth or whether they emerge as an immune response to cancer or supported prognosis. It was shown that the presence of TILs in the tumor region in advanced stages of diseases such as colon, breast, head, and neck cancers can extend the patient's life expectancy.[4]

Tumor lymphocyte infiltration demonstrates a positive effect on patient survival in breast cancer, melanoma, renal cell carcinoma, and lung cancer. New therapies, such as immune system checkpoint inhibitors, have been introduced in clinical practice. The interaction between immune response and tumor cells plays a crucial role in tumor formation and spread in CRC.[5] Within the scope of this research, we aimed to elucidate the relationship between TIL ratio and disease-free survival (DFS) and overall survival (OS) by considering localization, clinical and pathological features, microsatellite instability (MSI) status, mutation status, and demographic data.

Materials and Method

Setting and Study Population

Patients (n=248) diagnosed with CRC stages 1, 2, and 3 admitted to the department of Internal Medicine, division of Medical Oncology outpatient clinic between 2017 and 2020 were included in this retrospective analysis. The files of the patients included in the study were retrospectively analyzed. Patients with an Eastern Cooperative Oncology Group performance score of <2 were excluded. Clinical characteristics, age, gender, histopathologic features, TIL ratio, and carcinoembryonic antigen (CEA) level of the patients were recorded.

Ethical Statement

All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee approval was granted (approval number: 2020/0216, date: 29.04.2020), while as this was a retrospective analysis, no informed consent was required from the participants.

Pathological Analysis

Disease stages of the patients at the time of diagnosis were recorded. Histological subtypes were grouped as mucinous and non-mucinous adeno cancer. Biopsy specimens of four patients with a stony ring component were included in the mucinous group if they had a mucinous component and in the non-mucinous group if they did not. Tumors were examined in three groups: grade 1, grade 2, and grade 3. Lymphovascular involvement, MSI status (MSI-high and MSI-stable), and T and N stages were obtained. Lymphocyte infiltration level (high and low) was recorded. As shown in Figure 1, the TIL ratio cut-off value was 10% in the preparations evaluated at the tumor invasive margin on hematoxylin-eosin 200x magnification. All TIL ratios ≥10% were recorded as high and those ≤10% as low.

Statistical Analysis

Data recording and statistical analysis were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY). Number, percentage, median, mean, and standard deviation were used as descriptive statistical terms to evaluate the data. The Kaplan-Meier method was used for DFS and OS analysis, and the log-rank test was used to determine

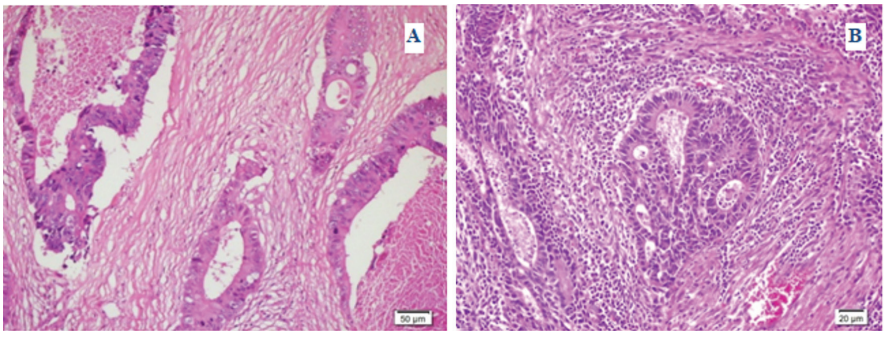


Figure 1. Hematoxylin-eosin 200x results. A: Low TIL (≤10%); B: High TIL (>10%)
TIL: Tumor-infiltrating lymphocyte

the relationship between prognostic factors and DFS. The MedicReS E-PICOS 21.3 program was used for Z-testing. Prognostic factors that showed statistical significance in the proportional hazards analysis test (Cox proportional hazards model) were re-evaluated via multivariate analysis. A p-value of <0.05 was accepted for statistical significance.

Here, G*Power 3.1.9.7 was used for the power analysis. The actual power of the study was calculated as 95% for categorical variables and 49% for censored variables. The required total number of events was 66. The power calculation for DFS was 0.5953, with a hazard ratio (HR) and 72 event count.

Results

Clinical and Pathological Characteristics of Patients

The mean age of the patients was 63.8±13.9 years. Regarding gender, 110 (44.4%) were women and 138 (55.6%) were men. The distribution of other parameters was as follows: Stage (stage 1: stage 2: stage 3-26:111:111 patients), location [right colon: left colon and rectum-81 (32.7%): 167 (67.3%)], CEA level [C0 (CEA<5 ng/mL): C1 (CEA>5 ng/mL) 166:82], grade (G1: G2: G3-37:206:5), histopathology (non-mucinous: mucinous-198:50), mismatch repair status (MSI-high: MSI-stable-23:151); TIL ratio (high: low-161:88), T stage (T1:T2:T3:T4-5:17:24:152:55), N stage (N0:N1:N2-141:76:31), lymphatic invasion (present: absent-69:163), vascular invasion (present: absent-36:196), neoadjuvant chemotherapy (no: yes-147:36), operated primary tumor (no: yes-16:232), adjuvant radiotherapy (no: yes-211:18), adjuvant chemotherapy (no: yes-107:141).

Occurrence of metastasis or recurrence appeared in 74 (29.7%) patients. Detailed clinical features, pathological features, and treatment regimens of the patients in relation to the TIL ratio are presented in Table 1. The median age in the low TIL ratio group was 62, whereas the median age in the high TIL ratio group was 66 (p=0.061).

OS and DFS Outcomes

Of the 248 patients included in the study, the DFS and OS of 32 (12.8%) deceased. The median OS was 102 months. Among the 248 patients, 44 developed metastasis and 30 experienced recurrence. The median time to recurrence and metastasis was 55 months.

OS and DFS Results by TIL Ratio

The number of patients in the low TIL ratio group was 88, and 32 (36.3%) of these patients progressed. In the high TIL ratio group, the number of patients was 160, and 42 (26%) of these patients progressed. While the median OS was not reached in the high TIL ratio group, it was found to be 89 months in the low TIL ratio group. The difference between OS and TIL ratios was not statistically significant. The median DFS was 138 months in the high TIL ratio group and 49 months in the low TIL ratio group. A statistically significant relationship was found between DFS and TIL ratio (p=0.046) (Graph 1) (Table 2).

In summary, the effect of prognostic factors on survival time was calculated. Here, disease stage, CEA level, TIL ratio, N stage, T stage, and lymphovascular invasion were statistically significant. Early stage (p=0.019), low CEA level (p<0.001), high TIL ratio (p=0.046), low N stage (p=0.004), low T stage (p=0.016), and absence of lymphovascular invasion (p=0.037 and p=0.046) were associated with longer DFS.

Lymphovascular invasion, N stage, CEA levels, and TIL ratio were analyzed using multivariate analysis. According to the results, the HR for the TIL ratio was 1.68 (95% confidence interval (CI): 1.005-2.807; p=0.048), and the HR for the CEA level was 0.49 (95% CI: 0.293-0.846; p=0.01).

Discussion

CRCs are diagnosed at earlier stages with the implementation of screening programs. In addition to the classical TNM staging, CRC is classified into high- and low-risk groups for treatment decision-making, treatment protocol, and duration. This risk grouping is based on prognostic markers such as lymphovascular invasion, lymph node status, differentiation status, MSI status, obstruction/perforation, and positive surgical margin.[6]

In current oncology, tumor immunity, the immune response of the organism, and the behavior pattern of the tumor are still part of the process in terms of both treatment and prognosis. Indeed, studies have shown that peritumoral lymphocytic reaction against CRC and TIL ratio are associated with prolonged survival in patients. This may be an indicator of the host's immune response. However, no consensus has been reached in the literature on the prognostic evaluation of the TIL ratio, and it has not yet been included in the guidelines. The reasons for this may be the lack of a sufficient number of studies, different levels of TIL ratio in the studies, and different localizations of TIL ratio in pathological evaluation.[7] When we reviewed the literature, Pagès et al.[8] suggested that the infiltrative growth pattern at the invasive tumor border was a significant independent prognostic factor for patients with CRC. Fuchs et al.[9] compared peritumoral lymphocyte infiltration with intraepithelial lymphocyte infiltration and showed that peritumoral infiltration was superior in survival analysis. The authors used the International Tumor Infiltrating Lymphocytes Working Group system for investigations involving CRC. Based on these studies, the current study examined TIL ratio levels at the tumor invasive margin.

In many types of cancer, intra- and extra-tumoral lymphocytic infiltration is the organism's response to newly emerging

Table 1. The relationship between TIL ratio and other prognostic factors

			TIL ratio						
	Total (n=248)		**Low (<10%) TIL ratio (n=88)**		**High (>10%) TIL ratio (n=160)**			
		n	%	n	%	n	%	p-value	1-β
Sex	Men	138	55.6%	50	56.8%	88	55.0%	NS	
	Women	110	44.4%	38	43.2%	72	45.0%		
Diagnosis age	<65	125	50.4%	49	36.2%	76	60.8%	NS	
	>65	123	49.6%	39	31.7%	84	68.3%		
ECOG performance scale	0	172	69.4%	68	77.3%	104	65.0%	0.045	0.55
	1	76	30.6%	20	22.7%	56	35.0%		
Stage	S1	26	10.5%	5	5.7%	21	13.1%	NS	
	S2	111	44.8%	43	48.9%	68	42.5%		
	S3	111	44.8%	40	45.5%	71	44.4%		
	S4	0	0.0%	0	0.0%	0	0.0%		
Histopathology	Non-mucinous	198	79.8%	68	77.3%	130	81.3%	NS	
	Mucinous	50	20.2%	20	22.7%	30	18.8%		
Grade	1	37	14.9%	10	11.4%	27	16.9%	NS	
	2	206	83.1%	75	85.2%	131	81.9%		
	3	5	2.0%	3	3.4%	2	1.3%		
Location	Right colon	81	32.7%	29	33.0%	52	32.5%	NS	
	Left colon	91	36.7%	34	38.6%	57	35.6%		
	Rectum	76	30.6%	25	28.4%	51	31.9%		
Lymphatic invasion	Absent	163	70.20%	63	38.6%	100	61.3%	NS	
	Yes	69	29.70%	25	36.2%	44	63.7%		
Vascular invasion	Absent	196	84.40%	75	38.2%	121	61.7%	NS	
	Yes	36	15.50%	13	36.1%	23	63.8%		
MSI status	MSI-stable	151	86.8%	55	88.7%	96	85.7%	NS	
	MSI-high	23	13.2%	7	11.3%	16	14.3%		
CEA levels	C0 (<5 mg/dL)	166	66.9%	56	63.6%	110	68.8%	NS	
	C1 (>5 mg/dL)	82	33.1%	32	36.4%	50	31.3%		
Neoadjuvant chemotherapy	No	147	80.3%	49	79.0%	100	82.6%	NS	
	Yes	36	19.7%	13	21.0%	21	17.4%		
Operated primary tumor	No	16	6.5%	5	5.7%	11	6.9%	NS	
	Yes	232	93.5%	83	94.3%	149	93.1%		
Adjuvant radiotherapy	No	211	92.1%	49	79.0%	98	81.0%		
	Yes	18	7.9%	13	21.0%	23	19.0%		
Adjuvant chemotherapy	No	107	43.1%	8	10.0%	10	6.7%		
	Yes	141	56.9%	0	0.0%	0	0.0%		
Adjuvant chemotherapy type	Capecitabine plus oxaliplatin	99	70.2%	42	75.0%	57	67.1%		

Table 1. Continued

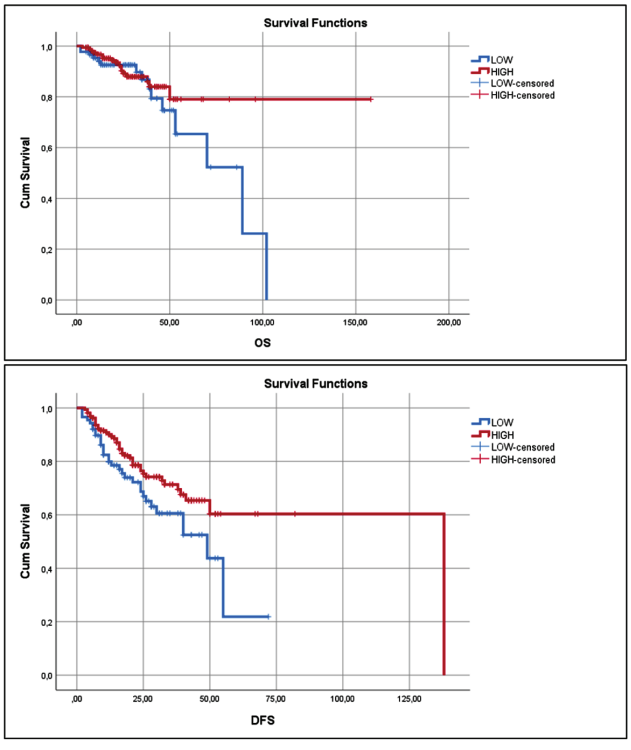
		TIL ratio							
	Total (n=248)		Low (<10%) TIL ratio (n=88)		High (>10%) TIL ratio (n=160)				
	5-fu, folinic acid plus oxaliplatin	9	6.4%	4	7.1%	5	5.9%		
	Capecitabine, 5-fu, folinic acid plus oxaliplatin	1	0.7%	1	1.8%	0	0.0%		
	Capecitabine only	27	19.1%	6	10.7%	21	24.7%	0.039	0.59
	Other	5	3.5%	3	5.4%	2	2.4%		
Mutation type	KRAS positive	16	51.6%	9	52.9%	7	50.0%	NS	
	NRAS positive	2	6.5%	1	5.9%	1	7.1%		
	Wild	13	41.9%	7	41.2%	6	42.9%		

TIL: Tumor-infiltrating lymphocyte, NS: Not significant, ECOG: Eastern Cooperative Oncology Group, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen, KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog, NRAS: Neuroblastoma RAS Viral Oncogene Homolog

Table 2. TIL ratio and survival time

TIL	Number of patients	Number of patients who progressed (percentage)	p-value=0.046	OS median (months)	DFS median (months)
Low	88	32 (36.3%)		89	49
High	160	42 (26%)		Not reached	138

DFS: Disease-free survival, OS: Overall survival



Graph 1. Survival graph of TIL ratio (left to right: OS and DFS)
DFS: Disease-free survival, OS: Overall survival, TIL: Tumor-infiltrating lymphocyte

neoplastic formations. This plays an essential immunological role in tumor regression, and is, therefore, extremely important. Previous literature elaborated that significant lymphocytic infiltration in CRCs was associated with increased survival. Rubio et al.[10] found intense lymphocytic infiltration to be an excellent prognostic indicator in their study of 277 cases of anal squamous cell carcinomas. Similarly, according to Schumacher et al.[11], the presence of lymphocytes positively affects the prognosis in esophageal carcinomas. The opposite is also possible. Scott et al.[12] showed that systemic inflammatory effects in 106 cases of inoperable non-small cell lung tumors reduced the patients' quality of life and negatively affected the prognosis. McArdle et al.[13] emphasized that lymphocytes are a poor prognostic indicator in prostate cancers, as did Curiel et al.[14], albeit in a different tumor type, ovarian cancer.

In the present study, the patients' median DFS was 55 months, and their OS was 102 months. The 3-year DFS rate was 74.2%, and the 5-year DFS rate was 70.6%. In the MOSAIC study, the 5-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups, respectively, with a median follow-up of 37.9 months.[15] The median follow-up period in the NSABP C-07 study was 42.5 months. The 3-year DFS rates were 71.8% in

the FULV arm and 73.2% in the FLOX group.[16] The DFS rates in the present study were comparable with those of previous data.

In this study, prognostic factors such as stage, lymph node metastasis, lymph node invasion, vascular invasion, and CEA level significantly affected DFS. Despite evidence supporting the prognostic value of the TIL ratio, this indicator has not been widely adopted due to previous controversial results. Ogino et al.[17] found that the TIL ratio was less significantly associated with patient survival than the other three components for Crohn-like reaction, peritumoral reaction, intratumoral peri glandular reaction, and lymphocytic reaction score using TIL ratio. On the other hand, Klintrup et al.[18] found a significant association between invasive borderline low-grade inflammatory infiltration and poor survival in a study of 386 patients undergoing surgery for CRC. Roxburgh et al.[19] reported that the degree of TIL ratio was independently associated with cancer-specific survival in patients undergoing curative resection for CRC.

The results of the Cox regression analysis conducted by Huh et al.[20] confirmed that low TIL ratio grade was an independent predictor of poor OS in patients with CRC. Prall et al.[21] showed that patients with stage-III CRC with high tumor density CD8 cells showed significant survival compared with those with low tumor density. In the present study, TIL ratio was examined in two categories, and progression was seen in 42 of 160 patients in the high TIL ratio group, with a TIL ratio of >10%. In contrast, progression was seen in 32 of 88 patients in the low TIL ratio group. This was statistically significant in the DFS curves (p=0.046). The median time to progression was 138 months for the high TIL ratio group and 49 months for the low TIL ratio group. Furthermore, 17% of patients in the low TIL ratio group and 10.6% in the high TIL ratio group died. In terms of OS, the median time was not reached in the high TIL ratio group, whereas it was 89 months in the low TIL ratio group. While the high TIL ratio group was associated with better survival in the OS analysis, it was not statistically significant. Few patients with death, differences in treatment regimens, and follow-up duration may be why the difference found in DFS could not be demonstrated in the case of OS.

Based on multivariate analysis, lymphovascular invasion, lymph node stage, CEA level, and TIL ratio were analyzed in terms of DFS. Here, CEA level and TIL ratio reached statistical significance regarding DFS. The HR for TIL ratio was 1.68 (95% CI: 1.005-2.807), with a risk reduction of 32% (p=0.048). The HR for CEA level was 0.498 (95% CI: 0.293-0.846; p=0.01). Statistical significance was not achieved in the other parameters. The lack of significance in multivariate analysis for parameters found to be significant in univariate analysis may be because of the poor prognostic effect or due to the low number of patients.

In this study, the prognostic effect of lymphocyte infiltration was statistically significant in DFS analysis (p=0.046). Its effectiveness in terms of survival could not be demonstrated due to the extended follow-up period required. We believe that lymphocyte infiltration around the tumor has a prognostic feature in CRCs. Immune response to tumors is effective in controlling the disease in CRC, the treatment options of which are mostly limited to chemotherapy. The present study found a 32% reduction in the risk of recurrence and relapse in the group with a high TIL ratio. Enhancing the immune response with immunotherapy treatments may have promising effects in adjuvant and metastatic diseases.

Study Limitations

The main limitation of this research is its relatively small sample size. Additionally, some of the patient files could not be obtained due to the study's retrospective nature.

Conclusion

Regarding the outcomes of this research, the TIL ratio was found to be an effective indicator of DFS, confirmed via multivariate analysis as presenting a 32% reduction in the risk of recurrence-relapse. The TIL ratio was identified as a prognostic factor beyond the effects of stage, grade, lymphovascular invasion, CEA level, and MSI status. The current data provides substantial evidence to support the ratio's consideration in staging guidelines.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee approval was granted (approval number: 2020/0216, date: 29.04.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., S.A.E., Ö.D., Concept: İ.S.O., M.G., Design: İ.S.O., S.A.E., M.G., Data Collection or Processing: İ.S.O., A.T., Analysis or Interpretation: İ.S.O., Ö.D., M.G., Literature Search: İ.S.O., A.T., Writing: İ.S.O., S.A.E.

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CASE REPORT

Intussusception Secondary to Metastatic Bladder Leiomyosarcoma: a Case Report and Review of the Literature

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ABSTRACT

Intussusception, where one intestinal segment telescopes into another, is rare in adults, representing 5% of all intussusception cases and 1% of bowel obstructions. This case details a 57-year-old man with primary bladder leiomyosarcoma metastatic to the liver, presenting with severe abdominal pain, nausea, and vomiting. A computed tomography scan suggested intussusception and bowel obstruction. An emergent laparotomy revealed small intestine intussusception. The affected segment was resected, and histopathology confirmed metastatic leiomyosarcoma. The patient recovered uneventfully and was discharged. This case highlights the importance of prompt diagnosis and treatment in adults with bowel obstruction and a cancer history.

Keywords: Bladder, neoplasm, intestinal obstruction, intussusception, surgery

Introduction

Intussusception, the telescoping of a segment of the intestine into an adjacent segment, is a common cause of intestinal obstruction in children but is relatively rare in adults, accounting for 5% of all intussusception cases and 1% of adult bowel obstructions.[1] Adult intussusception often has a different etiology, clinical presentation, and treatment approach compared with pediatric cases.[2,3] Intussusception in adults is a rare but serious condition, often associated with a pathological lead point, such as a tumor.[4] The occurrence of intussusception in the context of metastatic bladder cancer is exceptionally rare. This case report aims to detail the presentation, diagnosis, and management of a 57-year-old man in this unusual clinical scenario.

In contrast to pediatric cases, where intussusception is typically considered idiopathic, adult intussusception frequently has an identifiable pathological lead point. Among adult patients, neoplasms, both benign and malignant, represent the most common cause, accounting for approximately 30-50% of cases. Other etiologies include inflammatory lesions, postoperative adhesions, and idiopathic factors, while the clinical presentation of intussusception in adults is often non-specific and chronic, leading to delayed diagnosis.[5]

The most common symptoms are intermittent abdominal pain, nausea, vomiting, and, occasionally, gastrointestinal bleeding. The non-specific nature of these symptoms often results in a diagnostic process that may be complicated by several other gastrointestinal conditions that present with similar symptomatology.[6]

Imaging studies play a critical role in the diagnosis of intussusception in adults. Computed tomography (CT) scanning is the most sensitive and specific modality, often demonstrating the characteristic "target" or "sausage" mass.[7] Ultrasonography and magnetic resonance imaging may also be useful, particularly in cases where CT is contraindicated. Surgical intervention is the primary treatment for intussusception in adults because of the high likelihood that there is an underlying pathologic focus.[1]

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The affected segment of the intestine is typically resected to treat both the obstruction and the possible malignancy. Unlike pediatric cases, non-operative reduction of adult intussusception is rarely attempted due to the risk of perforation and the frequent presence of a pathologic stricture. The prognosis of adult intussusception depends largely on the underlying cause. Benign etiologies have a favorable prognosis following surgical intervention. Malignant etiologies require further oncologic management and have a variable prognosis depending on the stage and type of cancer. To improve outcomes, early diagnosis and intervention are essential.

Case Report

Clinical Findings

The patient was a 57-year-old man who had received chemotherapy and radiotherapy for advanced bladder cancer (primary leiomyosarcoma of the bladder with metastasis to the liver). No history of previous abdominal surgery existed. The patient presented to the emergency department with severe abdominal pain, nausea, and vomiting, which had persisted for 24 hours. Physical examination revealed a distended abdomen with generalized tenderness and signs of peritonitis. The patient exhibited cachexia, and multiple metastatic lesions were palpable beneath the skin. These findings collectively suggested that the obstruction may be due to a malignant obstructive mass.

Diagnostic Assessment

Laboratory Tests: Laboratory tests indicated the presence of anemia, chronic renal failure, and elevated acute phase reactants.

Imaging: An abdominal CT scan without intravenous contrast revealed a target-like mass suggestive of intussusception, accompanied by evidence of bowel obstruction (Figure 1). The presence of extensive metastases in the liver and lung was indicative of advanced disease.

Surgery

An emergent exploratory laparotomy was performed, revealing an intussusception involving the small intestine (Figure 2). The intussuscepted segment was resected, and a primary anastomosis was performed. Intraoperative findings confirmed a mural mass at the lead point of the intussusception, which was sent for histopathological examination. The remaining bowel segments were grossly normal. The intussuscepted segment was successfully manually reduced, as demonstrated in the accompanying video (Video 1).

Follow-Up and Outcomes

Postoperative recovery was uneventful. Histopathology confirmed the presence of metastatic leiomyosarcoma at the lead point of the intussusception. The patient was discharged

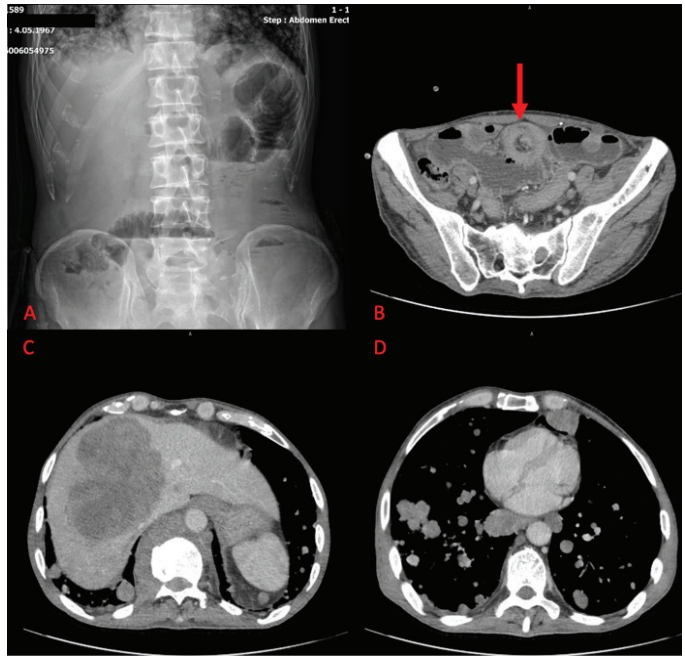

Figure 1. The air-fluid levels are observed at the level of the small intestine (A). The "target" finding on the CT scan is indicated by the arrow (B). The presence of liver metastases is evident (C). Widespread lung metastases are also observed (D)
CT: Computed tomography

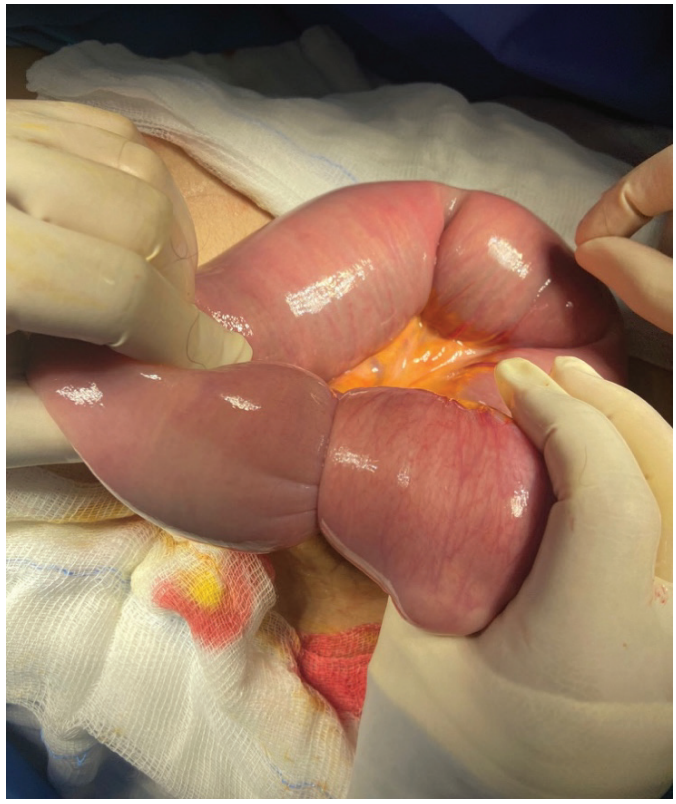

Figure 2. The condition of intussusception was observed in the small bowel segments. The image of a mass located within the lumen just distal to the area of interest is shown by an arrow

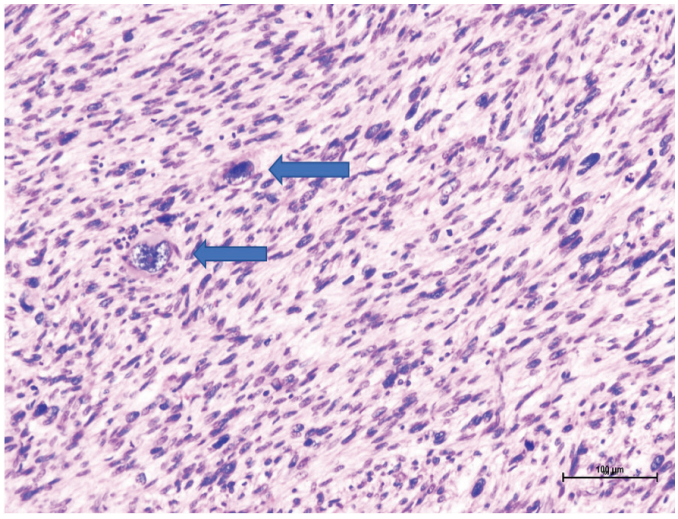

Figure 3. The spindle cells display moderate atypia, exhibiting eosinophilic cytoplasm and blunt edges. Additionally, the sample contains atypical cells with bizarre nuclei and prominent eosinophilic nucleoli (blue arrow) (H-E X200)

on postoperative day 7 and referred back to oncology for further management of metastatic disease. A pathological examination of multiple lesions in the small intestine, including the tumor causing the intussusception, revealed findings compatible with leiomyosarcoma (Figure 3).

Discussion

Intussusception in adults is rare and often presents with nonspecific symptoms, leading to delays in diagnosis.[8] The underlying causes are usually pathological, with malignant tumors being the most common in adults. In this case, the intussusception was secondary to metastatic bladder cancer, a highly unusual cause.

The diagnosis was facilitated by imaging, which remains the cornerstone in identifying intussusception in adults. The treatment of choice is surgical intervention, both for relief of obstruction and for addressing the underlying pathology.[9] Intussusception, though rare, should be considered as a potential diagnosis, and prompt surgical management can lead to favorable outcomes.[10]

Laparoscopy represents an effective option for the management of intussusception, particularly in cases where the obstruction is partial and the bowel is not significantly distended.[11] In instances where minimal or no bowel distension is observed, the likelihood of injury during laparoscopic manipulation is diminished, thereby rendering it a more secure approach.[12] In scenarios where there are no indications of bowel strangulation or ischemia, laparoscopy can be regarded as a less invasive alternative to open surgery, contingent upon the patient's hemodynamic stability.[13] Nevertheless, in cases of severe sepsis or extensive peritonitis, open surgery is frequently the preferred option for its expedited and more regulated intervention.

This case study serves to illustrate the exceptional rarity of intussusception as a secondary phenomenon in the context of metastatic bladder leiomyosarcoma. Leiomyosarcoma, a malignant neoplasm of smooth muscle tissue, accounts for only 0.1% of all adult malignancies and rarely metastasizes to the gastrointestinal tract.[14] The natural history of leiomyosarcoma is typified by aggressive local invasion and a proclivity for hematogenous dissemination, most commonly to the liver and lungs, as opposed to lymphatic dissemination. The atypical presentation of metastatic leiomyosarcoma causing intussusception highlights the importance of maintaining high clinical vigilance and utilizing comprehensive diagnostic imaging in patients with a history of malignancy who present with acute abdominal symptoms.

Furthermore, this case presents the possibility of a syndrome involving multiple primary leiomyosarcomas at disparate anatomical sites. The presence of primary leiomyosarcoma in both the bladder and the small intestine indicates the possibility of a systemic predisposition to the development of smooth muscle tumors. Although leiomyosarcomas are rare and typically singular, the occurrence of multiple primaries may indicate an underlying genetic or molecular syndrome predisposing to widespread smooth muscle neoplasia. This case serves to illustrate the complex interplay between rare malignancies and atypical clinical presentations, thereby reinforcing the importance of considering a broad differential diagnosis in similar clinical scenarios.

Acknowledgement

This case report has been structured according to the CARE guidelines, ensuring comprehensive and standardized reporting.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report, including any accompanying images or data. The patient was informed that their identity would remain confidential and that no personal details would be disclosed.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.S.S., İ.O.K., Concept: İ.O.K., Design: M.S.S., İ.O.K., Data Collection or Processing: M.S.S., E.P.E., Analysis or Interpretation: M.S.S., İ.O.K., E.P.E., Literature Search: M.S.S., Writing: M.S.S., İ.O.K., E.P.E.

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Video 1. The intussuscepted segment was successfully manually reduced, as demonstrated in the accompanying video (https://youtube.com/shorts/s9Su4n8KX0k)

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LETTER TO THE EDITOR

Refining the Triangle Advancement Flap Technique for Pilonidal Sinus Disease: a Commentary on Kiziltoprak et al.

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Keywords: Pilonidal, sinus disease, triangular flap technique

Dear Editor,

We appreciate the thoughtful article by Kızıltoprak et al.,[1] which explores the use of a triangle advancement flap in managing pilonidal sinus disease (PSD). The authors deserve commendation for their innovative approach; however, there are opportunities to further refine their technique and strengthen their manuscript.

The authors correctly highlight the importance of tailoring tissue resection and note that midline scars contribute to high recurrence rates. However, upon reviewing Figures 3 and 4 of their article, we observed that the distal edge of the flap is positioned in the midline. This placement is problematic, as Kaplan et al.[2] compellingly demonstrated that maintaining a 2 cm distance from the midline reduces healing complications and recurrence. Adjusting the lower tip of the triangle flap by 2 cm to the recipient side would be a minimal modification with substantial benefits, effectively eliminating the risk of a midline scar and its consequences.[3]

The introduction of this paper would benefit from a more contemporary and evidence-based perspective. The incidence of PSD is indeed increasing in developed countries, but attributing this solely to race is unfounded. The geographical location as well as epigenetic and genetic factors appear to play a more significant role.[4,5] Although obesity is frequently cited as a risk factor, robust evidence supporting its direct link to PSD is limited. The 1953 study by Dwight and Maloy[6] which identified a statistically significant difference in body weight between patients with PSD and controls, remains one of the few studies to report this association. However, subsequent research has not consistently corroborated these findings.

Prolonged sitting has also been suggested as a potential risk factor for PSD, but its role remains speculative. The assumption that young males aged 15-30 are more sedentary than other demographic groups lacks empirical support and risks perpetuating stereotypes. Similarly, the notion of a deep natal cleft as a risk factor, as suggested by Akinci et al.,[7] warrants scrutiny. Although PSD is often found in the natal cleft, the deepest part of the cleft near the anus rarely develops PSD, challenging the hypothesis that cleft depth is a significant risk factor.

The attribution of PSD to inadequate local hygiene is also problematic, as it is not substantiated by evidence and may stigmatize patients. If contamination by fecal material were causative, individuals in diaper-wearing age groups would show higher incidence rates of PSD. However, these groups demonstrate some of the lowest recurrence rates, undermining this theory.[8]

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It is critical to refrain from reiterating unsubstantiated claims, as doing so undermines the otherwise strong merits of this well-written article. Finally, the analysis could be enhanced by generally correlating recurrence rates with time since surgery, providing a clearer understanding of the temporal dynamics of recurrence.

In conclusion, the triangle flap technique proposed by Kızıltoprak et al.,[1] is promising, but modifying the flap placement to avoid midline scarring and strengthening the introduction with scientifically robust evidence could significantly enhance the quality and impact of their research. By addressing these points, the authors can further solidify the value of their contribution to the field.

Footnotes

Authorship Contributions

Literature Search: M.M., Writing: D.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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