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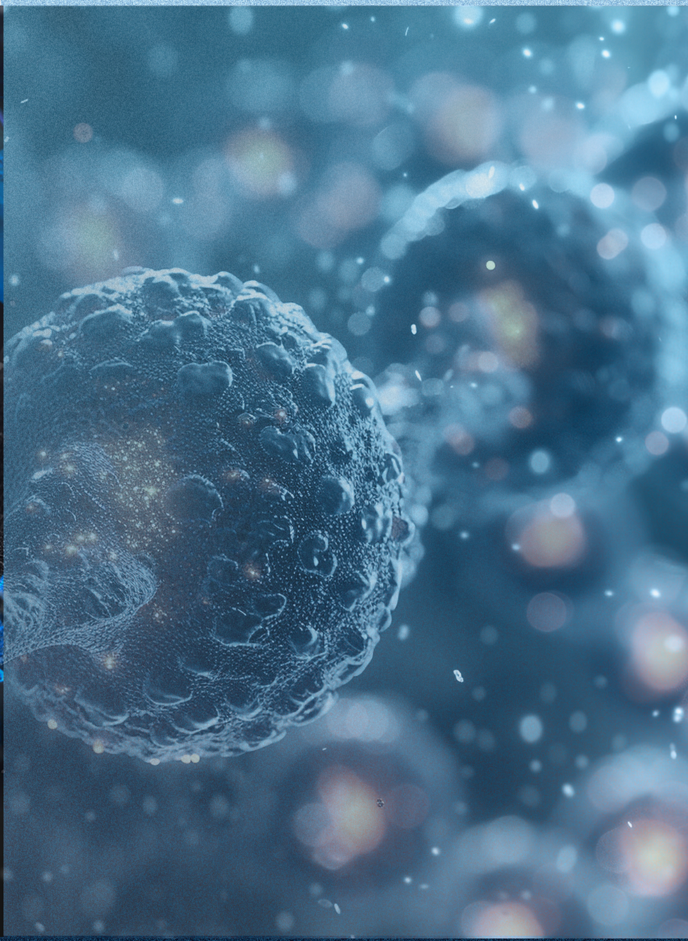

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REVIEW / DERLEME

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Reshaping Surgical Oncology: The Future Through Biology and Technology

Cerrahi Onkolojinin Yeniden Şekillenmesi: Biyoloji ve Teknoloji Ekseninde Gelecek

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Abstract

The fundamental transformation in surgical oncology in recent years is characterized by the transition from the traditional extensive resection approach to personalized, biology-based approaches. This transition has been made possible through the integration of knowledge from molecular biology, advanced imaging techniques, artificial intelligence-based analyses, and robotic systems into surgical decision-making processes. The modern surgical oncologist is no longer merely a technical operator but a decision-maker who interprets multidisciplinary data and develops patient-specific strategies. Biomarkers, such as circulating tumor DNA, together with minimally invasive techniques and intraoperative navigation systems, provide a scientific basis for the scope and timing of surgery. In the future, the effective synthesis of these technological and biological tools will pave the way for smarter surgical strategies that ensure oncological safety while preserving functional outcomes and become the standard.

Keywords: Surgical oncology, robotic surgery, artificial intelligence, molecular biology, personalized treatment

Öz

Cerrahi onkoloji alanında son dönemde yaşanan temel dönüşüm, geleneksel geniş rezeksiyon anlayışından biyolojik veriye dayalı kişiselleştirilmiş yaklaşımlara geçişle karakterize edilmektedir. Bu geçiş, moleküler biyolojiden elde edilen bilgilerin, gelişmiş görüntüleme tekniklerinin, yapay zeka tabanlı analizlerin ve robotik sistemlerin cerrahi karar süreçlerine entegrasyonu ile mümkün olmuştur. Modern cerrahi onkolog, artık yalnızca teknik bir uygulayıcı değil, bu çok disiplinli verileri yorumlayan ve hasta özelinde strateji geliştiren bir karar verici konumundadır. Dolaşımdaki tümör DNA'sı gibi biyobelirteçler, minimal invaziv teknikler ve intraoperatif navigasyon sistemleri, ameliyatın kapsamını ve zamanlamasını bilimsel temellere oturtmaktadır. Gelecekte, bu teknolojik ve biyolojik araçların etkin sentezi, fonksiyonel sonuçları korurken onkolojik güvenliği sağlayan daha akıllı cerrahi stratejilerin standart hale gelmesine zemin hazırlayacaktır.

Anahtar Kelimeler: Cerrahi onkoloji, robotik cerrahi, yapay zeka, moleküler biyoloji, kişiselleştirilmiş tedavi

Introduction

The transformation in surgical oncology over the past decade has led to a fundamental questioning of traditional approaches. Although the concept of "wider resection" in cancer treatment was often equated with success within the classical surgical paradigm, it is now recognized that this approach can cause unnecessary morbidity when it is not aligned with biological realities. The focus has now shifted to applying the "right resection" determined by tumor biology and patient-specific parameters (1). Modern surgical decision-making is shaped by molecular data, imaging techniques, and patient-centered factors at every stage, from treatment timing to the extent of

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surgery. This shifts the role of the surgeon from being merely a technical operator to becoming an interpreter of biological data and a strategy planner (2). In the redefinition of cancer surgery, the capacity for data analysis and the ability to integrate molecular biology into clinical practice are of central importance.

For instance, through biomarkers such as circulating tumor DNA (ctDNA), risks associated with minimal residual disease can be measured before or after surgery, thereby creating scientifically based rationales for increasing or decreasing the surgical scope (1). This approach enables decision-making based on each patient's biological behavior rather than on classical stage-based protocols. One of the most striking aspects here is that technology plays an active role not only during surgery but also in preoperative assessment and postoperative monitoring processes (3).

The integration of robotic systems has become an important part of this transformation. Robotic tools that enable minimally invasive interventions offer significant advantages, particularly in anatomically complex regions and tumor resections requiring precise maneuvers (4). Platforms such as the Da Vinci Surgical System enhance the surgeon's field of view three-dimensional during surgery, increase precision of movement, and reduce the risk of unnecessary tissue damage. Robotic technologies also contribute more reliably to determining correct resection boundaries by providing the surgeon with the capability to track anatomical details in real-time.

Historically, surgeons planned operations primarily on the basis of macroscopic anatomy, but today advanced imaging technologies and intraoperative navigation systems provide data support at every stage of surgery. The use of intraoperative magnetic resonance imaging (MRI) or computed tomography (CT) facilitates the precise identification of tumor boundaries and the preservation of healthy tissues (5). Thus, decisions about when and to what extent intervention is necessary become less subjective. This situation also increases the importance of multidisciplinary teams; coordinated work with medical oncologists, radiologists, and pathology specialists creates the foundation for more effective use of the data offered by technologies (2).

Taking the tumor microenvironment into account when determining surgical timing has become an increasingly common practice. The genetic profile of the tumor or the dynamics of the immune response can affect not only post-treatment prognosis but also the optimal timing of surgery. Risk predictions before surgery can be made by processing microenvironment data through artificial intelligence (AI)-based analyses (3). Moreover, supporting AI algorithms using deep learning (DL), computer vision, and natural language processing solutions enhances the safety of both clinical and surgical procedures. In this data-intensive environment, the surgeon's role is not merely to perform the operation; it is to read the appropriate algorithms, interpret outputs, and place them in clinical context.

The combined use of robotic systems and AI in complex oncological cases can be expected to improve outcomes. However, the optimal use of such technologies requires high experience beyond standard cases (2). For example, in challenging interventions such as vascular resection or combined thoracoabdominal approaches, the parameters affecting the decision are quite different; here, the surgeon must both understand biological processes and manage these in harmony with technology (2,4). Therefore, at the center of the modern surgical oncologist's profile is the accumulation of interdisciplinary knowledge; such a clinician must be competent both in recognizing tumor cells under the microscope and in planning the most efficient movement of the robotic arm in the operating room.

Personalized treatments are anticipated to reach near-standard levels. The creation of virtual models of organs or tumors through holograms or digital twin technologies is a natural extension of this process. Thus, different resection scenarios can be tested in a virtual environment before the patient undergoes surgery, and potential complications can be visualized. Additionally, communication infrastructures that provide high-speed connections such as 5G will clearly be preferred, particularly in remote surgical planning or training processes (6). High bandwidth and low-latency will facilitate real-time control of robotic operations.

In conclusion, what becomes clear at the introduction stage is this: In the new paradigm where cancer surgery is changing direction, the right resection is implemented not through technical proficiency alone but through the integration of molecular biology knowledge, advanced imaging support, and advanced technologies (1,2). It appears critical for the new generation of surgeons to develop their data-driven thinking skills and understand microenvironmental interactions. The steps taken along this path will lead to surgical strategies for cancer treatment that are more precise and more individualized.

Paradigm Shift in Surgical Oncology: From Where to Where?

Historical Development and Reasons

The historical process of cancer surgery has been shaped largely by the development of technical capacity and the deepening of biological knowledge about the disease. For many years, the dominant approach in surgical oncology was to remove tumor tissue along with the widest possible surrounding anatomical area. The assumption underlying this logic was that as the resection area increased, the risk of recurrence would decrease and survival would increase. However, this approach could produce negative outcomes, particularly the inability to preserve organ functions and high morbidity rates (1).

The past understanding favoring radical resection was also strengthened by limited imaging technologies and insufficient systemic treatment options. Surgeons made decisions and planned operations based on macroscopic anatomy, without support from microscopic or molecular data. However, advances in molecular biology, immunology, and imaging over the past thirty years have led to the questioning of this paradigm (7). Understanding cellular-level tumor heterogeneity has revealed that a one-size-fits-all surgical approach is not optimal for every patient. Biological diversity contained significant variability in terms of invasion pathways, metastatic potential, and response to treatment (8).

Among the reasons for this transformation is the increased effectiveness of systemic treatments. With chemotherapy, targeted agents, and immunotherapies, the surgical scope can be narrowed for some tumors. For instance, studies in gastric cancer have shown that routine removal of the omentum is not always necessary, prompting research into omentum-preserving approaches. Similarly, redefining the boundaries of lymphadenectomy in light of biological data has shown that unnecessary nodal dissections can be reduced. This places less physical burden on the patient and can shorten the recovery process (1).

With the development of technology, the surgical decision-making process has become more data-oriented. In the preoperative period, the location and spread pattern of the tumor can be determined in detail with advanced imaging systems, and real-time feedback can be obtained during surgery with intraoperative navigation technologies (3). AI algorithms produce clinically meaningful predictions from large datasets and provide the surgeon with additional information about which areas should be removed.

An examination of the historical process reveals another important factor: advances in communication infrastructure. 4G technology initially increased mobile data speeds, paving the way for early-stage virtual reality applications, while 5G has enabled new practices, such as low-latency remote surgery. This is important not only for overcoming geographical barriers but also for enabling multidisciplinary teams to collaborate simultaneously. Communication technologies have a share in the evolution of the paradigm, particularly in enabling international consultation in complex cases (6).

Economic factors have also played a role in the historical transformation. The problem of access created by high-cost treatments and technologies in low-resource regions has paved the way for a preference for minimally invasive yet effective surgical techniques and for equitable health policies (7). Since the capacity of health systems varies across different regions of the world, “right resection” has gained importance not only on biological grounds but also on socioeconomic grounds.

Another notable finding is the change in clinicians’ patient-centered thinking. In traditional models, surgical decisions were mostly based on tumor size and location; the current approach additionally takes into account the patient’s general condition, comorbidities, and the impact on quality of life. The trend toward avoiding aggressive surgery has increased, particularly in elderly patients or those with serious systemic diseases (8).

The widespread use of robotic systems throughout the process has also played a determinative role in the historical development. Platforms such as Da Vinci are not merely a technical innovation; they create new opportunities in strategic planning because they offer a working method that reduces the surgeon’s physical limitations (3). With advanced maneuverability and three-dimensional imaging support, precision in minimally invasive interventions improves. Thus, some of the extensive resections previously performed with open surgery can now be accomplished with smaller incisions.

The historical process of the paradigm shift can be regarded as a multi-layered movement arising from the combination of the deepening of scientific knowledge, the integration of technology, socioeconomic pressures, and the successes of systemic treatments. Surgical success, which was equated with the concept of “wider area” in the past, today is being replaced by the concept of “biologically appropriate right area” (1,7). The current approaches stated in section 1 gain meaning from this historical background because the change in criteria determining the scope of the procedure over time has redefined the identity of modern surgery.

What Does a Surgical Oncologist do Today?

Clinical Role and Research

In the modern surgical oncologist’s profile, clinical duties and scientific research activities constitute two fundamental areas that mutually reinforce each other. In daily practice, the surgical oncologist is beyond being a clinician who coordinates throughout the patient’s entire treatment process; they are a decision-maker who can interpret biological data and transform information from different disciplines into a single strategic plan (9). This function is reinforced by active leadership in multidisciplinary tumor councils because these environments enable the processing of information from fields such as medical oncology, radiation oncology, pathology, and genetics on common ground. Here, the surgical oncologist becomes not only the person planning the operation but also the main figure evaluating the harmony of biological and clinical parameters on a patient basis (7).

In research, the responsibilities of surgical oncologists are gradually expanding. The main goal in this field, ranging from the design and conduct of clinical studies to the organization of biobanks, is to make surgery biology-based (9). In particular, the collection of tissue samples and the provision of appropriate conditions for molecular analyses enable the identification of new biomarkers. Such studies strengthen treatment response predictions while also establishing a solid foundation for targeted therapies (10). Improved resolution of the complex biology of cancer can directly affect surgical timing; the effectiveness of neoadjuvant or adjuvant approaches is examined in this context, providing a scientific basis for the surgeon's decision to intervene.

Technology integration is an integral part of both clinical and research activities. Using imaging-guided surgical techniques to integrate preoperative data into intraoperative real-time navigation systems increases the accuracy of surgery (5). Fluorescence-guided resection or three-dimensional anatomical reconstructions allow a more precise determination of tumor boundaries. Additionally, AI-supported risk prediction models have the potential to optimize clinical decision processes by predicting postoperative complication likelihood in advance (3). The issue at this point is whether technology complements or directs the surgeon's decision-making ability because the data produced by algorithms always require interpretation appropriate to the clinical context.

One of the advantages of the multidisciplinary model is that it provides early access to experimental treatments. The transition process to the use of experimental agents can be faster in patients whose genetic profiles carry specific mutations; for instance, the integration of targeted drugs such as osimertinib in lung cancer patients carrying EGFR mutation into surgical planning increases survival (7). This demonstrates the importance of surgical oncologists' ability to incorporate pharmacogenomic knowledge into clinical procedures.

The biosocial medicine perspective also finds its place here. The patient's life story and sociocultural conditions, as much as their biological parameters, should be taken into account in the treatment plan (11). For example, among patients with socioeconomic constraints, minimally invasive interventions with shorter recovery periods may be preferred over aggressive surgeries requiring long-term hospitalization. Additionally, certain genetic variants observed in endemic regions may require adaptation of targeted protocols.

The effectiveness of the research direction is also measured by the knowledge transferred to younger surgeons. Programs that incorporate simulation-based learning, genetic counseling experience, and palliative care algorithms into the educational curriculum enable future surgical oncologists to reach a comprehensive skill set (9). Experts trained in this way will approach technical excellence in the operating room and will have the capacity to guide scientific research outside it.

Another dynamic observed in the clinic is an increase in data intensity. Genome sequencing, tumor microenvironment analyses, and ctDNA evaluations, when performed in the preoperative period, can shape not only post-treatment prognosis but also behavior during surgery (10). AI systems are employed to process this data rapidly; however, maintaining human oversight remains critical.

Finally, robotic platforms can be regarded as points where technology and biology merge. Robot-assisted systems offer high-precision movement capability while increasing safety in complex anatomies with three-dimensional imaging support (3). However, comprehensive training in the use of such devices; otherwise, it may not be possible to fully realize their advantages.

This multifaceted role and research identity, which can be seen as today's reflection of the historical change emphasized in section 2.1, place modern surgical oncologists in a different position than in the past. The concept of right resection is defined not only by technical skills at the operating table but also by the development of the ability to interpret data, the meaningful integration of molecular and genetic knowledge, and effective participation in the multidisciplinary ecosystem.

From Technical Surgeon to Biological Decision-maker

The technically focused approach that was dominant in cancer surgery in the past is today giving way to a decision-making process based on biological data that considers molecular and systemic integrity. The role of the surgical oncologist is no longer limited to that of a technician who merely performs the operations; it has evolved into a strategic role that determines the optimal timing and scope of intervention by integrating patient-specific biological parameters, the tumor's genetic profile, microenvironment dynamics, and data from multiple disciplines. At the foundation of this change lies the integration of AI-based analyses and advanced imaging techniques into preoperative preparation and intraoperative processes.

DL algorithms can analyze intraoperative CT or MRI data in real-time during surgery, enabling determination of the correct resection boundaries without damaging critical anatomical structures. The surgeon's area of responsibility now begins before surgery. During the preoperative period, the patient's electronic health record, biochemical indicators, and genomic data are jointly evaluated to predict surgical risk and prevent unnecessary interventions. Such risk predictions not only reduce complication rates but also affect clinical decisions across a wide spectrum from resource management to postoperative care planning (3).

One of the most prominent examples of the biological decision-making role is the analysis of ctDNA. For instance, in colorectal cancer patients at pathological T1 stage, the relationship between ctDNA positivity and lymph node metastasis has been clearly demonstrated; this finding can directly affect the surgeon's choice to perform additional resection or be satisfied with monitoring (1). In the operative field, the surgeon now considers not only anatomy but also the tumor's aggressiveness score and expected biological behavior. It has been shown that the aggressiveness score generated by AI works with higher accuracy than the TNM system in survival prediction; thus, the planned resection width is aligned with the tumor's biology (3). The practical equivalent of this approach is the prevention of unnecessary tissue loss and the increased preservation of organ function.

The survival advantage targeted by radical surgery in the past can also be achieved today with biologically optimized, minimally invasive applications. As multidisciplinary teamwork increases, surgical oncologists' decision-making is increasingly informed by external data. In regular tumor council meetings, pathology reports, molecular marker results (such as EGFR or ALK mutations), and advanced imaging findings can be evaluated at the same table to develop treatment plans specific to a single patient (7). Here, the task of the surgical oncologist is not only to receive this information but also to transform it into a tactical plan that uses this parametric information during surgery.

The role of technological platforms is undeniably significant. Robotic surgical systems are superior to classical manual techniques in both ergonomics and imaging depth. Particularly during resections near complex vascular structures, the precise movement capabilities of robotic arms minimize tissue damage, and the three-dimensional camera system enhances the surgeon's immediate visual assessment. AI-supported video analysis systems also have the potential to increase safety by detecting possible error risks in advance during the intraoperative phase (12).

One of the most striking components of the identity of the modern biological decision-maker is the integration of learning algorithms into operational strategies. Machine learning algorithms can simultaneously analyze different data types (image, genome sequence, proteomic data) and calculate complication probabilities from this information (4). Thus, the surgical oncologist has the flexibility to modify the surgical plan even while at the operating table; sudden developments, such as new mutation information revealed by biopsy results, can be immediately reflected in the surgical strategy.

In addition, surgical simulations and virtual training environments aim to develop the competence of biological decision-makers. Testing which resection is more appropriate in which biological situation in the preoperative period becomes possible through the trial of different tumor scenarios with digital twin technology (3). This approach offers young surgeons the opportunity to gain experience with different clinical variations. In the future, AI's capacity to analyze the microenvironment may lead to a redefinition of surgical timing. Correct modeling of factors such as tumor stromal structure or immune cell infiltration can show which moment is biologically more advantageous for intervention (10). Thus, individual timing windows can be created instead of classical protocols.

The clinical-research combination described in section 3.1 is elaborated here: the processes of generating scientific knowledge and developing technology become intertwined, and the ultimate goal is intervention at the right time and with the right scope. The shift from technique to biology requires not only expanding the professional skill set but also changing the mental framework. The surgical oncologist must now be able to scientifically explain not only which tissue to resect but also why that tissue should be resected. Molecular profile analysis, AI-based prediction systems, robotic precision, and multidisciplinary knowledge integration constitute the toolkit of this new identity (1,3). For the next generation of surgeons, the primary goal is not merely to eliminate the tumor but to achieve the most beneficial outcome in terms of quality of life and long-term prognosis.

Expanding Surgical Horizon with Technology

Robotics and AI

Robotic surgical systems and the integration of AI are effective tools for implementing the concept of "right resection" in cancer surgery. Particularly in anatomically complex regions, features offered by robotic systems such as three-dimensional vision, motion scaling, and tremor filtering increase the surgeon's precision during surgery (3). These technical advantages can preserve oncological safety by enabling complete tumor removal while reducing the morbidity associated with extensive resection. With motion scaling, millimetric maneuvers can be applied in regions close to vascular structures; an ergonomic working position helps the surgeon maintain concentration during long operations. This enables operations previously considered technically challenging to be performed using less invasive approaches.

AI brings a cognitive dimension to surgery beyond these mechanical advantages. Algorithms performing real-time image analysis can identify critical anatomical details during the intraoperative phase and provide instant alerts to the surgeon. For example, by processing super-resolution imaging data with AI, the boundary between normal and tumor tissue can be revealed much more clearly. This supports not only the complete removal of the tumor but also the preservation of surrounding healthy tissue. AI-based systems can also predict potential error risks by monitoring the intraoperative video stream, thereby reducing the likelihood of complications. The combination of AI and robotic navigation at different stages of surgery provides a seamless data flow from preoperative planning to postoperative evaluation (12).

Internet-based remote-access technologies enable these systems to eliminate geographical barriers, allowing experienced surgeons to provide consultation or guidance. This strengthens multidisciplinary decision-making processes at the international level, particularly for cases of rare tumors. From the perspective of integrating molecular biology data into surgical strategy, it is noteworthy that AI algorithms analyze genome sequencing results and histopathological data to produce risk scores (10). With these scores, classical TNM staging can be surpassed when determining resection boundaries; minimal or extensive resection decisions aligned with the tumor's biological behavior can be made (1). Thus, high rates of functional preservation are achieved without compromising oncological safety.

The simulation infrastructures offered by robotic platforms also play an important role in education (11). Through virtual reality-based scenarios, surgeons gain operational practice with different anatomical variations; during these sessions, AI-supported analyses identify potential error points or alternative maneuver routes. For inexperienced surgeons, these settings provide a safe environment for learning prior to actual surgery.

However, technology integration introduces certain limitations and topics for discussion. Robotic systems require high-cost investments and are not accessible in all hospital environments. Additionally, the data produced by AI algorithms need to be interpreted appropriately to the clinical context; otherwise, the risk of misguided strategies may arise (12). This risk decreases when used under the supervision of an experienced surgeon, but it is inappropriate for the algorithm alone to make the final decision. In this context, the human factor remains indispensable.

The ability of robotic systems to perform surgical planning on virtual models in the preoperative period enables testing the biological suitability of different resection scenarios (3). Using organ and tumor models created with digital twin technology, experiments are conducted to determine which interventions minimize loss of function or which conditions reduce the risk of recurrence. This approach strengthens the identity of the biological decision-maker mentioned in section 4 through technology.

In the postoperative period, AI-supported monitoring systems are employed. Recovery indicators and complication symptoms obtained from postoperative imaging data can be detected early (12). AI's rapid processing capacity is advantageous in these data-intensive analyses; however, it becomes meaningful only when combined with the clinician's evaluation.

In the future perspective, the robotic-AI combination with microenvironment information can be expected to form a new standard (10). Stromal structure analysis or immune cell distribution maps will enhance both technical capacity and biological predictive ability for determining the most appropriate intervention time. Thus, even the timing of the operation will be determined not by logistical factors alone but by molecular biology considerations.

In conclusion, robotic and AI-based applications are doing more than just providing technical convenience in surgical oncology; they are also becoming tools that encourage data-driven thinking (3,12). The surgeon is now becoming an expert defined not only by the sharpness of the scalpel in hand, but also by the problem-solving capacity of algorithms working alongside the surgeon and by the precision of the robotic arms. True "right resection" becomes possible through the controlled, scientifically appropriate, and harmonious use of these two forces.

Does Surgery Have a Future in Cancer, and How?

When discussing the future of cancer surgery, it is necessary to examine how elements formed by the paradigm shift from past to present will shape clinical and research practice. Today, operations planned with the "right resection" understanding are based not only on anatomical removal logic but also on the tumor's molecular characteristics, microenvironment interactions, and risk prediction models (1). In such a framework, the future of surgical oncology can preserve its raison d'être by relying on data-driven biological decision-making rather than on technical skill. If intervention can be performed for the right patient at the right time and to the right extent, surgery does not remain in the background against systemic treatments; on the contrary, it is positioned at the center of multidisciplinary integration (9).

In the future, robotic and AI systems are expected to improve the reliability of this decision-making process. The preservation of microstructures with the high precision of robot arms can prevent function loss while also preserving the advantage to be obtained with extensive resection in terms of survival (3). With three-dimensional image support, detailed viewing of the intraoperative wound area enables maneuvers that are limited by classical manual techniques. AI's production of dynamic risk scores during surgery by analyzing genomic data and histopathological findings can shape the surgeon's instant decisions on scientific ground (1). However, these technologies need to provide meaningful interpretations rather than raw data and to situate findings in a clinical context; otherwise, algorithmic outputs may remain disconnected from that context.

Ongoing studies on microenvironment analyses indicate that the timing factor in cancer surgery can be redefined (8). Changes in tumor stromal structure or immune cell infiltration patterns can provide clues about the risk of post-surgical recurrence, and it may be possible to determine whether early or late intervention is biologically more advantageous. In the development of these predictions, AI-based modeling and long-term follow-up of real patient data can be used together (3). Thus, moving away from classical protocols to create an optimized timing window for each patient is one of the factors strengthening the future position of surgery.

The surgical oncologist's identity will continue to transform internally. The expert of the future will be defined not only by the ability to perform surgery but also by the ability to integrate molecular biology into the clinical plan (9). This new generation of surgeons with high data reading capability will have the equipment to simultaneously analyze image and sensor data from robotic systems while applying information obtained from biomarkers such as ctDNA to surgical strategy (1). This requires educational curricula to focus not only on technical applications but also on understanding algorithm logic and developing data analysis capabilities.

The issue of access is also one of the topics for future discussion. Since robotic systems and advanced imaging technologies require costly investments, inequalities may grow if their use is not supported by equitable health service policies (4). In resource-limited regions, the principle of right resection should be implemented using minimally invasive yet highly effective techniques. Accordingly, research should address both high-technology solutions and optimization methods applicable in low-resource environments.

The power of multidisciplinary teamwork will become even more evident in the future. Thanks to tumor councils where different data types from genetic epithelial changes to proteomic analyses can be evaluated at the same table, surgical decisions will not be based solely on the knowledge set of a single discipline (7). The surgeon will assume the role of coordinator, becoming the person who transforms the information produced by different disciplines into an operational plan. This structure directly contributes to the realization of personalized treatment goals.

An examination of the research infrastructure reveals that there are still unresolved challenges. The design of high-quality prospective studies and reaching sufficient patient numbers still stand as serious obstacles (4). Due to limited clinical interest or insufficient surgeon participation, late validation of some potentially effective techniques may occur. Facilitating data collection through digital platforms and increasing sample sizes through international collaborations can be important steps in this regard.

Additionally, it will be critical to maintain the balance between technology and ethics. Issues such as data privacy, algorithmic bias, and responsibility boundaries should be clearly defined, particularly in AI-supported systems (3). If necessary regulations are not enacted in these areas, the rate of technology adoption may decrease, or clinical trust may be undermined.

Finally, in the new surgical paradigm shaped jointly by biology and technology, the goal should no longer be merely eliminating the tumor; it should be doing this while preserving the patient's quality of life and improving long-term prognosis (8). The concept of right resection is likely to persist in such a context: if both functional preservation and oncological safety can be achieved, surgery will continue to be an important step in modern cancer treatment. Technology integration, knowledge of molecular biology, and multidisciplinary thinking are fundamental components that will make this sustainable (3,9).

Conclusion

Developments in surgical oncology continue to transform the foundation of treatment approaches. In the future, cancer surgery will find direction not only through traditional methods based on anatomical removal, but also through the combination of technologies such as molecular biology, advanced imaging, and AI. This integration will enable the determination of the timing and scope of interventions appropriate to each patient's biological behavior.

The technical capabilities offered by robotic systems enable the preservation of functional tissues by increasing surgical precision, while AI algorithms can perform dynamic risk assessments by processing genomic and histological data. These tools support the surgeon's decision-making process and contribute to the creation of personalized treatment strategies.

Interdisciplinary collaboration will become an integral part of this process. The synthesis of information from different specialties through tumor councils will enrich surgical planning and help achieve patient-centered outcomes. Additionally, updating educational programs to develop skills in data analysis and technology use will prepare future surgeons for this complex environment.

Accessibility and ethical considerations in practice should also be carefully addressed. Cost and equity factors in the dissemination of high-tech solutions should be considered, and the transparency and accountability of algorithmic decision-making should be clarified.

Surgical oncology will continue to exist as a field enriched by scientific advances and technological innovations. The goal is to provide the most appropriate treatment for each patient by balancing tumor control with quality of life. This path requires progress through continuous learning, collaboration, and innovative thinking.

Footnotes

One of the author of this article (C.K.P.) is a member of the Editorial Board of this journal. He had no involvement in the peer-review process or editorial decision regarding this manuscript. The peer-review process and editorial decision were handled independently by another editor.

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The Relationship of Tumor Budding with TNM Stage, Histopathological Parameters, and Survival in Colorectal Cancer

Kolorektal Kanserlerde Tümör Tomurcuklanmasının TNM Evresi, Histopatolojik Parametreler ve Sağkalım ile İlişkisi

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Abstract

Objectives: Tumor budding is a well-recognized histopathological feature linked to aggressive tumor behavior in colorectal cancer. This study aimed to investigate the association between tumor budding and TNM stage, histopathological parameters, and survival outcomes in patients undergoing surgical treatment for colorectal cancer.

Material and Methods: A retrospective analysis was conducted of 481 patients who underwent surgery for colorectal cancer between January 2015 and February 2021. Demographic data, clinical characteristics, pathological findings, and survival outcomes were evaluated. Patients were categorized according to the presence or absence of tumor budding. Comparative analyses were performed to assess differences in TNM stage, histopathological features, and survival between the two groups. Statistical evaluation was carried out using appropriate parametric and non-parametric methods.

Results: Tumor budding was detected in 22 patients (4.6%). No significant associations were identified between tumor budding and sex, emergency surgery, tumor localization, surgical procedure type, or CA 19-9 levels ($p>0.05$). Conversely, tumor budding was significantly associated with ASA score ($p=0.006$) and with preoperative CEA levels ($p=0.015$). Pathological assessment demonstrated correlations between tumor budding and advanced T stage ($p<0.001$), and between tumor budding and the presence of distant metastasis (M stage) ($p=0.004$). No statistically significant relationship was observed between tumor budding and N stage, lymphovascular invasion, or perineural invasion. Survival analysis showed no significant differences between patients with and without tumor budding in terms of local recurrence, distant recurrence, or mean overall survival.

Conclusion: Tumor budding is associated with advanced T stage and distant metastasis in colorectal cancer and may serve as a marker of aggressive tumor biology. However, its influence on recurrence and long-term survival was not clearly demonstrated. These findings support the consideration of tumor budding as an additional prognostic parameter alongside TNM staging.

Keywords: Colorectal cancer, tumor budding, TNM stage, metastasis, survival

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Öz

Giriş / Amaç: Tümör tomurcuklanması, kolorektal kanserlerde agresif tümör davranışı ile ilişkilendirilen önemli bir histopatolojik bulgudur. Bu çalışmada, kolorektal kanser nedeniyle opere edilen hastalarda tümör tomurcuklanmasının TNM evresi, histopatolojik parametreler ve sağkalım üzerindeki etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Ocak 2015-Şubat 2021 yılları arasında kolorektal kanser tanısı ile opere edilen 481 hasta retrospektif olarak incelendi. Hastaların demografik özellikleri, klinik verileri, patolojik bulguları ve sağkalım verileri değerlendirildi. Hastalar, tümör tomurcuklanması varlığına göre iki gruba ayrıldı. Tümör tomurcuklanması olan ve olmayan gruplar; TNM evresi, histopatolojik parametreler ve sağkalım açısından karşılaştırıldı. İstatistiksel analizler uygun parametrik ve non-parametrik testler kullanılarak yapıldı.

Bulgular: Hastaların 22'sinde (%4,6) tümör tomurcuklanması saptandı. Tümör tomurcuklanması ile cinsiyet, acil cerrahi, tümör yerleşimi, cerrahi türü ve CA 19-9 düzeyleri arasında anlamlı ilişki izlenmedi (p>0,05). Buna karşın, ASA skoru (p=0,006) ve preoperatif CEA düzeyi (p=0,015) tümör tomurcuklanması ile anlamlı ilişkili bulundu. Patolojik incelemede tümör tomurcuklanması, ileri T evresi (p<0,001) ve uzak metastaz varlığı (M evresi) ile anlamlı ilişki gösterirken (p=0,004), N evresi, lenfovasküler invazyon ve perinöral invazyon ile anlamlı ilişki saptanmadı. Sağkalım analizlerinde tümör tomurcuklanması ile lokal nüks, uzak nüks ve ortalama sağkalım arasında istatistiksel olarak anlamlı fark bulunmadı.

Tartışma / Sonuç: Tümör tomurcuklanması, kolorektal kanserde ileri T evresi ve uzak metastaz ile ilişkili olup agresif tümör biyolojisinin bir göstergesi olarak değerlendirilebilir. Ancak uzun dönem takiplerde nüks ve sağkalım üzerine etkisi net olarak gösterilememiştir. Bu bulgular, tümör tomurcuklanmasının TNM evrelemesine ek prognostik bir biyobelirteç olarak değerlendirilmesi gerektiğini düşündürmektedir.

Anahtar Kelimeler: Kolorektal kanser, tümör tomurcuklanması, TNM evresi, metastaz, sağkalım

Introduction

Tumor budding refers to the presence of isolated tumor cells or small clusters of tumor cells that detach from neoplastic glandular structures at the invasive margin of adenocarcinomas. Neoplasms demonstrating tumor budding are associated with a significantly more aggressive clinical behavior (1). In colorectal cancer (CRC), tumor budding has been recognized as an independent prognostic indicator and may facilitate patient stratification into risk groups that are more clinically informative than those based solely on TNM staging. Furthermore, it holds potential value in therapeutic decision-making, particularly in patients with T1 and T3 N0 (stage II, Dukes B) disease. However, despite its prognostic relevance, widespread implementation in routine pathological reporting has been limited by the absence of a standardized definition, especially concerning its qualitative criteria and quantitative assessment (2).

Tumor budding has been shown to enhance the metastatic potential of cancer cells by increasing their invasive properties, and numerous studies have demonstrated the impact of this phenomenon on clinical outcomes (3). In recent years, growing evidence has emerged regarding the effects of tumor budding, particularly on lymph node metastasis and overall survival (4). The histological characterization of tumor budding and its interaction with immune responses are important for a better understanding of cancer biology, and research in this field continues to expand (5). Several studies have reported that specific characteristics of tumor buds, such as their number and size, exert a significant prognostic impact on disease progression (2). As in many other malignancies, tumor budding in CRC is associated with an aggressive disease course, influencing treatment strategies and becoming an important criterion in patient management (6).

The present study was designed to explore the association of tumor budding with TNM stage, histopathological characteristics, and survival outcomes in patients who underwent surgical treatment for CRC.

Materials and Methods

The study was conducted as a single-center retrospective investigation at Çukurova University Faculty of Medicine Balcalı Hospital, in accordance with ethical and scientific approval granted by the Çukurova University Research Ethics Committee at its meeting (approval no: 162, date: 09.01.2026). A total of 481 patients who underwent surgery between January 2015 and February 2021 were evaluated. Demographic data (age and sex), ASA score, emergency surgery status, tumor location, surgical procedure, preoperative CEA and CA 19-9 levels, pathological findings (tumor type, TNM stage, lymphovascular invasion, number of retrieved lymph nodes, number of malignant lymph nodes, and presence of perineural invasion), and survival data (local recurrence, peritoneal recurrence, liver recurrence, para-aortic recurrence, and mean survival) were evaluated.

Patients were categorized into two groups according to whether tumor budding was present or absent. The study cohort comprised 22 patients with tumor budding and 459 without evidence of tumor budding.

Statistical Analysis

All study data were entered and analyzed using the SPSS for Windows, version 10.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared between groups using the two-sided Student's t-test for normally distributed variables, while the Mann-Whitney U test was used for variables that did not meet the normality assumption. A p-value of <0.05 was considered statistically significant.

Results

Comparative analysis between patients with and without tumor budding revealed no statistically significant associations with sex (p=0.098), emergency surgical intervention (p=0.604), tumor localization (p=0.301), surgical procedure type (p=0.096), or preoperative CA 19-9 levels (p=0.128). None of these variables showed a statistically significant association with the presence of tumor budding.

In contrast, tumor budding showed a statistically significant association with the ASA score (p=0.006) and preoperative CEA levels (p=0.015) (Table 1).

A comparison of pathological variables revealed no significant associations of tumor budding with tumor type (p=0.999), lymphovascular invasion (p=0.639), number of retrieved lymph nodes (p=0.437), number of metastatic lymph nodes (p=0.827), or presence of perineural invasion (p=0.642). However, when TNM staging was evaluated, significant associations were identified between tumor budding and T stage (p<0.001) and M stage (p=0.004). No significant association was found between tumor budding and N stage (p=0.740) (Table 2).

Survival outcomes were also compared. No statistically significant associations were observed between tumor budding and local recurrence (p=0.463), peritoneal recurrence (p=0.406), liver recurrence (p=0.531), para-aortic recurrence (p=0.623), or mean overall survival (months) (p=0.078) (Table 3, Figure 1).

Table 1. Demographic data

Variable	Tumor budding present (n=22)	Tumor budding absent (n=459)	p-value
Age (years), mean ± SD	64.13±11.42	60.84±12.48	0.226
Sex			0.098
Male	10 (45.5%)	289 (63.0%)	
Female	12 (54.5%)	170 (37.0%)	
ASA score			0.006
I	2 (10.5%)	191 (41.9%)	
II	15 (78.9%)	194 (42.5%)	
III	2 (10.5%)	71 (15.6%)	
Emergency surgery	2 (9.1%)	59 (12.9%)	0.604
Tumor location			0.301
Right colon	8 (36.4%)	112 (24.4%)	
Transverse colon	0	18 (3.9%)	
Left colon	1 (4.5%)	41 (8.9%)	
Sigmoid colon	5 (22.7%)	62 (13.5%)	
Rectosigmoid	1 (4.5%)	45 (9.8%)	
Rectum	5 (22.7%)	165 (35.9%)	
Multiple	2 (9.1%)	16 (3.5%)	
Type of surgery			0.096
Open	8 (36.4%)	250 (54.5%)	
Laparoscopic	14 (63.6%)	209 (45.5%)	
Preoperative CEA, median (range)	5.7 (0.5-70.30)	2.81 (0-6620)	0.015
Preoperative CA 19-9, median (range)	17.9 (0-325)	11.6 (0-8040)	0.128

SD: Standard deviation, ASA: American Society of Anesthesiologists, CEA: Carcinoembryonic antigen, CA: Cancer antigen

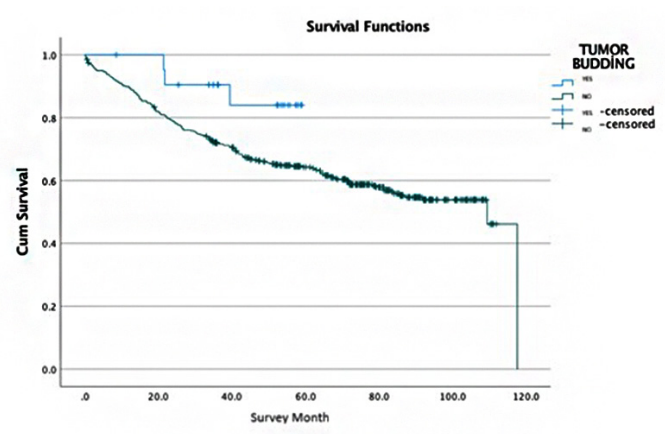

Figure 1. Kaplan-Meier survival curve

Table 2. Pathological characteristics

Variable	Present	Absent	p-value
Tumor type			0.999
Adenocarcinoma	22 (100%)	438 (95.4%)	
Other	0	21 (4.6%)	
T stage			<0.001
T0	0	30 (6.5%)	
T1	0	31 (6.8%)	
T2	1 (4.5%)	67 (14.6%)	
T3*	11 (50.0%)	71 (15.5%)	
T4	10 (45.5%)	260 (56.6%)	
N stage			0.740
N0	13 (59.1%)	255 (55.6%)	
N1	7 (31.8%)	121 (26.4%)	
N2	2 (9.1%)	82 (17.9%)	
M stage			0.004
M0	15 (68.2%)	407 (88.7%)	
M1	7 (31.8%)	52 (11.3%)	
Lymphovascular invasion	18 (81.8%)	356 (77.6%)	0.639
Number of lymph nodes, median (range)	17 (5-64)	15 (0-75)	0.437
Number of metastatic lymph nodes, median (range)	0 (0-6)	0 (0-46)	0.827
Perineural invasion	13 (59.1%)	248 (54.0%)	0.642

*: Statistically significant

Table 3. Survival data

Outcome	Present	Absent	p-value
Local recurrence	0	11 (2.4%)	0.463
Peritoneal recurrence	0	14 (3.1%)	0.406
Liver recurrence	1 (4.5%)	38 (8.3%)	0.531
Para-aortic recurrence	0	5 (1.1%)	0.623
Mean survival (months)	54.139	78.403	0.078

Discussion

In this study, which assessed the prognostic implications of tumor budding in CRC, tumor budding was significantly associated with advanced T stage and distant metastasis. Nevertheless, long-term follow-up analysis did not reveal a meaningful association between tumor budding and recurrence or overall survival outcomes.

The emergence of tumor budding is characterized by the detachment of individual tumor cells or small cellular clusters from the main tumor mass. These budding cells are regarded as precursors of metastatic spread, given their ability to infiltrate the extracellular matrix, enter lymphatic and vascular channels, and subsequently establish metastases in regional lymph nodes and distant organs. Histopathologically, tumor budding is widely considered a morphological correlate of epithelial-mesenchymal transitio (5,7-9).

Although initially established as a prognostic indicator in CRC, accumulating evidence has demonstrated its prognostic value in malignancies of other anatomical origins, including pancreatic, ampullary, gastroesophageal, pulmonary, and anal squamous cell carcinomas (3,6,10,11).

In 2016, the International Tumor Budding Consensus Conference established uniform criteria for the assessment and reporting of tumor budding and provided evidence-based guidance in line with the grading of recommendations assessment, development and evaluation framework (Table 4) (12).

When integrated with existing literature, this study demonstrates the relationship between tumor budding and TNM stages and indicates that tumor budding should be considered not only a histological criterion but also a prognostic biomarker for clinical outcomes. These findings necessitate further investigation into the defining characteristics of tumor budding, particularly in advanced-stage CRC (13).

The association between the number of tumor buds, their morphological characteristics, invasive potential, and survival rates highlights the complexity of cancer biology. In this context, the role of the tumor microenvironment must be considered. Specific features of tumor budding are associated with immune cell infiltration, and this interaction may influence clinical prognosis (14).

The histopathological evaluation of tumor budding in CRC is essential for detecting the initial steps of metastatic dissemination and should be considered within a multidisciplinary context. Incorporating tumor budding assessment into surgical decision-

Table 4. Statements of the ITBCC 2016 according to the GRADE system

No	Statement	Recommendation	Evidence
1	Tumor budding is defined as a single tumor cell or a cluster composed of four or fewer tumor cells.	Strong (vote: 22/22, 100%)	High
2	Tumor budding is an independent predictor of lymph node metastasis in pT1-stage colorectal cancer.	Strong (vote: 23/23, 100%)	High
3	Tumor budding is an independent predictor of survival in stage II colorectal cancer.	Strong (vote: 23/23, 100%)	High
4	Tumor budding should be considered together with other clinicopathological features in a multidisciplinary setting.	Strong (vote: 23/23, 100%)	High
5	Tumor budding should be counted on hematoxylin and eosin-stained sections.	Strong (vote: 19/22, 86%)	Moderate
6	Intratumoral budding exists in colorectal cancer and has been shown to be associated with lymph node metastasis.	Strong (vote: 22/22, 100%)	Low
7	Tumor budding should be assessed in a single hot spot area measuring 0.785 mm2 at the invasive front.	Strong (vote: 22/22, 100%)	Moderate
8	The hot spot method is recommended for the assessment of tumor budding in colorectal cancer.	Strong (vote: 22/22, 100%)	Moderate
9	A three-tier grading system should be used in combination with bud counting to facilitate risk stratification in colorectal cancer.	Strong (vote: 23/23, 100%)	Moderate
10	Tumor budding should be included in colorectal cancer reporting guidelines/protocols.	Strong (vote: 23/23, 100%)	High
11	Tumor budding is not synonymous with tumor grade.	Strong (vote: 23/23, 100%)	High

ITBCC: International tumor budding consensus conference, GRADE: Grading of recommendations assessment, development and evaluation

making, oncologic treatment planning, and systematic follow-up strategies may enhance current therapeutic algorithms and promote personalized management approaches (15).

In a large-scale meta-analysis encompassing 1.503 patients, Qu et al. (16) reported that high-grade tumor budding was significantly associated with adverse clinical outcomes in metastatic CRC. Consistent with these findings, our results indicate that tumor budding is a negative prognostic factor and is significantly associated with advanced T and M stages.

A substantial body of literature has investigated the association between tumor budding, nodal metastasis, and recurrence. In a study by Zhang et al. (17) tumor budding was found to be significantly correlated with both local recurrence and lymph node metastasis in patients undergoing surgery for early-stage CRC. Similarly, Rueda-Lara et al. (18) identified tumor budding as an unfavorable prognostic parameter that was significantly linked to recurrence in patients with stage II and III CRC. In contrast to these reports, our findings did not demonstrate a statistically significant relationship between tumor budding and either lymph node metastasis or tumor recurrence.

Study Limitations

The retrospective, single-center design and the relatively small number of patients with tumor budding may limit the study's generalizability and statistical power.

Conclusion

In patients treated surgically for CRC, the presence of tumor budding may reflect a more advanced T classification and a greater propensity for metastatic spread. Accordingly, such patients may warrant closer surveillance and consideration of more aggressive therapeutic strategies. Incorporating tumor budding into postoperative risk assessment may also facilitate the implementation of more individualized treatment approaches tailored to disease severity and metastatic potential.

Ethics

Ethics Committee Approval: The study was conducted as a single-center retrospective investigation at Çukurova University Faculty of Medicine Balcalı Hospital, in accordance with ethical and scientific approval granted by the Çukurova University Research Ethics Committee at its meeting (approval no: 162, date: 09.01.2026).

Informed Consent: Retrospective analysis.

Footnotes

Authorship Contributions

Concept/Design: Z.Z., B.Y., Data Collection or Processing: Z.Z., Y.K., İ.A., O.Y., Analysis or Interpretation: Z.Z., Y.K., İ.A., B.Y., İ.C.E., C.K.P., Literature Review: V.D., O.Y., Writing, Reviewing and Editing: Z.Z., V.D., İ.C.E., C.K.P.

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

Two of the authors of this article (İ.C.E. and C.K.P.) are members of the Editorial Board of this journal. They had no involvement in the peer-review process or editorial decision regarding this manuscript. The peer-review process and editorial decision were handled independently by another editor.

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Impact of Intraoperative Ultrasonography on Metastatic Lymph Node Detection in Laparoscopic Gastric Cancer Surgery

Mide Kanseri Cerrahisinde İntraoperatif Ultrasonografinin Metastatik Lenf Nodu Tayinindeki Yeri

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Abstract

Objectives: Laparoscopic D2 lymphadenectomy in gastric cancer surgery is technically demanding due to the close anatomical relationship with major vascular structures and the pancreatic parenchyma. This study investigated whether intraoperative ultrasonography (IOUS) influences early surgical and short-term oncologic outcomes in patients undergoing laparoscopic total gastrectomy.

Material and Methods: In this single-center retrospective comparative cohort study, between November 2023 and November 2025, a total of 78 patients underwent laparoscopic D2 lymph node dissection with IOUS guidance, of whom 31 underwent total gastrectomy. These patients were compared with 28 patients who underwent laparoscopic total gastrectomy and D2 lymph node dissection without IOUS between November 2021 and November 2023. The two groups were evaluated with respect to demographic characteristics, early perioperative outcomes, postoperative complications, and the total number of lymph nodes dissected and the number of metastatic lymph nodes.

Results: A total of 59 patients with gastric cancer were included in the analysis: 28 in the non-IOUS group and 31 in the IOUS group. No significant differences were observed between the groups with respect to demographic characteristics, clinical variables, or preoperative laboratory parameters (all $p>0.05$). Intraoperative complication rates (14.3% vs. 9.7%), postoperative complication profiles, requirements for erythrocyte suspension transfusion, operative time (median 200 minutes), intensive care unit stay, and total length of hospital stay were comparable between groups ($p>0.05$). There was no significant difference in the total number of dissected lymph nodes ($p=0.773$). The number of metastatic lymph nodes was low in both groups, and there was no significant difference associated with the use of IOUS ($p=0.605$).

Conclusion: IOUS may be considered a supportive technique that contributes to anatomical delineation and surgical safety during laparoscopic gastric cancer surgery. Further studies with larger patient cohorts are warranted to clarify its potential impact on oncological outcomes.

Keywords: Gastric cancer, intraoperative ultrasonography, laparoscopic lymphadenectomy, laparoscopic gastrectomy

Öz

Giriş / Amaç: Mide kanseri cerrahisinde laparoskopik D2 lenfadenektomi, majör vasküler yapılar ve pankreas parankimi ile yakın komşuluğu nedeniyle teknik olarak zorlayıcıdır. Bu çalışmada, laparoskopik total gastrektomi uygulanan hastalarda intraoperatif ultrasonografi (İU) kullanımının erken postoperatif cerrahi ve onkolojik sonuçlara etkisini değerlendirmeyi amaçladık.

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Gereç ve Yöntem: Kasım 2023-Kasım 2025 tarihleri arasında 31'i total gastrektomili olmak üzere toplam 78 hastaya İU eşliğinde laparoskopik D2 lenf nodu diseksiyonu uygulanmıştır. Bu 31 hasta Kasım 2021-Kasım 2023 arasında İU yardımsız laparoskopik total gastrektomi ve D2 lenf nodu diseksiyonu uygulanan 28 hasta ile karşılaştırılmıştır. İki grup demografik özellikler, perioperatif erken sonuçlar, komplikasyonlar, diseke edilen total ve metastatik lenf nodu sayıları açısından değerlendirilmiştir.

Bulgular: Çalışmaya İU uygulanmayan 28 hasta ve İU uygulanan 31 hasta olmak üzere toplam 59 mide kanseri hastası dahil edildi. Gruplar arasında demografik, klinik ve preoperatif laboratuvar parametreleri açısından anlamlı bir fark saptanmadı (tümü için p>0,05). İntraoperatif komplikasyon oranları (%14,3 vs. %9,7), postoperatif komplikasyon dağılımı, eritrosit süspansiyonu transfüzyon gereksinimi, operasyon süresi (medyan 200 dk), yoğun bakım yatış süresi ve toplam hastanede kalış süresi gruplar arasında benzerdi (p>0,05). Diseke edilen lenf nodu sayısı açısından gruplar arasında anlamlı fark izlenmedi (p=0,773). Metastatik lenf nodu sayıları her iki grupta da düşük olup, İU kullanımı ile anlamlı bir farklılık saptanmadı (p=0,605).

Tartışma / Sonuç: Sonuç olarak İU, laparoskopik mide kanseri cerrahisinde anatomik ayırım ve cerrahi güvenliğe katkı sağlayabilecek yardımcı bir yöntem olarak değerlendirilebilir. Daha geniş hasta serileri ile yapılacak çalışmalar, onkolojik sonuçlara etkisini daha net ortaya koyacaktır.

Anahtar Kelimeler: Mide kanseri, intraoperatif ultrasonografi, laparoskopik lenfadenektomi, laparoskopik gastrektomi

Introduction

Gastric cancer is the fifth most commonly diagnosed malignancy worldwide and ranks fourth among cancer-related causes of death (1). Surgical resection remains the cornerstone of curative treatment, and complete tumor removal with adequate lymph node dissection is one of the most critical determinants of long-term survival (2,3). Therefore, gastrectomy combined with systematic lymphadenectomy constitutes an essential component of current treatment strategies for resectable gastric cancer.

In recent years, laparoscopic gastrectomy has gained increasing acceptance due to its comparable oncological outcomes to open surgery and its more favorable early postoperative recovery profile (4). However, the lack of tactile feedback in the laparoscopic approach may complicate intraoperative decision-making during perivascular lymph node dissection (5). This limitation has increased interest in adjunctive imaging modalities that may enhance surgical safety.

Intraoperative ultrasonography (IOUS) provides real-time imaging with high resolution in differentiating vascular structures and soft tissues. Although IOUS is widely used in hepatobiliary and pancreatic surgery, its contribution to lymph node dissection in gastric cancer surgery has not yet been clearly established (6). Therefore, this study aimed to evaluate the impact of IOUS on early postoperative surgical and oncological outcomes in patients undergoing laparoscopic total gastrectomy.

Materials and Methods

Study Design and Patient Selection

Although the study was initially planned as a prospective investigation, it was converted to a retrospective cohort design due to insufficient patient recruitment. Patients who underwent laparoscopic surgery for gastric adenocarcinoma at the Surgical Oncology Department of Ankara University Faculty of Medicine were included.

Between November 2023 and November 2025, 78 patients underwent laparoscopic D2 lymph node dissection with IOUS guidance, 31 of whom underwent total gastrectomy. Between November 2021 and November 2023, these 31 patients were compared with 28 patients who underwent laparoscopic total gastrectomy with D2 lymph node dissection without IOUS.

Inclusion criteria were:

- age ≥18,
- histopathologically confirmed gastric adenocarcinoma, and
- curative-intent gastrectomy.

Exclusion criteria were:

- presence of distant metastasis at diagnosis,
- palliative surgery,
- missing clinical or laboratory data,
- loss to follow-up.

Patients were divided into two groups according to the use of IOUS: the IOUS group and the non-IOUS group.

Demographic characteristics, comorbidity burden assessed by the Charlson comorbidity index (CCI), tumor-related variables, and laboratory parameters (serum albumin level, lymphocyte count, and neutrophil count) were recorded. Perioperative data and postoperative outcomes were systematically collected. Postoperative complications were graded according to the Clavien-Dindo classification (7).

Intraoperative and postoperative outcomes included operative time, requirement for erythrocyte suspension transfusion, intensive care unit (ICU) stay, total length of hospital stay, total number of dissected lymph nodes, and total number of metastatic lymph nodes. The two groups were compared with respect to postoperative outcomes and surgical complications.

Written informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Committee of Ankara University Faculty of Medicine (approval no: İ01-07-23, date: 12.01.2023).

Surgical Technique and IOUS

All procedures were performed by an experienced surgical team. Total gastrectomy was performed in all included patients. The fundamental principles of the surgical procedure and the extent of lymph node dissection were based on the Japanese Gastric Cancer Treatment Guidelines (2). Roux-en-Y reconstruction was performed in all cases.

In the IOUS group, suspected metastatic lymph nodes, the pancreas, and major vascular structures were evaluated during D2 dissection using IOUS. Decisions regarding surgical strategy were made based on intraoperative findings and the surgeon's judgment.

Statistical Analysis

Statistical analyses were conducted using Jamovi (version 2.7.13). The distribution of continuous variables was examined with the Shapiro-Wilk normality test. Because most continuous variables were not normally distributed, they were summarized as medians with interquartile ranges (IQRs). Differences between groups in continuous variables were assessed using the Mann-Whitney U test. Categorical variables were summarized as counts and percentages and compared using the chi-square test or Fisher's exact test when appropriate. Statistical significance was defined as a two-sided p-value of less than 0.05.

A post-hoc power analysis was conducted based on the observed group differences in perioperative outcomes. With a total sample size of 59 patients and an alpha level of 0.05, the study had approximately 78% power to detect moderate effect sizes in continuous outcomes such as total hospital stay. However, for categorical endpoints such as intraoperative complications and postoperative morbidity, the observed effect sizes were small, resulting in reduced statistical power (<70%). These findings indicate that the study was adequately powered to detect moderate differences but may be underpowered to detect small differences in complication rates.

Results

A total of 59 patients with gastric cancer were included in the analysis, comprising 28 patients in the non-IOUS group and 31 patients in the IOUS group. There was no significant difference in sex distribution between the groups (p=0.985). The median age was 66 years (IQR: 17.8) in the non-IOUS group and 65 years (IQR: 13.5) in the IOUS group, with no statistically significant difference between the groups (p=0.665). The distribution of the CCI was similar between the two groups (p=0.308).

Tumors were predominantly located in the non-cardia region in both groups, there was no significant difference in tumor localization between patients with and without IOUS (p=0.225). The pathological stage distribution was comparable between the groups, and stage I disease was the most common in both cohorts (p=0.825). No significant differences were detected between the groups in preoperative laboratory parameters, including serum albumin level (p=0.903), lymphocyte count (p=0.559), and neutrophil count (p=0.202). Neoadjuvant therapy was administered to 25.0% of patients in the non-IOUS group and to 38.7% in the IOUS group; however, this difference did not reach statistical significance (p=0.260). The demographic, clinical, and preoperative laboratory characteristics of the groups are summarized in Table 1.

Intraoperative complication rates were comparable between the non-IOUS and IOUS groups (14.3% vs. 9.7%, p=0.585). According to the Clavien-Dindo classification, the distribution of postoperative complications did not differ significantly between groups (p=0.291). The majority of patients had no complications (grade 0). The requirement for erythrocyte suspension transfusion was similar between the non-IOUS and IOUS groups (32.1% vs. 48.4%; p=0.205). The median operative time was identical in both groups (200 minutes; p=0.493). Likewise, no significant difference was observed in ICU stay (median 1 day in both groups; p=0.659) or in total hospital stay. However, a trend toward longer total hospital stay was observed in the IOUS group (median 11 vs. 8 days; p=0.085). The median total number of dissected lymph nodes was 27 (IQR: 18.8) in the non-IOUS group and 31 (IQR: 16.5) in the IOUS group (p=0.773). The median number of metastatic lymph nodes was low in both groups; no statistically significant difference was observed between groups [0.5 (IQR: 5) vs. 0 (IQR: 3), p=0.605]. Overall, the use of IOUS did not have a significant impact on intraoperative, postoperative, or short-term oncological outcomes (Table 2).

The distribution of metastatic lymph node counts by IOUS use and pathological stage was visually evaluated using raincloud plots (Figure 1). In both non-IOUS and IOUS groups, counts of metastatic lymph nodes were predominantly clustered at or near zero. Color-coding by pathological stage demonstrated that metastatic lymph node counts had a wider distribution in more advanced stages. However, no obvious visual in the distribution of metastatic lymph nodes was observed between patients with and without IOUS.

Discussion

In this study, we evaluated the impact of IOUS on early postoperative surgical and short-term oncological outcomes in patients undergoing laparoscopic total gastrectomy for gastric cancer. The principal findings demonstrated that the use of IOUS

Table 1. Demographic and clinicopathological characteristics of gastric cancer patients with and without intraoperative ultrasonography

Variable	No USG (n=28)	USG (n=31)	p-value
Gender, n (%)			0.985[1]
Male	18 (64.3)	20 (64.5)	
Female	10 (35.7)	11 (35.5)	
Age, years, median (IQR)	66 (17.8)	65 (13.5)	0.665[2]
CCI, n (%)			0.308[1]
2	16 (57.1)	24 (77.4)	
3	9 (32.1)	5 (16.1)	
4	2 (7.1)	2 (6.5)	
5	1 (3.6)	0 (0.0)	
Tumor location, n (%)			0.225[1]
Cardia	3 (10.7)	7 (22.6)	
Non-cardia	25 (89.3)	24 (77.4)	
Pathological stage, n (%)			0.825[1]
Stage I	17 (60.7)	19 (61.3)	
Stage II	5 (17.9)	7 (22.6)	
Stage III	6 (21.4)	5 (16.1)	
Albumin (g/L), median (IQR)	41.5 (3.2)	41.8 (5.95)	0.903[2]
Lymphocyte count ($\times 10^9$/L), median (IQR)	2.00 (1.11)	1.78 (1.20)	0.559[2]
Neutrophil count ($\times 10^9$/L), median (IQR)	4.48 (2.24)	4.05 (1.70)	0.202[2]
Neoadjuvant therapy, n (%)			0.260[1]
No	21 (75.0)	19 (61.3)	
Yes	7 (25.0)	12 (38.7)	

Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. A two-sided p-value <0.05 was considered statistically significant

[1]: Chi-square test, [2]: Mann-Whitney U test, USG: Ultrasonography, IQR: Interquartile range, CCI: Charlson comorbidity index

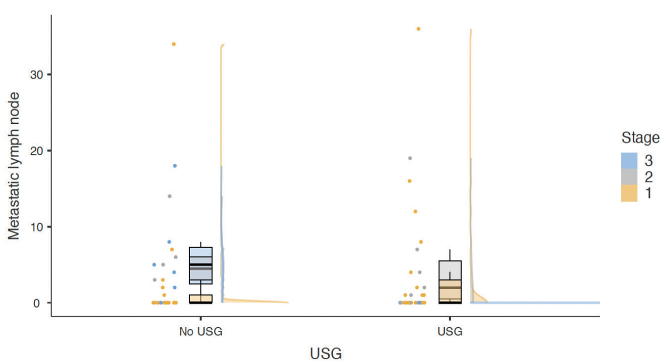

Figure 1. Raincloud plot analysis
USG: Ultrasonography

did not result in a statistically significant difference in operative time, perioperative complications, total and metastatic lymph node counts, or early postoperative outcomes. Notably, the low number of metastatic lymph nodes observed in both groups and the similarity in their distribution patterns suggest that IOUS did not meaningfully enhance the detection of pathological lymph nodes in this patient cohort. Nevertheless, the demonstration that IOUS can be integrated into laparoscopic gastric cancer surgery without disrupting surgical workflow, prolonging operative time, or increasing morbidity may be considered an important finding regarding clinical feasibility.

The primary objective established during project planning was to improve the detection of metastatic lymph nodes and to minimize the risk of leaving positive nodes behind through the use of IOUS. However, the present results indicate that this objective was not achieved to the expected extent. One possible explanation is the relatively high proportion of early-stage disease and the overall low metastatic nodal burden in the study population. As demonstrated in the raincloud plot analysis, metastatic lymph node counts in both groups were largely clustered near zero. This finding suggests that the potential benefit of IOUS may become more apparent in patient populations with more advanced disease and a higher expected nodal burden.

The present study demonstrated that IOUS can be incorporated into laparoscopic gastric cancer surgery without prolonging operative time. The comparable operative durations between

Table 2. Intraoperative and postoperative outcomes of gastric cancer patients with and without intraoperative ultrasonography			
Variable	**No USG (n=28)**	**USG (n=31)**	**p-value**
Intraoperative complication, n (%)			0.585[1]
Presence	4 (14.3)	3 (9.7)	
Absence	24 (85.7)	28 (90.3)	
Clavien-Dindo classification, n (%)			0.291[1]
Grade 0	19 (67.9)	15 (48.4)	
Grade I	4 (14.3)	5 (16.1)	
Grade II	1 (3.6)	6 (19.4)	
Grade IIIa	3 (10.7)	4 (12.9)	
Grade IIIb	1 (3.6)	0 (0.0)	
Grade IVa	0 (0.0)	1 (3.2)	
Erythrocyte suspension transfusion, n (%)			0.205[1]
No	19 (67.9)	16 (51.6)	
Yes	9 (32.1)	15 (48.4)	
Operation time, min, median (IQR)	200 (45)	200 (40)	0.493[2]
ICU stay, days, median (IQR)	1 (1.5)	1 (1)	0.659[2]
Total hospital stay, days, median (IQR)	8 (8)	11 (6)	0.085[2]
Total lymph node, median (IQR)	27 (18.8)	31 (16.5)	0.773[2]
Metastatic lymph node, median (IQR)	0.5 (5)	0 (3)	0.605[2]

Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables. A two-sided p-value <0.05 was considered statistically significant
[1]: Chi-square test, [2]: Mann-Whitney U test, USG: Ultrasonography, ICU: Intensive care unit, IQR: Interquartile range

the two groups indicate that this technique does not disrupt surgical flow and has high practical feasibility. Furthermore, the single-center nature of the study ensured homogeneity of surgical techniques and perioperative care protocols, thereby strengthening the internal validity of the findings. Although difficult to quantify, the additional anatomical awareness provided by IOUS during dissections involving the pancreas and major vascular structures may represent a clinically meaningful advantage in terms of surgical safety. The current study may serve as a preliminary step for future investigations focusing on larger cohorts and selected high-risk patient populations.

Although IOUS has been widely used for various purposes in other intra-abdominal malignancies, studies directly evaluating its contribution to lymph node dissection in laparoscopic gastric cancer surgery remain limited (8,9). Shen et al. (10) reported that the use of IOUS increased the number of retrieved lymph nodes, particularly at stations 10, 11, and 12, with a more noticeable effect in patients with advanced-stage disease. However, that study did not identify a statistically significant difference between groups regarding the total number of dissected lymph nodes or the overall metastatic lymph node count. In line with these observations, our results showed no meaningful increase in total or metastatic lymph node counts associated with IOUS. Overall, these findings indicate that the potential advantage of IOUS may become more apparent in patients with advanced disease and a higher anticipated nodal burden, whereas its benefit may be limited in early-stage cases.

Study Limitations

Some limitations that may affect the results of our study. First, although the study was initially planned as a prospective randomized investigation, it was converted to a retrospective cohort design because of insufficient patient recruitment, and this conversion increased the risk of selection bias. Second, the relatively small sample size reduced the statistical power, particularly for infrequent endpoints such as the detection of metastatic lymph nodes. In addition, the focus on short-term outcomes precluded evaluation of the potential impact of IOUS on long-term outcomes such as local recurrence and survival.

Conclusion

IOUS can be safely applied in laparoscopic gastric cancer surgery and integrated into the surgical workflow without prolonging operative time. Although no statistically significant superiority was demonstrated in terms of intraoperative, postoperative, or short-term oncological outcomes in the current patient cohort, our findings provide preliminary evidence for a potential role of IOUS in laparoscopic gastric cancer surgery. Rather than for routine use, IOUS may be more appropriately considered in selected patient populations, particularly in advanced-stage disease, in cases with a high risk of nodal burden, or in anatomically challenging dissections. Larger and more comprehensive studies are warranted to further clarify the potential oncological benefits of IOUS, especially in carefully selected patient groups.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of Ankara University Faculty of Medicine (approval no: İ01-07-23, date: 12.01.2023).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept/Design: S.T., A.E.Ü., Data Collection or Processing: S.Ç., K.E., M.Ş.B., Analysis or Interpretation: S.T., C.C., E.C., Literature Review: S.T., Writing, Reviewing and Editing: S.T., S.Ç.

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

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Evaluation of the Immunohistochemical and Molecular Characteristics of Breast Cancers Exhibiting Fibrotic Scar Formation Following Neoadjuvant Chemotherapy

Neoadjuvan Kemoterapiye Fibröz Skarlaşma ile Yanıt Veren Meme Kanserlerinin İmmunhistokimyasal ve Moleküler Özelliklerinin Değerlendirilmesi

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Abstract

Objectives: Neoadjuvant chemotherapy (NACT) is widely used in breast cancer to reduce tumor burden and enable breast-conserving surgery. While pathological complete response is commonly used to assess efficacy, residual disease often shows heterogeneous morphological and biological patterns. Understanding this heterogeneity, particularly within fibrotic scar-dominant tumor beds, can provide insights into tumor biology, guide surgical planning, and optimize pathological sampling. This study aimed to examine the relationship between residual tumor distribution patterns and hormone receptor expression and discuss the clinical implications.

Material and Methods: We retrospectively analyzed 113 patients who underwent surgery following NACT between 2019 and 2025. Residual disease within the tumor bed was classified as either confined to the fibrotic scar or dispersed across a broader area. Immunohistochemical analyses included estrogen receptor (ER) and progesterone receptor (PR) expression. Morphological features were correlated with clinical and radiological findings, and ROC curves assessed the predictive capacity of receptor expression for residual patterns.

Results: In 87.6% of cases, residual tumor was confined within the fibrotic scar, while 12.4% exhibited a dispersed pattern. ER and PR expression levels were significantly higher in cases with a dispersed residual pattern (ER AUC=0.718; PR AUC=0.736), suggesting an association with hormone receptor-positive tumors. Ki-67 proliferation index did not differ significantly between patterns, indicating that proliferation alone does not explain the morphological spectrum. Clinically, dispersed patterns increased the risk of underestimating residual disease on imaging, highlighting the importance of comprehensive tumor bed evaluation.

Conclusion: These findings indicate that NACT response is not a uniform biological process and that residual tumor distribution may correlate with hormone receptor expression. The morphological and biological heterogeneity of residual disease is essential for guiding surgical planning and pathological sampling. In cases with likely dispersed patterns, ensuring margin safety and intensifying sampling may improve assessment of true residual extent. Recognizing these patterns can help anticipate discrepancies between imaging and actual disease, improve interpretation of treatment response, and support more personalized, biology-driven post-NACT management.

Keywords: Breast cancer, fibrotic scar, neoadjuvant chemotherapy, residual tumor, tumor heterogeneity

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Öz

Giriş / Amaç: Neoadjuvan kemoterapi (NAKT) meme kanseri tedavisinde tümör yükünü azaltmak ve meme koruyucu cerrahiyi mümkün kılmak amacıyla yaygın olarak kullanılmaktadır. Patolojik tam yanıt sıklıkla tedavi yanıtını değerlendirmek için kullanılsa da rezidü hastalık çoğu zaman heterojen morfolojik ve biyolojik özellikler sergiler. Özellikle tümör yatağı içindeki bu heterojenliğin anlaşılması tümör biyolojisi, cerrahi planlama ve patolojik örnekleme stratejilerinde kritik bilgiler sağlayabilir. Bu çalışmanın amacı NAKT sonrası fibrotik skar dokusu içinde kalan rezidü invaziv tümörün morfolojik olarak dağılım paternleri ile hormon reseptör ekspresyonu arasındaki ilişkiyi incelemek ve bulguların klinik önemini tartışmaktır.

Gereç ve Yöntem: 2019-2025 yılları arasında NAKT sonrası cerrahi tedavi uygulanmış 113 hasta retrospektif olarak analiz edildi. Rezidü hastalık paterni fibrotik skar içinde sınırlı veya daha geniş bir alana dağılmış olarak sınıflandırıldı. İmmünohistokimyasal analizlerde östrojen reseptörü (ER) ve progesteron reseptörü (PR) ekspresyonu değerlendirildi. Morfolojik özellikler klinik ve radyolojik bulgularla karşılaştırıldı, ROC eğrileri ile reseptör ekspresyonlarının dağılım paterni tahmin kapasitesi incelendi.

Bulgular: Olguların %87,6'sında rezidü tümör fibrotik skar içinde sınırlıyken, %12,4'ünde dağınık bir paterne rastlandı. Dağınık patern gösteren olgularda ER ve PR ekspresyonları anlamlı derecede yüksek bulundu (ER AUC=0,718; PR AUC=0,736). Ki-67 proliferasyon indeksi paternlere göre farklılık göstermedi; bu da proliferatif aktivitenin tek başına morfolojik spektrumu açıklamada yetersiz olabileceğini gösterdi. Klinik olarak dağınık patern görüntüleme ile rezidü hastalığın küçümsenme riskini artırdı ve tümör yatağının kapsamlı değerlendirilmesinin önemini vurguladı.

Tartışma / Sonuç: Elde edilen veriler NAKT'ye yanıtın tek tip bir biyolojik süreç olmadığını ve dağılım paterninin hormon reseptör ekspresyonlarıyla ilişkili olabileceğini göstermektedir. Rezidü hastalığın morfolojik ve biyolojik heterojenliği cerrahi planlama ve patolojik örnekleme stratejileri açısından önemlidir. Dağınık patern olasılığı bulunan olgularda cerrahi sınır güvenliğinin sağlanması ve patolojik örneklemenin yoğunlaştırılması gerçek rezidü yayılımının doğru değerlendirilmesini kolaylaştırabilir. Bulguların daha geniş hasta serilerinde ve prospektif çalışmalarda doğrulanması, rezidü hastalık değerlendirmesinde bütüncül ve biyoloji temelli stratejilerin geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Meme kanseri, fibrotik skar, neoadjuvan kemoterapi, rezidü tümör, tümör heterojenitesi

Introduction

The principal goals of neoadjuvant chemotherapy (NACT) in breast cancer include decreasing the size of the primary tumor to facilitate breast-conserving surgery; decreasing axillary tumor burden, thereby reducing the need for axillary dissection and its associated surgical morbidity; enabling early treatment of systemic micrometastases; allowing *in vivo* assessment of biological response to therapy; and supporting the planning of de-escalation or escalation strategies in adjuvant treatment. In addition, achievement of a pathological complete response (pCR) is a key prognostic indicator, especially among patients with triple-negative breast cancer (TNBC) or human epidermal growth factor-2 (HER2)-positive subtypes (1).

pCR refers to the complete absence of invasive tumor cells following NACT, indicating no residual invasive carcinoma is detectable. Attaining a pCR has been consistently associated with improved long-term survival, especially in individuals with TNBC or HER2-positive breast cancer (2). In contrast, residual disease exhibits considerable morphological heterogeneity, thereby obscuring the prognostic distinction between pCR and residual cancer burden. Consequently, numerous studies, including that of Symmans et al. (3) have proposed quantitative parameters-ranging from primary tumor size to tumor bed cellularity-to assess residual cancer burden. However, these scoring systems do not sufficiently incorporate the morphological patterns of tumor regression, limiting their capacity to comprehensively characterize residual disease.

In clinical practice, a fragmented regression pattern is frequently observed following NACT, characterized by residual invasive tumor foci embedded within fibrotic scar tissue in the tumor bed. This pattern suggests that the therapeutic effect is mediated predominantly through stromal fibrosis and tissue remodeling. Importantly, it is biologically distinct from pCR, in which cytotoxic tumor cell eradication represents the dominant mechanism of response (4).

It is well established that breast cancers of the luminal molecular subtype exhibit relatively low pCR rates following NACT; however, they often demonstrate treatment responses characterized by prominent stromal alterations and partial tumor regression. These findings suggest that such responses may be closely related to the underlying biology of fibrotic scar formation and residual disease (5).

In this study, we aimed to elucidate the biological determinants underlying this distinct response pattern by analyzing the immunohistochemical and molecular characteristics of breast cancers that demonstrate residual invasive tumor foci within a fibrotic scar background and exhibit a fragmented regression pattern following NACT.

Materials and Methods

The study protocol received approval from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval no: E-50687469-799-302082838, date: 03.02.2026). All procedures were conducted in accordance with internationally recognized ethical standards, consistent with the principles set forth by the Declaration of Helsinki.

This retrospective, observational, single-center study evaluated the morphological and immunohistochemical characteristics of residual disease in patients with breast carcinoma who, following NACT, underwent definitive surgery-either mastectomy or breast-conserving surgery at the Department of Surgical Oncology, University of Health Sciences Türkiye, Gülhane Training and Research Hospital.

Between January 2019 and December 2025, 3358 patients with breast cancer who received surgical treatment were retrospectively screened from the hospital information system. Among them, 1119 patients who underwent surgery following NACT were identified, and their pathological specimens were re-evaluated in detail. The study included 113 female patients who demonstrated a fragmented regression pattern, characterized by residual invasive tumor foci within a fibrotic tumor bed, who did not meet the criteria for pCR.

Clinicopathological variables retrieved from hospital records included age; histological subtype; type of surgery and axillary management; number of excised and metastatic lymph nodes; presence of an *in situ* component; microcalcifications; multifocality (defined as the presence of two or more spatially separate invasive tumor foci within the breast parenchyma on pathological examination); lymphovascular invasion (LVI); tumor necrosis; fibrotic scar size; estrogen receptor (ER) and progesterone receptor (PR) expression; HER2 status; Ki-67 proliferation index; and response to NACT in both the breast and axillary lymph nodes.

The tumor bed was evaluated based on macroscopic and microscopic findings, with particular attention to treatment-related morphological changes. The size of the residual invasive tumor focus was determined based on the invasive component identified in the fibrotic tumor bed.

Within the study protocol, the distribution pattern of residual tumor foci and treatment-related stromal alterations following NACT was analyzed in two subgroups: group 1 (limited) and group 2 (dispersed). Group 1 (limited pattern) was defined by minimal treatment-related fibrosis, with either a single residual tumor focus or small clusters of tumor cells separated by limited fibrotic scarring, but confined to a well-demarcated area. Group 2 (dispersed pattern) was defined by the presence of three or more spatially separated residual tumor foci within the fibrotic tumor bed, each separated by intervening fibrotic stroma. In these cases, isolated single tumor cells or very small clusters were irregularly distributed within the stroma, and treatment-related fibrosis represented the predominant morphological feature.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with ranges (minimum-maximum), and categorical variables as frequencies (percentages). The normality of distribution was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. Normally distributed variables were compared using the independent samples t-test, whereas non-normally distributed variables were analyzed with the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value. A p-value <0.05 was considered statistically significant.

Results

The study included 113 patients with a mean age of 48.08±12.21 years (range, 26-86). Among cases with a fragmented regression pattern in a fibrotic tumor bed following NACT, invasive ductal carcinoma was the most common histological subtype (81.4%, n=92). This was followed by invasive lobular carcinoma (8.0%, n=9), papillary carcinoma (3.5%, n=4), and other less frequent histological subtypes. Regarding surgical management, 46 patients (40.7%) underwent breast-conserving surgery, while 67 patients (59.3%) underwent mastectomy.

In terms of axillary surgical management, sentinel lymph node biopsy (SLNB) was performed in 35 patients (31%), whereas 78 patients (69%) underwent axillary lymph node dissection (ALND). The mean number of dissected lymph nodes was 12.88±7.36 (range, 1-30), and the mean number of metastatic lymph nodes was 3.42±4.27 (range, 0-21). The clinicopathological characteristics of the study cohort are summarized in Table 1.

Following NACT, patients were categorized into two groups according to residual disease morphology: a limited residual pattern (group 1) and a dispersed residual pattern (group 2). Ninety-nine patients (87.6%) were classified as group 1, while 14 patients (12.4%) were classified as group 2 (Table 2). In group 1, residual invasive tumor foci were observed as solitary lesions or small clusters confined to limited fibrotic areas. In contrast, group 2 was characterized by scattered, irregularly distributed small clusters or single tumor cells within extensive fibrotic stromal areas. No statistically significant differences were identified between the two groups in terms of age, histological subtype, surgical approach, axillary management, number of dissected lymph nodes, or number of metastatic lymph nodes (all $p>0.05$).

Table 1. Demographic and histo-pathological distrubition of all patients	
Age, year, mean ± SD, range	48.08±12.21 (26-86)
Tumor type, n (%)	
Ductal	92 (81.4%)
Lobular	9 (8%)
Mixed	2 (1.8%)
Papillary	4 (3.5%)
Neuroendocrine	3 (2.7%)
Metaplastic	1 (0.9%)
Mucinous	2 (1.8%)
Operation type, n (%)	
Breast-conserving surgery	46 (40.7%)
Mastectomy	67 (59.3%)
Axillary treatment, n (%)	
SLNB	35 (31%)
ALND	78 (69%)
Lymph node dissection, nb, mean ± SD, range	12.88±7.36 (1-30)
Lymph node metastasis, nb, mean ± SD, range	3.42±4.27 (0-21)
***In situ* component, n (%)**	
Absent	39 (34.5%)
Present	74 (65.5%)
Microcalcification cluster, n (%)	
Absent	37 (32.7%)
Present	76 (67.3%)
Multifocality, n (%)	
Absent	10 (8.8%)
Present	103 (91.2%)
LVi, n (%)	
Absent	45 (39.8%)
Present	68 (60.2%)
Tumor necrosis, n (%)	
Absent	87 (77%)
Present	26 (23%)
ER, %, mean ± SD, range	62.89±39.08 (0-100)
PR, %, mean ± SD, range	29.43±35.87 (0-95)
HER2, n (%)	
0+	74 (65.5%)
1+	16 (14.2%)
2+	4 (3.5%)
3+	19 (16.8%)
Ki-67, %, mean ± SD, range	20.22±19.35 (1-80)
Breast neoadjuvant response, n (%)	
Circumscribed (≤2 area)	99 (87.6%)
Scattered (≥3 area)	14 (12.4%)
Tumor fibrous area, mm^3, mean ± SD, range	95.29±498.93 (0.7-5292)
Lymph node neoadjuvant response, n (%)	
No response	30 (26.5%)
Partial response	68 (60.2%)
Partial-complete response	11 (9.7%)
Complete response	4 (3.5%)

SD: Standard deviation, ER: Estrogen receptor, PR: Progesterone receptor, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, LVi: Lymphovascular invasion, HER2: Human epidermal growth factor-2

Similarly, no statistically significant differences were observed between the groups regarding the presence of an *in situ* component (p=0.617), microcalcification (p=0.116), multifocality (p=0.077), LVI (p=0.804), or tumor necrosis (p=0.597) (Table 2). In the overall study population, the mean ER expression was 62.89±39.08% (range, 0-100), and the mean PR expression was 29.43±35.87% (range, 0-95). HER2 overexpression (3+) was observed in 19 cases (16.8%).

A statistically significant difference in ER expression was observed among residual tumor distribution patterns (p=0.008). Median ER expression was higher in group 2 than in group 1. Similarly, PR expression differed significantly between the groups. The median PR level was 70% (range, 0-90) in group 2 and was 4% (range, 0-95) in group 1 (p=0.004). No statistically significant difference was observed in the Ki-67 proliferation index between the groups (group 1: median 12%; group 2: median 6.5%; p=0.117).

An *in situ* component was present in 74 patients (65.5%) and absent in 39 (34.5%). Microcalcifications were identified in 76 cases (67.3%). LVI was present in 68 patients (60.2%) and absent in 45 patients (39.8%). Tumor necrosis was observed in 26 cases (23%), while 87 cases (77%) showed no necrosis (Table 1). No statistically significant differences between the groups were observed for the Ki-67 proliferation index (p=0.117) or fibrotic tumor bed volume (p=0.438) (Table 2).

When axillary lymph node response to NACT was assessed, no statistically significant difference was observed between the groups (p=0.065) (Table 2). Partial-to-complete response rates were numerically higher in the dispersed residual pattern group.

ROC curve analysis was performed to evaluate the ability of ER and PR expression to distinguish residual tumor distribution patterns. The AUC for ER was 0.718 [95% confidence interval (CI): 0.578-0.858; p=0.008]. A cut-off value of 92.5 yielded 50% sensitivity and 76.8% specificity. The AUC for PR was 0.736 (95% CI: 0.610-0.862; p=0.004). A cut-off value of 45 yielded a sensitivity of 57.1% and a specificity of 69.7% (Figure 1).

Discussion

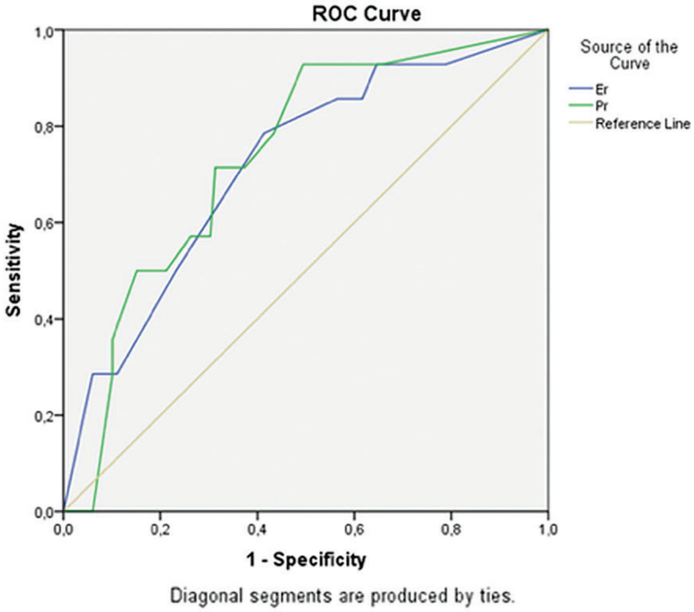
Although residual disease following NACT is generally regarded as an adverse prognostic indicator, the biological and clinical implications of its spatial distribution within the tumor bed and the accompanying stromal alterations remain insufficiently explored. Patients who do not achieve pCR exhibit marked morphological heterogeneity, which may reflect not only differences in residual tumor burden but also distinct patterns of tumor-stroma interaction and biological response to therapy.

In studies evaluating surgical approaches following NACT, Song et al. (6) reported that in appropriately selected patients, breast-

Table 2. Association between residual diseases groups and clinicopathological factors

Clinicopathological factors	No of patients (%)		p-value
	Limited residual group (99 patients 87.6%)	Dispersed residual group (14 patients 12.4%)	
Age, year, median, range	45 (26-86)	45 (32-65)	p=0.349^U
Tumor type, n (%)			
Ductal	80	12	p=0.097$^{\chi 2}$
Lobular	9	0	
Mixed	2	0	
Papillary	4	0	
Neuroendocrine	1	2	
Metaplastic	1	0	
Mucinous	2	0	
Operation type, n (%)			
Breast-conserving surgery	42	4	p=0.323$^{\chi 2}$
Mastectomy	57	10	
Axillary treatment, n (%)			
SLNB	30	5	p=0.682$^{\chi 2}$
ALND	69	9	
Lymph node dissection, nb, median, range	13 (1-30)	13.5 (3-29)	p=0.986^U
Lymph node metastasis, nb, median, range	2 (0-21)	1 (0-9)	p=0.633^U
***In situ* component, n (%)**			
Absent	35	4	p=0.617$^{\chi 2}$
Present	64	10	
Microcalcification cluster, n (%)			
Absent	35	2	p=0.11$^{\chi 2}$
Present	69	12	
Multifocality, n (%)			
Absent	7	3	p=0.077$^{\chi 2}$
Present	92	11	
LVi, n (%)			
Absent	39	6	p=0.804$^{\chi 2}$
Present	60	8	
Tumor necrosis, n (%)			
Absent	77	10	p=0.597$^{\chi 2}$
Present	22	4	
ER, %, median, range	80 (0-100)	92.5 (0-100)	p=0.008^U
PR, %, median, range	4 (0-95)	70 (0-90)	p=0.004^U
HER2, n (%)			
0+	63	11	p=0.297$^{\chi 2}$
1+	14	2	
2+	3	1	
3+	19	0	
Ki-67, %, median, range	12 (1-80)	6.5 (3-60)	p=0.117^U
Tumor fibrous area, mm^3, median, range	23 (0.70-5292)	15 (1.79-200)	p=0.438^U
Lymph node neoadjuvant response, n (%)			
No response	26	4	p=0.065$^{\chi 2}$
Partial response	62	6	
Partial-complete response	7	4	
Complete response	4	0	

SD: Standart deviation, $^{\chi 2}$: Pearson chi-square test, ^U: Mann-Whitney U test, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy, HER2: Human epidermal growth factor-2



Variables	Sensitivity	Specificity	Area under curve	95% CI		Cut-off value	p-value
				Lower bound	Upper bound		
Estrogen receptor (ER)	50%	76.8%	0.718	0.578	0.858	92.5	**0.008**
Progesterone receptor (PR)	57.1%	69.7%	0.736	0.610	0.8.62	45	**0.004**

Figure 1. ROC curve analysis of ER and PR for neoadjuvant response residual diseases area
ROC: Receiver operating characteristic, CI: Confidence interval

conserving surgery achieves oncologic outcomes and local control rates comparable to those after mastectomy. Patient preferences, however, tend to favor mastectomy, particularly in cases of locally advanced tumors prior to NACT. Despite significant reductions in tumor volume after NACT, factors such as initially large tumor size, multifocality, extent of residual disease, and the need for safe surgical margins frequently lead to choosing mastectomy over breast-conserving surgery. This pattern is also reflected in our data and consistently reported in the literature (6).

SLNB and ALND were performed in 31% (n=35) and 69% (n=78) of patients, respectively. This high rate of ALND may be associated with the prevalence of clinically node-positive disease and/or locally advanced tumors, and with the inclusion of patients treated through 2019.

In the OPBC-05/ICARO trial, following neoadjuvant therapy, the rate of additional axillary metastases in cases with isolated tumor cells during SLNB was approximately 11%, and routine ALND did not provide additional benefit in the presence of planned adjuvant radiotherapy (7). Similarly, in the MF18-02/MF18-03 NEOSENTITURK studies, selected patients achieving clinical complete response after NACT with ypN+ status showed no significant differences in axillary or locoregional recurrence, or in 5-year disease-free survival and disease-specific survival, between SLNB and targeted axillary dissection groups (8). SLNB-based de-escalation strategies have been increasingly adopted in recent years, which partly explain the high ALND rates observed in our cohort. These findings should be interpreted in the context of evolving evidence and contemporary surgical practice.

Tumor response to NACT is not always reflected by a pCR; it is heterogeneous and cannot be fully captured by quantitative measures alone. The morphological features of treatment response provide additional insights into the underlying tumor biology. While the concept of residual cancer burden can partially quantify this heterogeneity, it does not capture the full spectrum of regression patterns as assessed morphologically (3).

In this study, we focused on a disease pattern frequently observed in clinical practice but less emphasized in the literature: residual invasive tumor foci within a fibrotic scar in the tumor bed. The morphology of residual disease may serve not only as an indicator of treatment response but also as a reflection of tumor biology. Notably, cases with a dispersed residual pattern showed significantly higher expression of ER and PR (ER p=0.008; PR p=0.004); ER and PR values showed moderate discriminative performance in differentiating residual patterns (ER AUC=0.718; PR AUC=0.736). These findings suggest that the residual disease phenotype represents a biological trait in addition to its morphological characteristics. Due to the limited number and dispersion of cases, multivariable modeling was not performed to avoid overfitting.

It is well-established that hormone receptor-positive tumors generally have lower pCR rates following NACT, with responses often manifesting as partial regression accompanied by stromal remodeling or fibrosis. The lower pCR rates in luminal subtypes and the possibility of alternative biological mechanisms of response have been previously highlighted (5). In this context, a fibrotic scar-dominant response pattern-particularly observed in hormone receptor-positive tumors-may reflect a stromal remodeling process rather than purely cytotoxic eradication.

However, the lack of a statistically significant difference in Ki-67 proliferation index among the residual patterns suggests that proliferative activity alone may be insufficient to fully explain the spectrum of morphological responses. This observation indicates that treatment response is likely shaped by more intricate mechanisms, including stromal components, tumor microenvironment, immune infiltration, vascular alterations, and clonal selection of tumor cells. Therefore, our study underscores the need to consider not only receptor expression but also tumor microenvironment markers and stromal analyses in future translational research to achieve a comprehensive understanding.

An additional clinical implication of morphological heterogeneity is its role as a critical variable in assessing the extent of residual tumor, which is paramount to ensuring surgical margin safety and achieving effective local control. In their investigation of residual disease patterns following NACT, Pastorello and colleagues emphasized that response morphologies may be associated with distinct biological subtypes and highlighted the importance of these morphological features in surgical planning (4).

In our study, residual tumor was confined to a specific area within the fibrous scar substrate in 87.6% of cases, whereas 12.4% exhibited a more dispersed pattern. This heterogeneity represents a more challenging clinical scenario for assessing surgical margins and performing pathological sampling of the tumor bed. Another notable finding is the ROC performance of ER and PR expression for distinguishing residual patterns (ER AUC=0.718; PR AUC=0.736). Although these AUC values indicate only moderate discriminatory ability and the sensitivity of the proposed ER cut-off is limited, these findings should be considered exploratory. They primarily suggest a potential association between hormone receptor expression and morphological response patterns, rather than establishing a clinically applicable predictive tool.

A dispersed pattern particularly increases the risk of discordance between post-neoadjuvant imaging and actual residual disease. Therefore, preoperative evaluation and surgical planning should interpret the tumor bed not only in terms of its overall size but also in terms of the distribution of treatment-induced structural changes. A more cautious approach is warranted to ensure safe surgical margins, and parameters that could guide the preoperative distribution of residual tumor should be incorporated into clinical decision-making.

Our study highlights that in cases exhibiting a residual response within a predominantly fibrotic scar matrix following NACT, the tumor's distribution pattern-not merely its volume-may independently influence surgical strategy. When a dispersed residual pattern is present, residual invasive tumor foci may be observed as small clusters or even single cells within extensive fibrotic areas. This can complicate clinical and radiological assessments, raising the possibility that, despite appearing "reduced" or "localized," residual disease may actually extend over a broader area than initially appreciated.

Consequently, preoperative assessment should adopt a comprehensive approach, incorporating not only the maximum tumor diameter but also the extent of fibrotic changes, the distribution pattern of microcalcifications, and detailed mapping of the tumor bed. In surgical planning, a more cautious approach-particularly in cases suspected to exhibit a dispersed pattern-may warrant wider excisions or enhanced margin control strategies to ensure complete removal. Similarly, in histopathological practice, meticulous and systematic sampling of the tumor bed is essential in cases with potential for a dispersed pattern, facilitating accurate evaluation of the true extent of residual invasive disease.

Study Limitations

The retrospective, single-center design of our study limits the generalizability of the results. Although the sample size represents a clinically meaningful cohort, the limited number of patients exhibiting a dispersed response pattern (n=14) may have diminished the statistical power of subgroup analyses and contributed to non-significant findings in some parameters. Nevertheless, the study's strengths include the large number of post-neoadjuvant therapy surgeries, the consistent application of criteria for identifying dispersed regression within fibrotic scar tissue, and the thorough re-examination of all pathological specimens.

Conclusion

This study elucidates that the fibrotic scar-dominant residual response observed within the tumor bed following NACT is not a uniform biological process and that the distribution pattern of residual invasive tumor may be associated with immunohistochemical characteristics. Notably, significantly higher expression of ER and PR in cases exhibiting a dispersed residual pattern suggests that this response modality may represent a distinct treatment phenotype linked to hormone receptor-positive biology.

These findings highlight the importance of evaluating not only the quantity of residual disease but also its distribution within the tumor bed and the associated stromal alterations. Such an approach is crucial for ensuring surgical margin safety, optimizing pathological sampling strategies, and accurately interpreting biological responses to therapy.

Validation of this integrative assessment-addressing both the morphological and biological heterogeneity of residual disease-in larger patient cohorts and prospective studies could facilitate the development of more personalized, biology-driven decision-making frameworks in the post-neoadjuvant therapy setting.

Ethics

Ethics Committee Approval: The study protocol received approval from the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval no: E-50687469-799-302082838, date: 03.02.2026).

Informed Consent: Retrospective, observational, single-center study.

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Footnotes

Authorship Contributions

Concept/Design: S.G., İ.B.B., Data Collection or Processing: S.G., Ö.K., Analysis or Interpretation: İ.B.B., M.T., M.A.G., Literature Review: Ö.K., M.T., M.A.G., Writing, Reviewing and Editing: S.G.

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CASE REPORT / OLGU SUNUMU

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Posterior Reversible Encephalopathy Syndrome (PRES) in a Patient Who Developed Visual Loss After Total Thyroidectomy: A Case Report

Total Tiroidektomi Sonrası Görme Kaybı Gelişen Hastada Posterior Reversible Ensefalopati Sendromu (PRES): Bir Olgu Sunumu

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a rare but potentially severe neurological disorder most commonly associated with pregnancy toxemia (preeclampsia and eclampsia), hypertension, acute glomerulonephritis, and cytotoxic or immunosuppressive agents. Clinical manifestations typically include headache, visual disturbances, altered mental status, and generalized or focal seizures, often accompanied by hypertension. Diagnosis is based on a detailed neurological examination and neuroradiological investigations, particularly cranial magnetic resonance imaging. In this case report, we present PRES and describe its clinical presentation in a 40-year-old male patient with no known comorbidities; the condition developed secondary to head hyperextension following total thyroidectomy.

Keywords: Thyroidectomy, visual loss, posterior reversible encephalopathy syndrome

Öz

Posterior reversible ensefalopati sendromu (PRES); çoğunlukla gebelik toksemisi (preeklampsi/eklampsi), hipertansiyon, akut glomerülonefrit, sitotoksik ve immünosüpresif ajan kullanımı ile ilişkili olarak gelişen, nadir ancak potansiyel olarak ciddi seyir gösterebilen bir nörolojik sendromdur. Klinik tabloda sıklıkla baş ağrısı, görme bozuklukları, mental durum değişiklikleri ve jeneralize veya fokal nöbetler izlenmekte olup bu bulgulara çoğu zaman eşlik eden hipertansiyon bulunmaktadır. Tanı; ayrıntılı nörolojik muayene ile birlikte nöroradyolojik görüntüleme yöntemleri, özellikle kraniyal manyetik rezonans görüntüleme bulguları temel alınarak konulmaktadır. Bu olgu sunumunda, total tiroidektomi sonrası başın hiperekstansiyonu sonucu gelişen ve bilinen herhangi bir ek hastalığı bulunmayan 40 yaşında bir erkek hastadaki press sendromunu ve klinik belirtilerini sunuyoruz.

Anahtar Kelimeler: Tiroidektomi, görme kaybı, posterior reversible ensefalopati sendromu

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare but potentially serious neurological disorder that affects the central nervous system. Although it is more commonly observed in the adult population, it has also been described in pediatric cases (1,2). The most common etiological factors include pregnancy toxemia (preeclampsia/eclampsia), acute or uncontrolled hypertension, acute glomerulonephritis, and the use of cytotoxic or immunosuppressive agents; sepsis and autoimmune diseases are also considered predisposing factors. The clinical presentation is characterized by headache, visual disturbances, altered mental status, and generalized or focal seizures, often accompanied by hypertension (3).

In the pathophysiology of PRES, hyperperfusion resulting from impaired cerebral autoregulation and/or endothelial dysfunction leads to disruption of the blood-brain barrier, increased capillary leakage, and ultimately vasogenic cerebral edema (4). Diagnosis is based on a combination of detailed medical history, clinical findings, and neuroradiological imaging. Computed tomography (CT), and cranial magnetic resonance imaging (MRI) in particular, typically reveal bilateral, symmetric areas of edema, most commonly involving the occipital and parietal lobes, which are characteristic of the diagnosis.

When the condition is diagnosed early and the underlying cause is promptly eliminated with appropriate treatment, patients often show a complete and dramatic recovery. However, delayed diagnosis and treatment may result in serious complications such as cerebral ischemia, infarction, permanent neurological deficits, and even death (2).

In this report, we aim to present a patient who developed PRES in the early postoperative period following total thyroidectomy for thyroid cancer and who was discharged without sequelae after early diagnosis and appropriate treatment, in light of the existing literature.

Case Presentation

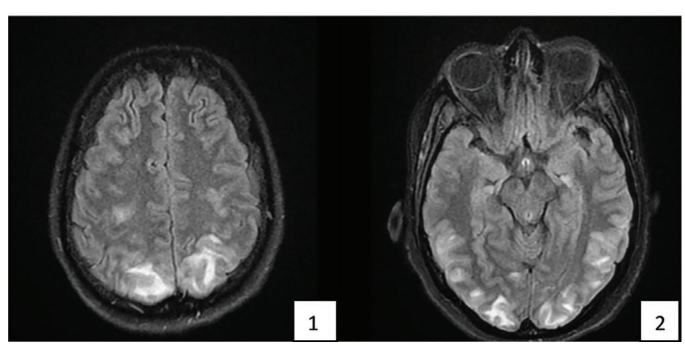
A 40-year-old male patient presented to our clinic after a thyroid nodule was incidentally detected on CT performed to evaluate a cough. Thyroid function tests were within normal limits. Neck ultrasonography revealed a 1-cm TIRADS 5 nodule in the left thyroid lobe and an 8-mm TIRADS 3 nodule in the right thyroid lobe. Fine-needle aspiration biopsy of the left lobe was consistent with papillary thyroid carcinoma. The patient was prepared for surgery, and the vocal cords were examined. At the patient's request, total thyroidectomy was performed. The patient gave informed consent for total thyroidectomy.

No intraoperative complications occurred. Postoperatively, serum calcium, parathyroid hormone, and electrolyte levels were within normal limits. The patient's postoperative course was uneventful until the 4^{th} postoperative hour, when presyncope and sudden-onset bilateral visual loss were noted. The patient was transferred to the intensive care unit. The initial blood pressure measurement was 170/100 mmHg. Arterial blood gas analysis revealed no significant abnormalities, and detailed hematological and biochemical tests were unremarkable.

Neurological examination showed no lateralizing motor or sensory deficits. Deep tendon reflexes were globally brisk (+++). The patient reported a complete loss of vision. On visual acuity examination, there was no blink response to threat or to finger counting, and no light perception was detected in either eye.

A non-contrast cranial CT scan performed to rule out hemorrhage revealed no acute bleeding. The patient was referred to the neurology department. Cranial MRI and contrast-enhanced brain and neck CT angiography were requested. CT angiography demonstrated normal carotid arteries and branches without thrombosis or stenosis. MRI revealed cortical and subcortical hyperintense areas on T2-weighted and FLAIR sequences in the bilateral parieto-occipital lobes (Figures 1-2). These findings were reported as consistent with PRES.

Based on clinical findings and imaging studies, a diagnosis of PRES secondary to head hyperextension during surgery was established. The patient was started on amlodipine 10 mg and dexamethasone 8 mg, the latter administered four times daily. Laboratory values remained stable during follow-up. The patient was transferred to the ward on the second day. On the fifth day, neurological reevaluation revealed improvement on visual examination, with the return of the blink response to threat and bilateral finger counting. It was recommended that steroid therapy be tapered and discontinued while antihypertensive treatment was continued. The patient was discharged in good condition on postoperative day 7, in accordance with the neurology recommendations.



Figures 1-2. Brain MRI images of the patient showing hyperintense areas in the parieto-occipital regions
MRI: Magnetic resonance imaging

Discussion

PRES is a rare but potentially serious neurological disorder presenting with headache, altered mental status, visual loss, and generalized or focal seizures. Although its pathophysiology has not been fully elucidated, it is most commonly associated with bilateral cerebral edema predominantly involving the occipital and parietal regions (5). While the clinical course is often transient and reversible, severe morbidity and mortality may occur due to complications. The syndrome was first described in 1996 by Hinchey et al. (4). The most common etiological factors include hypertension, eclampsia, and the use of immunosuppressive or cytotoxic drugs. Additionally, collagen vascular diseases, human immunodeficiency virus infection, celiac disease, chronic renal failure, sepsis, and organ transplantation have also been reported as contributing factors (4).

An initial hypothesis of the pathophysiology of PRES proposed that acute, severe hypertension causes cerebral vasoconstriction, leading to hypoperfusion and cytotoxic edema. However, the more widely accepted theory today proposes that hypertension-induced disruption of cerebral autoregulation results in hyperperfusion, blood-brain barrier breakdown, and subsequent vasogenic edema (6). In the present case, positional hypoxia resulting from head hyperextension during thyroidectomy, followed by reperfusion injury, was considered a distinctive and noteworthy etiological mechanism leading to vasogenic edema and PRES.

Diagnosis of PRES relies on high clinical suspicion following thorough history-taking and physical examination, with neuroradiological imaging playing a critical role in confirmation. CT, and especially cranial MRI, typically demonstrate edema predominantly affecting the posterior cerebral hemispheres, particularly the occipital and parietal regions, appearing as hyperintense lesions on T2-weighted and FLAIR sequences. The presence of bilateral cortical and subcortical hyperintense lesions on MRI is highly valuable for diagnosis (7-9). Differential diagnoses include posterior circulation infarctions, encephalitis, cerebral edema secondary to hyponatremia, demyelinating diseases, and cerebral venous thrombosis.

Early diagnosis and prompt treatment are the most important determinants of prognosis in PRES. Delayed management may result in irreversible brain damage, cerebral ischemia, chronic epilepsy, or death (1). Treatment primarily aims at controlled blood pressure regulation, effective seizure management, reduction of cerebral edema, and elimination of the underlying etiological factor (1,10). Calcium channel blockers and organic nitrates are commonly used for antihypertensive therapy; however, rapid and excessive blood pressure reduction should be avoided due to the risk of cerebral infarction and organ dysfunction.

Because cerebral edema is the central pathological feature, anti-edema therapy is essential. Benzodiazepines and phenytoin are frequently used to control generalized seizures, while refractory cases may require intubation and intensive care support. In cases of PRES associated with preeclampsia, magnesium sulfate is preferred as an anticonvulsant following blood pressure control, as it does not cross the blood-brain barrier and is considered safe during pregnancy (11). In patients with persistent or worsening symptoms, cesarean section may become unavoidable to improve maternal and fetal outcomes.

A review of the literature shows that publications and case reports on PRES indicate that the syndrome is predominantly observed in pregnant women with preeclampsia/eclampsia and in patients with autoimmune connective tissue diseases. Only a single case report has been published following thyroidectomy, in which the development of press syndrome was attributed to excessive calcium replacement administered for the treatment of postoperative hypoparathyroidism (12). In contrast, the primary cause of press syndrome in our case was ischemia-reperfusion injury secondary to head hyperextension. From this perspective, our case report provides a novel contribution to the existing literature.

Conclusion

Although rare, PRES can cause serious neurological morbidity and mortality if not diagnosed and treated promptly. Its clinical presentation typically includes headache, altered consciousness, visual disturbances, and seizures, which collectively may mimic many other neurological disorders; therefore, high clinical awareness is essential, particularly in patients with risk factors.

Diagnosis is primarily based on clinical suspicion supported by neuroradiological imaging, especially cranial MRI findings of bilateral cortical and subcortical vasogenic edema in the posterior regions. Early imaging plays a crucial role in preserving the syndrome's reversibility and preventing complications.

In the present case, positional hypoxia caused by intraoperative head hyperextension followed by reperfusion injury-an infrequently reported mechanism-was considered a noteworthy etiological factor for PRES. This highlights that even in the absence of classical risk factors such as hypertension, perioperative cerebral perfusion disturbances may predispose patients to PRES. Therefore, appropriate patient positioning and maintenance of cerebral oxygenation during surgical procedures are essential preventive measures.

Treatment focuses on blood pressure control, seizure control, reduction of cerebral edema, and elimination of the underlying cause. With this comprehensive approach, most patients achieve complete clinical and radiological recovery. However, delayed diagnosis and treatment may result in irreversible brain injury, chronic epilepsy, or death.

Early recognition of PRES, inclusion in the differential diagnosis, and prompt implementation of etiologically targeted treatment strategies are the most critical factors determining patient prognosis. Reporting atypical etiological mechanisms contributes to a better understanding of the syndrome's pathophysiology and increases clinical awareness.

Ethics

Informed Consent: The patient gave informed consent for total thyroidectomy.

Footnotes

Authorship Contributions

Concept/Design: K.K.Ö., İ.B.B., M.A.G., Data Collection or Processing: K.K.Ö., M.T., Analysis or Interpretation: İ.B.B., M.A.G., Literature Review: M.T., Writing, Reviewing and Editing: K.K.Ö.

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CASE REPORT / OLGU SUNUMU

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An Unexpected Destination of Breast Cancer: Appendiceal Metastasis

Meme Kanserinin Beklenmedik İstasyonu: Appendiks Metastazı

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Abstract

Appendiceal metastasis from breast cancer is rare and most commonly encountered in patients with advanced-stage disease. Such metastases typically occur in the setting of intra-abdominal dissemination. Appendiceal involvement may remain clinically silent and may not present with specific symptoms. In cases of asymptomatic appendiceal enlargement, a primary appendiceal tumor is often suspected, which may impede consideration of metastatic lesions, particularly those originating from breast cancer. However, some patients may present with gastrointestinal symptoms such as abdominal pain, nausea, and vomiting. The diagnosis is typically established using imaging modalities, including ultrasonography, computed tomography, and magnetic resonance imaging, in conjunction with histopathological confirmation by biopsy. Metastatic lesions should not be misinterpreted as primary appendiceal malignancies. Treatment strategies depend on the patient's overall condition, the extent of metastatic disease, and other clinical factors; they may include surgical intervention, chemotherapy, or targeted therapies. Overall, the prognosis of metastatic breast cancer remains poor. The treatability of appendiceal metastasis and the patient's overall health status are important factors influencing prognosis. In this report, we present the case of a 49-year-old woman diagnosed with estrogen receptor-positive and progesterone receptor-positive breast cancer who was evaluated for abdominal pain and subsequently found to have acute appendicitis secondary to metastatic breast carcinoma, and we review the relevant literature.

Keywords: Appendiceal metastasis, breast cancer, colon, ileum

Öz

Meme kanserinin appendiks metastazı, nadir görülen bir durumdur. Genellikle ileri evre meme kanseri olan hastalarda ortaya çıkar. Appendiks metastazı, genellikle karın içi yayılım sırasında gerçekleşir. Appendiks metastazı genellikle belirgin semptomlar göstermeyebilir. Asemptomatik apendiks büyümesinde genellikle birincil apendiks tümörü olduğunda şüphelenilir ve bu da metastatik tümörlerden, özellikle de meme kanserinden kaynaklanan metastazlardan şüphelenmeyi zorlaştırır. Ancak bazı hastalarda karın ağrısı, bulantı, kusma veya sindirim problemleri gibi belirtiler ortaya çıkabilir. Tanı genellikle görüntüleme yöntemleri (ultrason, bilgisayarlı tomografi, manyetik rezonans görüntüleme) ve biyopsi ile konur. Metastatik lezyonlar, primer appendiks kanseri ile karıştırılmamalıdır. Tedavi, hastanın genel durumu, metastazın yaygınlığı ve diğer faktörlere bağlıdır. Cerrahi müdahale, kemoterapi veya hedefe yönelik tedaviler içerebilir. Genel olarak, metastatik meme kanseri prognozu daha kötüdür. Appendiks metastazının tedavi edilebilirliği ve hastanın genel sağlık durumu, prognozu etkileyen önemli faktörlerdir. Bu olguda östrojen reseptörü ve progesteron reseptörü pozitif, meme kanseri tanısı almış 49 yaşındaki bir kadın hastanın karın ağrısı nedeniyle değerlendirildiği ve sonrasında meme karsinom metastazlarına bağlı akut apandisit olan vakayı ve ilgili literatürün bir incelemesini sunuyoruz.

Anahtar Kelimeler: Apandiks metastazı, meme kanseri, kolon, ileum

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Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for approximately 25% of all cancer cases, with an estimated 2.3 million new diagnoses annually (1). The reported five-year survival rate for breast cancer reached 92% during the 2013-2017 period, representing a substantial improvement compared with the 76% rate reported for 1988-1992. This progress largely reflects earlier detection through effective screening programs, as well as advances in surgical, radiological, and systemic treatment strategies (2). The most common metastatic sites of primary breast cancer include regional lymph nodes, bone, liver, lung, brain, and skin (3). Appendiceal tumors are often detected incidentally during radiological examinations or abdominal surgery, most commonly initiated for tumor-related acute appendicitis.

Case Presentation

A 49-year-old woman presented to the emergency department with a one-day history of abdominal pain. Her medical history revealed that she had undergone a left modified radical mastectomy in 2014 for invasive lobular carcinoma (ILC) of the breast. Immunohistochemical analysis demonstrated estrogen receptor (ER) positivity in 80% of tumor cells, progesterone receptor positivity in 40% of tumor cells, HER2 (c-erbB2) negativity, and a Ki-67 proliferation index of 5%. Following surgery, the patient received chemotherapy and attended regular breast cancer follow-up visits; however, she had discontinued routine follow-up approximately one year prior to presentation. Physical examination revealed diffuse abdominal pain with more pronounced tenderness in the right lower quadrant, accompanied by guarding, abdominal rigidity, and rebound tenderness. Contrast-enhanced computed tomography (CT) showed areas of air-fluid levels and inflammatory changes in the mesenteric fat consistent with possible peritonitis, along with increased appendiceal wall thickness. These findings were interpreted as indicating possible appendicitis secondary to colonic inflammation (Figure 1). Preoperative laboratory investigations demonstrated elevated tumor markers, with a CA-125 level of 45.3 U/mL and a CA 15-3 level of 32.7 U/mL. In addition, inflammatory and biochemical parameters were elevated, including C-reactive protein at 30.7 mg/L and total bilirubin at 1.36 mg/dL.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The patient was taken for emergency surgery. Intraoperative exploration revealed widespread peritoneal implants. A perforation was identified at the site of tumor implantation in the appendix and was partially contained by the omentum. Adhesions were present within the bowel. Adhesiolysis and appendectomy were performed, and multiple biopsies were obtained from the peritoneum. Postoperatively, the patient received antibiotic therapy and intravenous fluid replacement. Enteral nutrition was initiated on postoperative day 2, and the patient was discharged on postoperative day 4. Histopathological examination revealed metastases consistent with metastatic breast carcinoma involving the appendiceal wall (appendectomy specimen), small-bowel mesentery, peritoneum, and omentum (excisional biopsies). Immunohistochemical analysis demonstrated CK7 and GATA-3 positivity, ER positivity in 100% of tumor cells, CK20 negativity, and HER2 (c-erbB2)1+ positivity (Figure 2). For restaging purposes, an F-18 FDG positron emission tomography (PET)/CT scan was performed and showed focally low-to-moderate hypermetabolic lymph nodes in both cervical lymphatic chains (reactive?); right axillary lymph nodes with fatty hila and thin cortices without increased metabolic

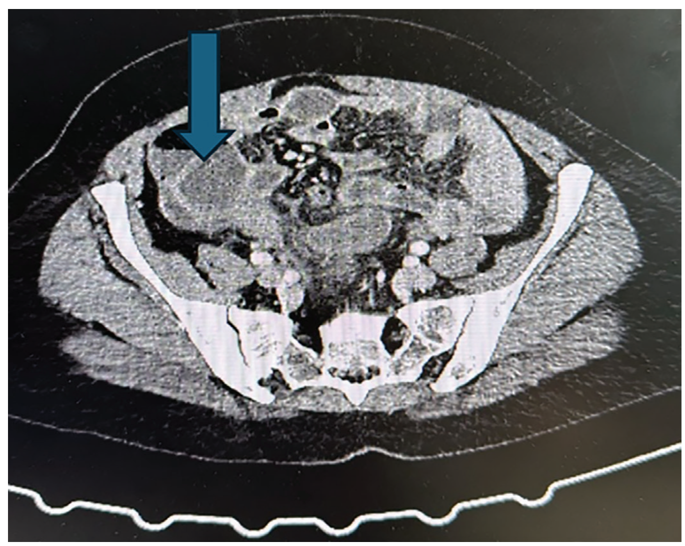

Figure 1. CT image demonstrating the appendix and surrounding tissues (900×512)
CT: Computed tomography

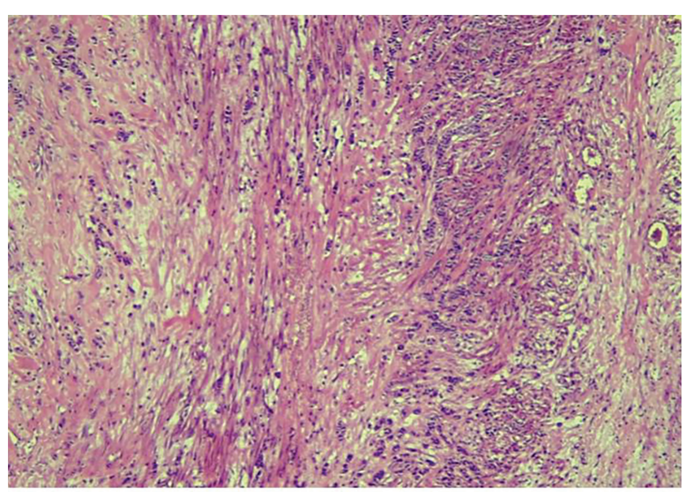

Figure 2. Tumor cells infiltrating the appendiceal wall

activity (reactive?); hepatomegaly; paraaortic and mesenteric lymph nodes without increased metabolic activity; and a fluid collection along the midline of the anterior abdominal wall, both infra- and supraumbilical, suggestive of postoperative changes. The patient was subsequently referred to the medical oncology department.

Discussion

The most common site of distant metastasis in breast cancer is the bone (3). Isolated metastasis to the appendix is rare, and most cases are presumed to result from peritoneal seeding. ILC demonstrates a distinct metastatic pattern compared with invasive ductal carcinoma, largely due to the loss of E-cadherin expression, a transmembrane adhesion molecule encoded by the *CDH1* gene. Loss of E-cadherin disrupts intercellular adhesion and promotes a discohesive growth pattern, allowing tumor cells to infiltrate tissues in a diffuse manner and disseminate more easily to distant sites. This molecular alteration is considered a key factor underlying the increased tendency of ILC to metastasize to the gastrointestinal tract (GIT), peritoneum, retroperitoneum, and gynecological organs (4). Previous studies have shown that the metastatic pattern of breast cancer is influenced by two major factors. The first is ER status, because ER-negative tumors are more likely to metastasize to the GIT. The second is histopathological subtype, with lobular carcinomas demonstrating a greater propensity for GIT metastasis (5,6). While ER-positive tumors typically show a predilection for bone metastasis, gastrointestinal and peritoneal metastases may still occur, particularly in ILC. Despite ER positivity, the biological behavior of lobular carcinoma, especially the loss of E-cadherin and its diffuse infiltrative growth pattern, facilitates dissemination to the peritoneal cavity and gastrointestinal organs. Therefore, ER positivity does not exclude the possibility of gastrointestinal metastasis, particularly in patients with lobular histology, as observed in the present case (7-9). ILC has a higher tendency to metastasize to the GIT, gynecological organs, peritoneum, and retroperitoneum, whereas ductal carcinoma more frequently spreads to the liver, lungs, and brain (10). ILC accounts for approximately 14% of all breast cancer cases (11). Our case involved peritoneal carcinomatosis and appendiceal metastasis arising in the setting of invasive lobular breast carcinoma, thereby supporting the majority of findings reported in the literature. Peritoneal involvement is thought to occur primarily through transcoelomic spread. Tumor cells with reduced intercellular adhesion may detach from the primary tumor or metastatic deposits and disseminate within the peritoneal cavity. These free tumor cells can subsequently implant on peritoneal surfaces, proliferate, and form metastatic nodules. In cases of peritoneal carcinomatosis, metastatic implants may directly involve adjacent intra-abdominal organs, including the appendix (12). In 1946, Oldfield (8) reported the first case of metastatic breast cancer presenting as acute appendicitis (13). McLemore et al. (9) performed a retrospective analysis of histopathological findings from appendectomy specimens and emphasized the rarity of metastatic tumors involving the appendix. Among 7,970 analyzed specimens, 0.9% contained tumors, the most common of which were carcinoid tumors. Only 15% of all identified tumors were secondary malignancies, the majority of which were metastatic colorectal cancers (14). Yoon et al. (15) also reported 139 cases of secondary appendiceal tumors, with the ovary being the most common primary site (56 cases). According to a comprehensive literature review by Ng et al., (16) among 15 reported cases of breast cancer with appendiceal metastasis, appendiceal perforation occurred in seven cases. Histopathological evaluation revealed ductal carcinoma in 10 cases, lobular carcinoma in four cases, and an undifferentiated tumor in one case. Hormone receptor status was reported in only four cases, with ER positivity in three cases, progesterone receptor positivity in three cases, and HER2 positivity in two cases. Regarding treatment, nine patients were managed with appendectomy alone, while six underwent right hemicolectomy (16).

Appendiceal metastasis may occur through hematogenous spread, lymphatic dissemination, or peritoneal seeding. In the presence of peritoneal carcinomatosis, peritoneal implantation is considered the most likely mechanism. Tumor infiltration of the appendiceal wall may lead to luminal obstruction, impaired vascular supply, inflammation, and eventual perforation, clinically mimicking acute appendicitis, as observed in the present case (14).

Although current clinical findings are often non-specific, CT remains the gold standard for the diagnosis of appendiceal tumors (17). PET may be useful in the evaluation of stage IV patients without abdominal pain. Non-neoplastic perforated appendicitis and perforated appendiceal tumors are often difficult to distinguish from one another (18).

Conclusion

Metastasis of breast cancer to the GIT is rare, and appendicitis resulting from metastatic breast cancer is exceedingly uncommon. With advances in systemic therapies that have improved survival in patients with advanced-stage breast cancer, unusual sites of distant metastases have been increasingly recognized. The diagnosis of atypical metastatic sites is challenging and requires a combination of clinical, laboratory, and radiological findings for confirmation. Nevertheless, gastrointestinal involvement can be anticipated and observed, particularly in patients with a history of advanced (stage IV) breast cancer. Although appendicitis is primarily regarded as an inflammatory condition, oncologic etiologies should be considered in patients with a known history of advanced breast cancer to ensure appropriate therapeutic decision-making. In most reported cases of appendicitis secondary to metastatic breast cancer, appendiceal perforation is observed. Treatment is generally managed by appendectomy, although right hemicolectomy may be required in selected cases. Early intervention in such patients helps prevent serious complications such as sepsis. While this management approach may not directly influence overall survival from the primary malignancy, multidisciplinary management may lead to improved clinical outcomes.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Concept/Design: Z.Z., Data Collection or Processing: Z.Z., Y.K., İ.A., G.S., Analysis or Interpretation: Z.Z., Y.K., İ.C.Y., A.A., İ.C.E., Literature Review: B.Y., Writing, Reviewing and Editing: Z.Z., B.Y., İ.C.E.

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CASE REPORT / OLGU SUNUMU

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Appendix Within a Previous Drain-site Hernia Sac After Pancreaticoduodenectomy for Ampulla of Vater Carcinoma: A Rare Case Report

Ampulla Vateri Karsinomu Nedeniyle Yapılan Pankreatikoduodenektomi Sonrası Eski Dren Yeri Herni Kesesi İçinde Appendiks: Nadir Bir Olgu Sunumu

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Abstract

Drain-site hernias and acute appendicitis are frequently encountered in surgical practice; however, identification of the vermiform appendix within a hernia sac constitutes an exceptionally uncommon clinical scenario. Incarceration of the appendix is most commonly described in association with inguinal hernias (Amyand's hernia) and femoral hernias (De Garengeot's hernia). Sporadic reports have additionally documented appendiceal involvement in umbilical and Spigelian hernias. In the present study, we report a case of a 57-year-old male who presented with right lower quadrant pain and detail his prior surgical history, physical examination findings, radiological assessment, and intraoperative confirmation of appendiceal entrapment within a hernia sac that developed at the site of a previous drain insertion. A focused review of previously published cases is also provided.

Keywords: Appendix, hernia, Amyand, drain

Öz

Dren yeri hernileri ve akut apandisit cerrahi pratikte sık karşılaşılan durumlar olmakla birlikte, herni kesesi içerisinde apendiks vermiformisin saptanması son derece nadir bir klinik tablodur. Apendiksin herni içerisinde inkarsere olması en sık inguinal hernilerle ilişkili olarak tanımlanmış olup bu durum Amyand hernisi olarak adlandırılmaktadır; ayrıca femoral hernilerde görülen formu De Garengeot hernisi olarak bilinmektedir. Bunun yanında, umbilikal ve Spigelian hernilerde apendiks varlığına ilişkin sporadik olgular da literatürde bildirilmiştir. Bu çalışmada, sağ alt kadran ağrısı ile başvuran 57 yaşındaki erkek hastada, önceki cerrahi öykü, fizik muayene bulguları, radyolojik değerlendirme ve daha önce yerleştirilen dren yerinde gelişen herni kesesi içerisinde apendiksin intraoperatif olarak saptanması ayrıntılı şekilde sunulmuştur. Ayrıca literatürde bildirilen benzer olgulara yönelik bir derleme de sunulmuştur.

Anahtar Kelimeler: Apendiks, herni, Amyand, dren yeri

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Introduction

The term Amyand's hernia originates from Claudius Amyand, who performed the first recorded appendectomy in the eighteenth century on a pediatric patient whose appendix was located within a right inguinal hernia sac. This rare surgical entity continues to generate discussion due to the diagnostic uncertainty it may create preoperatively and the variability in operative management strategies (1,2). Encountering the appendix within a hernia sac may alter intraoperative decision-making and surgical planning. Although the exact mechanism underlying this condition has not been definitively clarified, increased intra-abdominal pressure remains the most widely accepted explanation. According to this concept, episodes of elevated intra-abdominal pressure may facilitate migration of the appendix into a pre-existing hernia defect, where subsequent incarceration may compromise vascular perfusion and eventually provoke inflammatory changes (3). While the classical description of Amyand's hernia involves the appendix within an inguinal hernia sac, the present report differs in that the appendix was identified within a hernia defect formed at a prior drain-site. The occurrence of a non-inflamed vermiform appendix protruding through a drain-site defect has been documented only sporadically in previously published case reports (4-6).

Case Presentation

A 57-year-old man underwent pancreaticoduodenectomy (Whipple procedure) in 2015 for a tumor of the ampulla of Vater. Apart from this history, he had no other systemic diseases. He presented to our outpatient clinic with intermittent right lower quadrant pain that had persisted for approximately two months. On examination, palpation revealed a reducible hernia at the previous drain insertion site in the right lower quadrant. No rebound tenderness, guarding, or other abnormal physical findings were observed. Laboratory investigations, including complete blood count, serum biochemistry, and urinalysis, were within normal limits. Contrast-enhanced abdominal computed tomography (CT), performed with both oral and intravenous contrast, demonstrated a tubular structure extending through the abdominal wall defect into the hernia sac at the former drain-site (Figure 1). The radiological appearance was consistent with the vermiform appendix. Based on these findings, elective surgical management was planned. Laparoscopic exploration confirmed the presence of the appendix within the hernia sac. Careful dissection enabled separation of the appendix from surrounding tissues. The mesoappendix was sealed and divided using a LigaSure™ energy device. Two Hem-o-lok clips were applied to the appendiceal base, and transection was performed proximal to the clips. Laparoscopic appendectomy was then completed, and the specimen was retrieved using an endoscopic specimen bag. Following appendectomy, the hernia defect was closed laparoscopically using two interrupted primary sutures with 2-0 Vicryl. The postoperative course was uneventful, and the patient was discharged on postoperative day one without complications.

Discussion

The presence of the appendix within an inguinal hernia sac, commonly referred to as Amyand's hernia, represents an uncommon anatomical finding. A non-inflamed appendix is reported in approximately 0.5-1% of external hernias, whereas the coexistence of acute appendicitis within an inguinal hernia is considerably rarer, accounting for roughly 0.1-0.13% of all appendicitis cases (1,4). Establishing the diagnosis prior to surgery is often challenging, particularly when clinical signs of inflammation are absent. In many patients, the condition is discovered incidentally during operative intervention. Weber et al. (5) documented that only one out of sixty cases received a correct preoperative diagnosis. Recent studies and systematic reviews continue to highlight the rarity of appendiceal involvement in abdominal wall hernias and emphasize the diagnostic challenges associated with these conditions. Advances in cross-sectional imaging, particularly CT, have improved the ability to identify unusual hernia contents preoperatively, although most cases are still diagnosed during surgery (7-9). In the current case, localized pain corresponding to the drain-site raised suspicion and contributed to preoperative identification. The optimal imaging modality in such circumstances remains debated. When physical findings are subtle and peritoneal irritation signs are lacking, CT provides valuable cross-sectional visualization and may facilitate accurate diagnosis (10). In our patient, CT imaging clearly demonstrated a tubular structure entering the hernia sac. Classification systems proposed for Amyand's hernia assist in guiding therapeutic decisions and are summarized in

Figure 1. Oral+IV contrast-enhanced computed tomography cross-sectional image
IV: Intravenous

Table 1. Although our case involved a drain-site defect rather than a classical inguinal hernia, similar principles may be applied when planning management. The decision to perform an appendectomy in cases where the appendix appears non-inflamed remains controversial. Some authors advocate routine removal to eliminate future risk, whereas others recommend preservation when no inflammatory signs are present in order to minimize potential postoperative morbidity (11). In the present case, the decision to perform an appendectomy was made based on several considerations. Although the appendix appeared macroscopically normal, its presence within the hernia sac and the possibility of prior incarceration raised concerns regarding potential vascular compromise and future inflammatory changes. In addition, removal of the appendix eliminated the risk of subsequent appendicitis, which could complicate clinical evaluation. Therefore, appendectomy combined with repair of the abdominal wall defect was considered a safe and definitive surgical strategy. Restoration of fascial integrity can be achieved using either open or minimally invasive techniques. Recent publications have highlighted potential benefits of laparoscopic hernia repair, including reduced postoperative pain and shorter hospitalization periods (12-14). Nevertheless, consensus regarding the superiority of one operative approach over another has not yet been reached. This case highlights the importance of considering unusual hernia contents in patients with a history of major abdominal surgery.

Conclusion

Appendiceal entrapment within a hernia defect arising from a previous drain-site constitutes an exceptionally rare clinical occurrence. Because of its infrequency, awareness among surgeons is essential to prevent delayed recognition and possible complications. CT serves as a useful tool for early detection and operative planning.In this patient, successful management was achieved through laparoscopic appendectomy combined with laparoscopic repair of the hernia defect. However, due to the limited number of reported cases, definitive treatment guidelines cannot yet be established.

Written informed consent for the publication of this case was obtained from the patient's legal representative.

The patient's intraoperative images are shown in Figures 2 and 3.

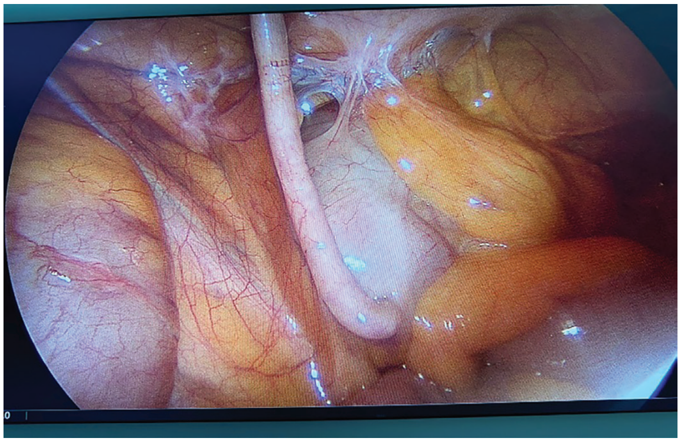

Figure 2. Intraoperative view of appendix vermiformis

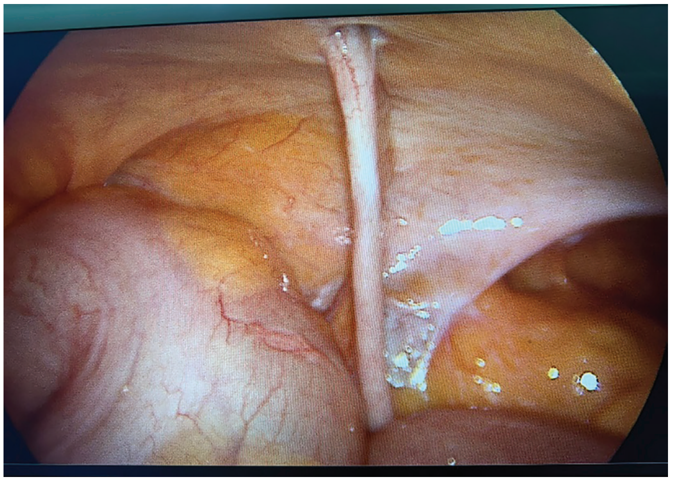

Figure 3. View of appendix vermiformis extending into the hernia sac

Table 1. Losanoff and Basson classification of Amyand's hernia and recommended surgical management

Classification	Definition	Surgical management
Type 1	Normal appendix within an inguinal hernia	Hernia reduction and mesh repair; appendectomy only in young patients
Type 2	Acute appendicitis within an inguinal hernia without abdominal sepsis	Appendectomy through an inguinal incision and hernia repair without mesh placement
Type 3	Acute appendicitis within an inguinal hernia with abdominal/ peritoneal sepsis	Laparotomy, appendectomy, and primary hernia repair without mesh
Type 4	Acute appendicitis within an inguinal hernia with related or unrelated abdominal pathology	Managed as types 1-3; additional pathology is investigated and treated appropriately

Ethics

Informed Consent: Written informed consent for the publication of this case was obtained from the patient's legal representative.

Footnotes

Authorship Contributions

Concept/Design: K.F.I., İ.A., O.Y., İ.C.E., Data Collection or Processing: K.F.I., B.Y., Analysis or Interpretation: K.F.I., M.K.D., İ.A., Literature Review: K.F.I., B.Y., O.Y., Writing, Reviewing and Editing: K.F.I., M.K.D., B.Y., İ.A., İ.C.E.

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LETTER TO THE EDITOR / EDİTÖRE MEKTUP

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Current Status of Right Colon Adenocarcinoma: The Oncological Role of D2 and D3 Dissection

Sağ Kolon Adenokarsinomda Güncel Durum: D2 ve D3 Diseksiyonun Onkolojik Rolü

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The extent of lymphadenectomy in right-sided colon cancer remains one of the most debated topics in surgical oncology. The central question is whether extended nodal dissection beyond D2 confers a meaningful survival benefit. Efforts to align the Japanese D1/D2/D3 classification with Western concepts of complete mesocolic excision (CME) and central vascular ligation (CVL) are hindered by inconsistencies in anatomical boundaries and in procedural standardization. The CME philosophy emphasizes the integrity of the mesocolic fascia as an embryological plane to ensure an intact mesocolic envelope, whereas the Japanese D3 approach focuses on the systematic removal of apical lymph nodes along the feeding vessels. These differing conceptual frameworks complicate direct comparisons of the optimal extent of resection for right colon cancer.

The RICON trial by Balaban et al. (1) is an international multicenter randomized controlled trial (RCT) investigating the impact of D2 vs. D3 lymphadenectomy on 5-year overall survival (OS) in stage II-III right colon cancer. The trial addresses geographical heterogeneity in surgical technique and the well-recognised limitations of prior retrospective, single-institution series by applying strict eligibility criteria and a standardised surgical protocol. As one of the few prospective RCTs using 5-year OS as its primary endpoint rather than surrogate measures, RICON directly addresses a critical evidence gap and has the potential to meaningfully inform future surgical guidelines (1).

The RELARC trial compared laparoscopic CME with D2 dissection across 17 Chinese centers, initially confirming the short-term safety and feasibility of CME (2). However, long-term data published in the Journal of Clinical Oncology (2024) substantially tempered this optimism: no significant difference was found in 3-year disease-free survival [CME 86.1% vs. D2 81.9%; hazard ratio (HR)=0.74; p=0.06] or 3-year OS (CME 94.7% vs. D2 92.6%; HR 0.70; p=0.17), leading investigators to conclude that D2 should remain the standard of care (3). The COLD trial similarly compared D2 and D3 in a multicenter RCT; preliminary data from the first 100 patients confirmed D3 feasibility and safety with no significant increase in major perioperative complications and a higher nodal yield in the D3 arm, though mature survival data remain awaited (4).

A retrospective propensity-matched analysis by Desouza et al. (5) compared CME+D3 with CME+CVL, with both groups undergoing CME and the sole technical difference being additional excision of the surgical trunk of Gillot in the D3 arm. Despite a significantly higher nodal count in the CME+D3 arm (median 31 vs. 25; p=0.003), no improvement in disease-free or OS was observed at a median follow-up of 57 months (5). The D3 group also demonstrated a higher rate of chyle leak (5.6% vs. 0%; p=0.013), attributed to aggressive dissection along the superior mesenteric vein, cautioning against routine D3 adoption outside high-volume centers with dedicated expertise (5).

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The optimal extent of lymphadenectomy for right-sided colon cancer remains unresolved. Previous studies have shown that higher nodal yields do not necessarily translate into better oncological outcomes. The mature results of the RICON and COLD trials will be pivotal in determining whether D3 offers a tangible survival advantage or serves primarily as a staging tool, ultimately shaping future international surgical guidelines.

Keywords: Right-sided colon cancer, lymph node dissection, D2 dissection, D3 dissection

Anahtar Kelimeler: Sağ kolon kanseri, lenf nodu diseksiyonu, D2 diseksiyonu, D3 diseksiyonu

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