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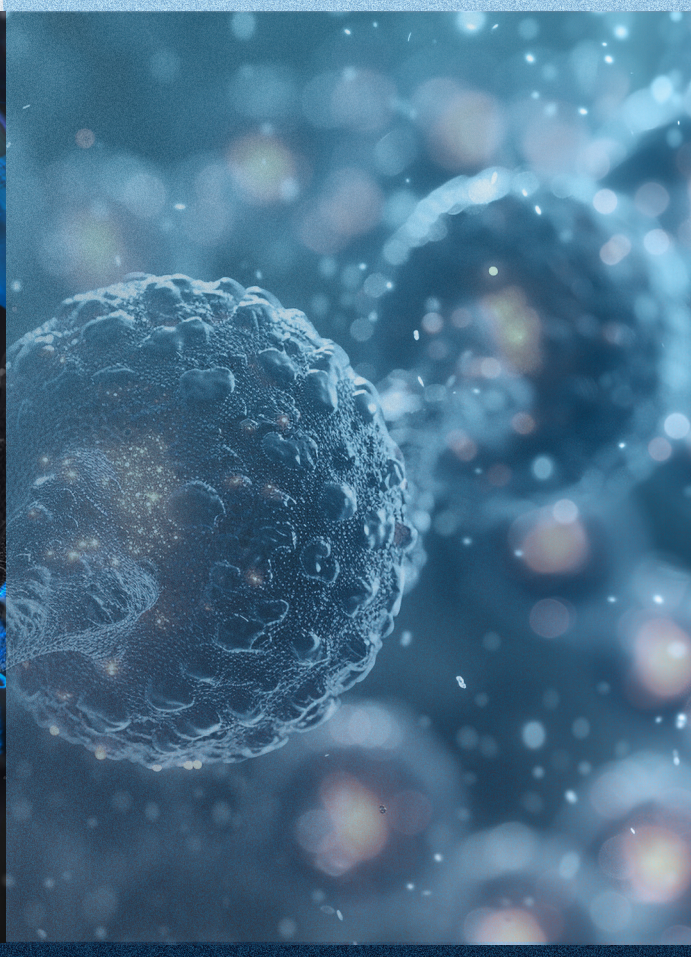

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REVIEW / DERLEME

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Medical Oncology in the Era of Molecular Biomarkers: Clinical Integration, Organ-specific Translation, Immuno-oncology, and Future Perspective

Moleküler Biyomarkırlar Çağında Tıbbi Onkoloji: Klinik Entegrasyon, Organ-spesifik Uyarlama, İmmüno-onkoloji, ve Gelecek Perspektif

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Abstract

The rapid expansion of molecular biomarkers has fundamentally reshaped contemporary oncology practice, transitioning it from morphology-based classification toward biologically driven precision medicine. In line with current scientific advancements, oncology treatment practices will increasingly be patient-centered, driven by genetic analysis and targeted therapy. Personalized treatment based on next-generation sequencing (NGS) will assume a central role. A narrative review of recent literature was conducted, focusing on NGS, liquid biopsy and circulating tumor DNA (ctDNA), minimal residual disease (MRD), immuno-oncology biomarkers, and organ-specific clinical implementation. Biomarker-driven oncology now informs systemic therapy selection, adjuvant strategies, recurrence risk stratification, and multidisciplinary sequencing across major solid tumors, including lung, colorectal, breast, gastric, hepatobiliary, and prostate cancers. ctDNA-based MRD detection has emerged as a dynamic risk stratification tool, while immuno-oncology biomarkers such as programmed death-ligand 1, tumor mutational burden, and microsatellite instability guide checkpoint inhibitor therapy; these biomarkers have varying predictive performance. Future oncology practice will rely on integrated biomarker ecosystems combining genomics, dynamic monitoring, immunologic profiling, and artificial intelligence-assisted decision support systems.

Keywords: Molecular biomarkers, precision oncology, ctDNA, liquid biopsy, minimal residual disease, immuno-oncology, TMB, MSI, digital pathology, multi-omics, AI

Öz

Moleküler biyobelirteçlerdeki hızlı gelişmeler, çağdaş onkoloji pratiğini yeniden şekillendirmiş ve klinik uygulamayı morfolojiye dayandıran sınıflandırmadan biyolojik temelli hassas tıbba doğru kaydırmıştır. Mevcut bilimsel gelişmeler doğrultusunda, onkoloji tedavi uygulamaları giderek daha çok hasta merkezli olacak ve genetik analiz ve hedefe yönelik tedavi ile yönlendirilecektir. Yeni nesil dizileme (NGS) temelli kişiselleştirilmiş tedavi gelecekte esas rolü üstlenecektir. Bu çalışmada, NGS, sıvı biyopsi ve dolaşımdaki tümör DNA'sı (ctDNA), minimal rezidüel hastalık (MRD), immüno-onkoloji biyobelirteçleri ve organa özgü klinik uygulamaya odaklanan yakın zamandaki literatürden derleme incelemesi yapılmıştır. Biyobelirteç odaklı onkoloji, artık akciğer, kolorektal, meme, mide, hepatobiliyer ve prostat kanserleri de dahil olmak üzere başlıca solid tümörlerde sistemik tedavi seçimi, adjuvant stratejiler, nüks riski sınıflandırması ve multidisipliner yaklaşım konusunda yaklaşım salamaktadır. ctDNA bazlı MRD tespiti, dinamik bir risk sınıflandırma aracı olarak ortaya çıkarken, programmed death-ligand 1, tümör mutasyon yükü ve mikrosatellitinstabilitesi gibi immüno-onkoloji biyobelirteçleri, farklı prediktif özellikleri ile immünkontrol inhibitör tedavilerine rehberlik etmektedir.

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Geleceğin onkoloji pratiği, genomik, dinamik izleme, immünolojik profil oluşturma ve yapay zeka destekli kararları birleştiren entegre biyobelirteç ekosistemlerine dayanacaktır.

Anahtar Kelimeler: Moleküler biyobelirteçler, kişselleştirilmiş onkoloji, ctDNA, sıvı biyopsi, minimal rezidüel hastalık, immüno-onkoloji, TBM, MSI, dijital patoloji, çoklu-omikler, YZ

Introduction

Oncology is undergoing a structural reorganization of its decision-making language to treat the diseas faced. Historically, tumor histology and anatomic stage were the primary coordinates for prognosis and treatment selection. On the other hand, in the molecular biomarker era, these coordinates remain essential, but they are increasingly complemented and sometimes superseded by biological features that predict therapeutic vulnerability, resistance, and recurrence risk (1-4) as well. This transition is not merely technological; it changes how clinicians conceptualize risk. A "high-risk" tumor is no longer defined only by size, nodal status, or grade, but in the age modern treatment era also by driver alterations, immune contexture, and the presence of molecular residual disease after definitive therapy (Figure 1) (5-11).

From a medical oncology daily perspective, biomarkers are matter for three practical reasons. First, they compress uncertainty: a predictive biomarker increases the probability that a treatment works for a given patient while reducing exposure to ineffective therapy and to avoid toxicity. Second, biomarkers can convert time into an actionable resource: longitudinal measurements [e.g., circulating tumor DNA (ctDNA)] allow clinicians to detect disease relapse earlier or to show resistance mechanisms without re-biopsy. Third, biomarkers reshape multidisciplinary care by influencing neoadjuvant sequencing, adjuvant intensification or de-escalation, and postoperative surveillance strategies areas where surgical oncology and medical oncology increasingly intersect together (5,6,9,11,12).

The last five years have been particularly dynamic in terms of oncology practice. Precision oncology reviews highlight a steady expansion of targeted therapies and a maturing ecosystem of trial designs (basket, umbrella, platform studies) that operationalize biomarker-driven hypotheses (2,3). In conjuction with this, minimal residual disease (MRD) concepts have moved from hematologic malignancies into solid tumors, with ctDNA technologies enabling molecular detection below radiographic thresholds (5-11). Finally, artificial intelligence (AI) and multi-omics integration are shifting biomarker work from single assays to fused, multimodal predictors that may support clinical decision-making in clinical evaluation (13-15).

Biomarker Taxonomy and the Shift from Static to Dynamic Risk

As known that clinically, biomarkers are often categorized as diagnostic, prognostic, predictive, and monitoring biomarkers. In real daily practice these categories overlap, and the same biomarker can serve multiple roles. For example, microsatellite instability (MSI) can act as a prognostic marker in certain settings as in lung cancer, a predictive biomarker for immune checkpoint inhibitors as in colorectal cancer (CRC), and a clue to inherited cancer risk via mismatch repair deficiency pathways as in Lynch syndrome (16).

A useful contemporary distinction is between static biomarkers (typically measured once from baseline tissue) and dynamic biomarkers (measured repeatedly to capture evolution). Static biomarkers [e.g., epidermal growth factor receptor (EGFR) mutation in non-small cell lung cancer (NSCLC), human epidermal growth factor receptor 2 (HER2) amplification in breast or gastric cancer, *breast cancer gene 2* alterations in prostate cancer] are foundational to targeted therapy selection and often guide first-line strategy (17-23). Dynamic biomarkers especially ctDNA capture changing tumor burden and emergent resistance, and are increasingly discussed as tools for MRD detection after curative-intent surgery or chemoradiation, respectively (5-11).

The dynamic view reframes postoperative surveillance: rather than waiting for radiographic recurrence, clinicians may stratify recurrence risk molecularly and tailor surveillance intensity and adjuvant therapy. However, earlier detection does not automatically imply improved outcomes; clinical utility ultimately depends on whether an intervention triggered by MRD status changes survival or quality of life, a point emphasized in emerging analyses of ctDNA-led recurrence detection (10,11).

Enabling Technologies: Next-generation Sequencing (NGS), Liquid Biopsy, Digital Pathology, and Multi-omics NGS

NGS has become the main platform for identifying actionable alterations, characterizing resistance mechanisms, and enabling tumor-agnostic therapies in oncology practice. Contemporary reviews highlight the clinical translation of diverse biomarker classes oncogenic drivers, homologous recombination deficiency, gene fusions, and mutational signatures that often within panel based workflows that can be deployed across tumor types (1-4). The real-world challenge is less about the existence of sequencing and more about the operational pipeline: tissue adequacy, turnaround time, bioinformatics standardization, and how possible results are integrated into multidisciplinary decision pathways (18,24).

Figure 1. Evolution from histology-based oncology to dynamic biomarker ecosystems combining NGS, ctDNA MRD, and immuno-oncology biomarkers (1-3,5-11)

ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, NGS: Next-generation sequencing, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, PCR: Polymerase chain reaction, BRC-ABL: Breakpoint cluster region-Abelson murine leukemia viral oncogene homolog, CTCs: Circulating tumor cells

Liquid Biopsy and ctDNA

Liquid biopsy encompasses multiple analytes: ctDNA, circulating tumor cells, extracellular vesicles, and other cell-free components. Among these, ctDNA has emerged as the most measurable clinical tool due to assay sensitivity, relative standardization, and direct linkage to tumor genomics (6-9). Narrative and systematic reviews describe applications in (I) baseline genotyping when tissue is unavailable, (II) monitoring treatment response and resistance, and (III) detecting MRD after curative-intent therapy (6-9,11).

The field distinguishes tumor-informed assays (custom panels based on the patient's tumor) from tumor-agnostic assays (fixed panels without prior tumor sequencing). Tumor-informed approaches may offer higher specificity for MRD, while tumor-agnostic assays favor speed and simplicity; both approaches remain under active evaluation for clinical utility and cost-effectiveness as well (10,11).

Digital Pathology and AI

Digital pathology is increasingly considered as a biomarker platform. AI models applied on hematoxylin and eosin images can predict genomic alterations, immune phenotypes, and even immunotherapy response in specific contexts, potentially reducing barriers where molecular testing is delayed or inaccessible (14,15). Importantly, AI outputs should be treated as probabilistic decision aids rather than definitive biomarkers, and prospective validation plus interpretability remain prerequisites for clinical deployment (13-15).

Multi-omics and Multimodal Fusion

Multi-omics integration combines genomics, transcriptomics, epigenomics, proteomics, metabolomics, imaging, and clinical data to build more robust predictors than any single data layer. Recent reviews summarize AI-driven approaches in which including graph-based models and transformers for cross modal fusion and emphasize the need for standardization, reproducibility, and clinically meaningful endpoints (14,15).

Organ-specific Translation: What Actually Changes in Clinical Practice (Figure 2, Table 1) (17,20,21,24-26)

NSCLC

NSCLC represents the model of biomarker-driven systemic therapy. Contemporary guidelines and implementation reviews emphasize comprehensive molecular profiling for key drivers [EGFR, anaplastic lymphoma kinase, ROS proto-oncogene 1,

Table 1. Organ-specific molecular biomarkers and clinical implications in contemporary oncology

Tumor type	Key molecular biomarkers	Primary clinical role	Impact on clinical management
NSCLC	EGFR, ALK, ROS1, RET, MET exon 14, KRAS G12C, PD-L1	Predictive	Genotype-matched targeted therapy; immunotherapy stratification; longitudinal ctDNA monitoring
Colorectal cancer	KRAS/NRAS, BRAF, MSI/dMMR, ctDNA (MRD)	Predictive+monitoring	Anti-EGFR selection; immunotherapy eligibility (MSI-H); adjuvant risk stratification; MRD-guided decisions
Breast cancer	ER, PR, HER2, ESR1 (ctDNA), genomic signatures	Predictive+prognostic	Endocrine therapy guidance; anti-HER2 therapy; resistance monitoring; recurrence risk assessment
Gastric/GEJ cancer	HER2, MSI, CLDN18.2	Predictive	HER2-directed therapy; immunotherapy in MSI-high disease; CLDN18.2-targeted therapy (e.g., zolbetuximab)
Cholangiocarcinoma	FGFR2 fusions, IDH1 mutations	Predictive	FGFR inhibitor therapy; IDH1-targeted treatment
Prostate cancer	BRCA1/2, HRR/DDR genes, AR alterations	Predictive	PARP inhibitor eligibility; treatment sequencing; resistance monitoring

NSCLC: Non-small cell lung cancer, GEJ: Gastroesophageal junction, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS1: ROS proto-oncogene 1, RET: Rearranged during transfection, MET exon 14: MET proto-oncogene, receptor tyrosine kinase exon 14 alteration, KRAS G12C: Kirsten rat sarcoma viral oncogene G12C mutation, KRAS: Kirsten rat sarcoma viral oncogene, NRAS: Neuroblastoma RAS viral oncogene homolog, BRAF: B-Raf proto-oncogene, serine/threonine kinase, MSI/dMMR: Microsatellite instability/mismatch repair deficiency, ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, ESR1: Estrogen receptor 1, FGFR2: Fibroblast growth factor receptor 2, IDH1: Isocitrate dehydrogenase 1, AR: Androgen receptor, HRR/DD: Homologous recombination repair/DNA damage response, CLDN18.2: Claudin 18.2 (a cell surface protein), PD-L1: Programmed death-ligand 1, BRCA1/2: Breast cancer gene 1/2, PARP: Poly (ADP-ribose) polymerase

B-Raf proto-oncogene (BRAF), MET exon 14 skipping, rearranged during transfection, neurotrophic tyrosine receptor kinase (NTRK), Kirsten rat sarcoma viral oncogene G12C mutation) because targeted therapy selection depends on accurate identification of actionable subsets and resistance pathways (18-20,25). Transactionally, delays and inconsistent testing remain major barriers; practical solutions include reflex testing, standardized pathways, and early integration of liquid biopsy when tissue is limited (18,24).

In the perioperative setting, the biomarker story is expanding from driver genotyping to dynamic assessment of response and residual disease. ctDNA-based monitoring after curative-intent therapy has shown prognostic value in early-stage NSCLC and may enable risk adapted adjuvant strategies, although prospective interventional evidence is still emerging (7,10). The clinical potential is clear: how to integrate molecular relapse signals without over-treatment or anxiety, and how to act when an MRD-positive result appears months before radiographic disease is detectable (5-11).

CRC

CRC biomarker practice involves both static and dynamic components. Static biomarkers include rat sarcoma virus and BRAF for targeted therapy selection and MSI status for immunotherapy eligibility and prognostic stratification (17). The most disruptive addition is ctDNA-based MRD. Multiple reviews synthesize evidence that postoperative ctDNA positivity is strongly associated with recurrence risk and may outperform clinicopathologic risk factors for MRD assessment (5,6,10,11,27,28).

A key next-step question is whether MRD-guided treatment changes survival. Prospective work has begun to link MRD status to overall survival and to evaluate intervention strategies based on ctDNA results (11,29). However, clinical utility requires more than prognostic correlation; pathways especially for adjuvant escalation, de-escalation, and the definition of actionable thresholds must be standardized (10,11,27-29).

Breast Cancer

Breast cancer remains structured by receptor biomarkers (estrogen receptor/progesterone receptor and HER2) as in luminal classification and genomic risk signatures, but molecular biomarker practice is evolving in two directions: resistance mapping in advanced disease and ctDNA applications in early-stage surveillance (20,30-33). Estrogen receptor 1 mutations in ctDNA illustrate how liquid biopsy can operationalize endocrine resistance mechanisms and support treatment selection in hormone receptor-positive disease especially in progressive disease (30-32). Meanwhile, ctDNA MRD concepts in early-stage breast cancer are being actively investigated; reviews emphasize the consistent association between ctDNA positivity and recurrence risk while highlighting assay sensitivity, standardization, and interventional trial evidence as key gaps (33-35).

Gastric and Gastroesophageal Junction (GEJ) Cancers

In gastric/GEJ cancers, the biomarker landscape is expanding beyond HER2 and MSI to include Claudin 18.2 (CLDN18.2) as a therapeutic target. Recentlly, phase 3 trials have shown clinical benefit for zolbetuximab plus chemotherapy in CLDN18.2-positive, HER2-negative disease, motivating routine testing considerations (20-23). Reviews and prevalence studies suggest CLDN18.2 is

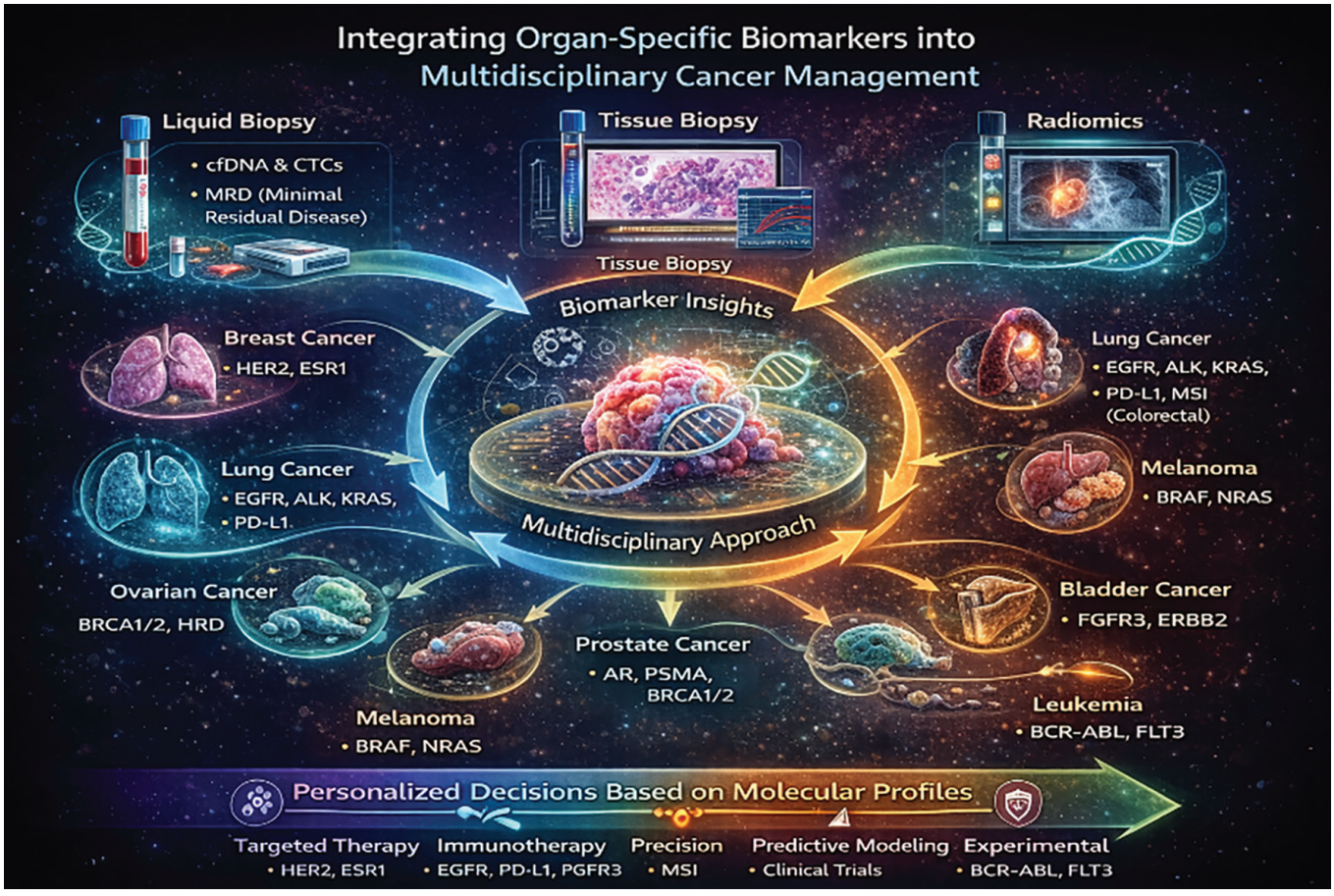

Figure 2. Organ-specific integration of biomarkers into multidisciplinary pathways across NSCLC, CRC, breast, gastric/GEJ, hepatobiliary, and prostate cancers (17-29,36-38)

NSCLC: Non-small cell lung cancer, CRC: Colorectal cancer, GEJ: Gastroesophageal junction, BRAF: B-Raf proto-oncogene, serine/threonine kinase, KRAS: Kirsten rat sarcoma viral oncogene, NRAS: Neuroblastoma RAS viral oncogene homolog, ALK: Anaplastic lymphoma kinase, AR: Androgen receptor, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, ESR1: Estrogen receptor 1, FGFR3: Fibroblast growth factor receptor 3, MSI: Microsatellite instability, HRD: Homologous recombination deficiency, ERBB: Epidermal growth factor receptor, PD-L1: Programmed death-ligand 1, BRCA1/2: Breast cancer gene 1/2, cfDNA: Cell free DNA, CTCs: Circulating tumor cells, PSMA: Prostate-specific membrane antigen, BRC-ABL: Breakpoint cluster region-Abelson murine leukemia viral oncogene homolog, FLT3: Fms-like tyrosine kinase 3

common and may remain relatively stable over time, supporting its feasibility as a clinical biomarker (22,23).

Hepatobiliary Cancers and Cholangiocarcinoma

Cholangiocarcinoma illustrates the value of biomarker stratification in rare, aggressive tumors. Fibroblast growth factor receptor 2 (FGFR2) rearrangements and isocitrate dehydrogenase 1 mutations are clinically actionable subsets. Targeted therapies (including FGFR inhibitors) have demonstrated activity in FGFR-altered disease, and multiple reviews address resistance mechanisms and safety profiles, emphasizing the importance of longitudinal molecular monitoring (25,36,37).

Prostate Cancer and Genitourinary Malignancies

Prostate cancer biomarkers increasingly span inherited and acquired alterations in DNA damage repair pathways, with poly (ADP-ribose) polymerase inhibitors demonstrating benefit in selected molecular subsets. Recent reviews summarize emerging biomarkers across genetic, RNA-based, metabolic, and epigenetic classes and discuss how molecular stratification may refine prognosis and therapy (26,38). The near-term clinical direction is toward more systematic germline and somatic testing pipelines, earlier integration of targeted therapies, and biomarker guided combinations, while retaining careful toxicity management and validation (38).

Immuno-oncology Biomarkers: Promise, Friction, and Composite Approaches (Table 2) (12-16,39)

The immunotherapy era introduced biomarkers that reflect tumor immune interaction rather than solely tumor-intrinsic genetics. PD-L1 expression, tumor mutational burden (TMB), tumor-infiltrating lymphocytes, and MSI are the most widely discussed in oncology practice. Narrative reviews emphasize

Table 2. Immuno-oncology biomarkers: utility and limitations

Biomarker	Method	Clinical use	Limitations
PD-L1	IHC	Checkpoint inhibitor selection	Intratumoral heterogeneity; assay variability; dynamic expression changes
TMB	NGS-based assay	Immunotherapy stratification (selected tumor types)	Platform variability; lack of standardized thresholds
MSI/dMMR	IHC/PCR/NGS	Strong predictor of PD-1/PD-L1 inhibitor response	Tumor-type dependent prevalence; variable sensitivity
TILs	Histopathology/RNA-based profiling	Prognostic value; emerging predictive utility	Lack of universal scoring standardization

PD-L1: Programmed death-ligand 1, TMB: Tumor mutational burden, MSI/dMMR: Microsatellite instability/mismatch repair deficiency, TILs: Tumor-infiltrating lymphocytes, IHC: Immunohistochemistry, NGS: Next-generation sequencing, PCR: Polymerase chain reaction

that predictive performance is inconsistent across tumor types and disease stages, limited by assay variability, sampling bias, and dynamic expression (12,16,39). MSI remains one of the most robust predictors of response to PD-1 blockade in several contexts, and guideline recommendations emphasize standardized MSI testing approaches (17).

Beyond baseline prediction, biomarkers are increasingly used to understand resistance to therapy. In NSCLC, for example, reviews dissect tumor-intrinsic and microenvironmental drivers of immunotherapy resistance even in PD-L1-high disease, underscoring why single marker strategies often fail and motivating composite or longitudinal biomarker approaches (12).

Composite biomarker strategies combine tumor genomics (TMB/MSI), immunohistochemistry, spatial immune architecture, and dynamic signals such as ctDNA kinetics. This reflects a broader principle: immunotherapy response is a systems property, not a single gene event. Multimodal AI approaches that integrate histopathology, omics, and imaging may become particularly useful here, provided prospective validation demonstrates incremental value over existing clinical models (13-15).

MRD: From Prognostic Signal to Interventional Tool (Figure 3)

MRD in solid tumors is often termed molecular residual disease and refers to tumor derived fragments that persist after definitive therapy but remain below detection of conventional imaging. Reviews describe ctDNA MRD as a dynamic biomarker that can identify recurrence risk earlier than radiology and may support risk adapted adjuvant strategies (5,6,8-11).

CRC provides the most mature MRD evidence base, with prospective data linking MRD to outcomes and ongoing trials testing ctDNA-guided adjuvant therapy strategies (10,11,27-29). Breast and lung cancer are rapidly following, but the key obstacles are consistent: assay sensitivity (especially in low-shedding tumors), pre-analytic variables, false positives from clonal hematopoiesis, and the need for clinically actionable algorithms (8-11,33-35).

From a multidisciplinary viewpoint, MRD has surgical implications. It could influence adjuvant therapy decisions after R0 resection, surveillance intensity, and selection for clinical trials. Until now the field must avoid premature over reliance: MRD is a powerful risk stratifier, but patient benefit depends on evidence that MRD-guided actions improve survival, reduce toxicity, or meaningfully enhance quality of life (10,11,29).

Tumor-agnostic Biomarkers and the Expansion of "Biology-First" Treatment

Tumor-agnostic therapy targets are specific molecular alterations of whom independent of the tumor's site of origin. Reviews highlight both the clinical promise and practical challenges: assay standardization, rare biomarker prevalence, equitable access to testing, and the need for multidisciplinary interpretation (40). NTRK fusions represent a canonical example of a biomarker enabling tumor-agnostic targeted therapy; clinical translation depends on robust fusion detection and careful diagnostic workflows (41).

Future Perspective

From Single Biomarkers to Biomarker Ecosystems (Table 3) (13-15)

The next phase of biomarker oncology is likely to be characterized by integration rather than proliferation. Instead of adding isolated markers, clinical value will come from (I) standardized pipelines, (II) longitudinal monitoring frameworks, and (III) multimodal fusion of omics, imaging, histopathology, and real-world clinical data for decision support (13-15).

AI-driven multi-omics integration reviews emphasize two themes. First, model performance must translate into clinical utility, meaning measurable improvement in decisions compared with current standards. Second, interpretability, robustness, and governance are not optional; they determine whether a model can be trusted in heterogeneous real-world settings (13-15).

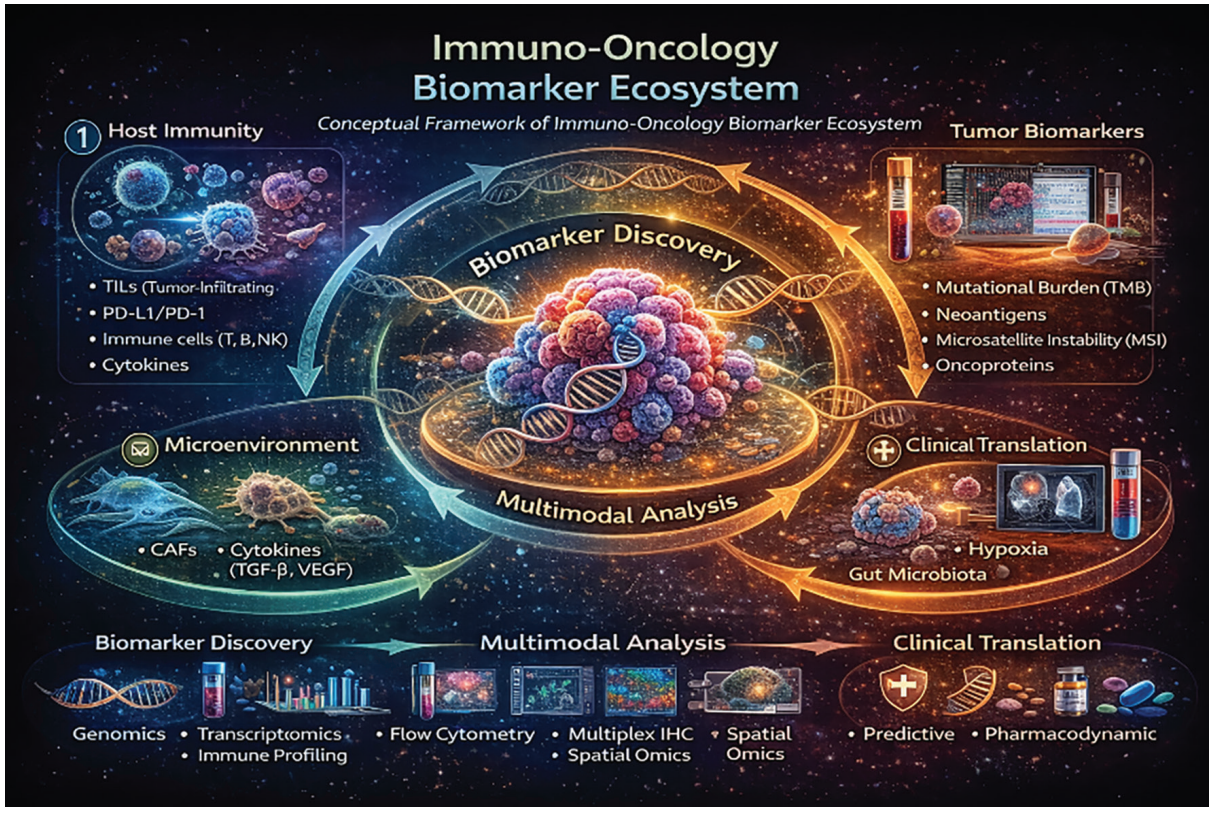

Figure 3. Immuno-oncology biomarker ecosystem: tumor-intrinsic genomics (TMB/MSI), microenvironment, and dynamic monitoring approaches (12-16,39)

TMB: Tumor mutational burden, MSI: Microsatellite instability, IHC: Immunohistochemistry, TGF-β: Transforming growth factor-beta, VEGF: Vascular endothelial growth factor, CAFs: Cancer-associated fibroblasts, TILs: Tumor-infiltrating lymphocytes, PD-L1: Programmed death-ligand 1, PD-1: Programmed cell death-1, T: T lymphocyte, B: B lymphocyte, NK: Naturel killer

Table 3. Emerging directions in molecular oncology

Emerging field	Technology	Potential application	Current challenge
ctDNA MRD-guided therapy	Tumor-informed ctDNA assays	Adjuvant therapy escalation or de-escalation	Requirement for long-term survival validation
AI-based histopathology	Deep learning applied to H&E slides	Immunotherapy response prediction	Need for prospective clinical validation
Multi-omics integration	Genomics+transcriptomics+imaging platforms	Composite predictive modeling	Data harmonization and standardization challenges
Tumor-agnostic treatment strategies	Comprehensive NGS panels	Biology-first, mutation-driven therapy selection	Access limitations and cost barriers

ctDNA: Circulating tumor DNA, MRD: Minimal residual disease, AI: Artificial intelligence, H&E: Hematoxylin and eosin, NGS: Next-generation sequencing

Transactionally, the future is also about systems: turnaround time, reimbursement, laboratory capacity, and multidisciplinary tumor boards capable of interpreting complex results. Biomarker innovation will not achieve its potential unless health systems can deliver timely, standardized testing and embed results into care pathways.

Practical Recommendations for Clinical Integration

• Use guideline concordant comprehensive profiling in biomarker-driven diseases (e.g., NSCLC) and ensure reflex testing pathways in daily practice (17-19,24).

• Prefer validated, clinically actionable biomarkers; treat exploratory multi-omics predictors as decision aids until prospectively validated (13-15).

• For MRD/ctDNA, integrate results into predefined clinical pathways (adjuvant escalation/de-escalation, trial referral) and communicate uncertainty clearly (5-11,27-29,33-35).

• Anticipate tumor heterogeneity: when tissue is limited, consider liquid biopsy as complementary rather than substitutive when feasible (6-9,11).

• Maintain multidisciplinary review of complex findings, especially for tumor-agnostic indications and rare alterations (40,41).

Footnotes

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Classic and Follicular Variants of Papillary Thyroid Carcinoma: A Comparative Clinicopathological Analysis

Papiller Tiroid Karsinomunun Klasik ve Foliküler Varyantları: Karşılaştırmalı Klinikopatolojik Analiz

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Abstract

Objectives: Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximately 70% of all thyroid cancers, and its prevalence has been increasing steadily. Although the prognosis is generally favorable, disease recurrence may occur in approximately 10% of patients, and disease-related mortality has been reported in nearly 5% of cases. The most frequently observed histopathological subtypes of PTC are the classic variants (CV) and follicular variants (FV). However, it has been suggested that clinical behavior and prognosis may differ among the histopathological subtypes, and studies directly comparing these variants remain limited. Pathological features such as capsular invasion, lymphatic invasion, and extrathyroidal extension have been reported to play a critical role in predicting the biological behavior and prognosis of the disease.

The aim of this study was to compare the CV and FV of PTC with respect to clinical and histopathological characteristics and to identify potential differences between these variants.

Material and Methods: This retrospective study involved reviewing the medical records and final pathology reports of patients who underwent thyroid surgery at a tertiary referral center between 2012 and 2023. Pathology reports for 401 patients were screened. Among these, 98 patients with a final pathological diagnosis of PTC were identified. Those with tall-cell variant, anaplastic carcinoma, and other rare histopathological variants were excluded; a total of 77 patients diagnosed with CV-PTC or FV-PTC were included in the analysis. Demographic data, clinical presentation, surgical and adjuvant treatments, and pathological features, including capsular invasion, lymphatic invasion, and extrathyroidal extension, were evaluated. Tumors were staged according to the AJCC/TNM 8th edition staging system. Survival analyses were performed using the Kaplan-Meier method.

Results: Of the 77 patients, 48 were in the FV-PTC group and 29 were in the CV-PTC group. The age at diagnosis was significantly higher in the FV-PTC group compared with the CV-PTC group (51.6±12.9 vs. 44.8±13.5 years; p=0.031). No significant differences were observed between the groups in clinical presentation, surgical management, or rates of radioactive iodine therapy. Capsular invasion was significantly more frequent in the CV-PTC group (p=0.029). Lymphatic invasion was also higher in the CV-PTC group (p=0.017). Extrathyroidal extension was significantly more frequent in the CV-PTC group (p<0.001). No significant differences were detected between the groups in terms of stage distribution or overall survival (log-rank p=0.921).

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Conclusion: This study demonstrates marked differences in histopathological aggressiveness between the CV and FV of PTC, with capsular invasion, lymphatic invasion, and extrathyroidal extension observed more frequently in the CV. However, these differences did not translate into significant disparities in stage distribution or survival outcomes between the two groups. Histopathological variants should therefore be considered alongside other clinical and pathological risk factors when making clinical decisions for PTC.

Keywords: Classic variant, follicular variant, papillary thyroid carcinoma, clinicopathological features, prognosis

Öz

Giriş / Amaç: Papiller tiroid karsinomu (PTK), tüm tiroid kanserlerinin yaklaşık %70'ini oluşturan en sık görülen tiroid malignitesidir ve prevalansı istikrarlı bir şekilde artmaktadır. Prognoz genel olarak olumlu olmakla birlikte, hastaların yaklaşık %10'unda hastalık nüksü gelişebilmekte ve olguların yaklaşık %5'inde hastalığa bağlı mortalite bildirilmektedir. PTK'nın en sık gözlenen histopatolojik alt tipleri klasik varyant (KV) ve foliküler varyanttır (FV). Bununla birlikte, histopatolojik alt tipler arasında klinik davranış ve prognozun farklılık gösterebileceği öne sürülmüş olup bu varyantları doğrudan karşılaştıran çalışmalar sayıca sınırlı kalmıştır. Kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım gibi patolojik özelliklerin, hastalığın biyolojik davranışını ve prognozunu öngörmede kritik bir rol oynadığı bildirilmiştir.

Bu çalışmanın amacı, PTK'nın KV ve FV'lerini klinik ve histopatolojik özellikler açısından karşılaştırmak ve bu varyantlar arasındaki olası farklılıkları ortaya koymaktır.

Gereç ve Yöntem: Bu retrospektif çalışma, 2012-2023 yılları arasında üçüncü basamak bir referans merkezde tiroid cerrahisi uygulanan hastaların tıbbi kayıtları ve nihai patoloji raporlarının incelenmesiyle gerçekleştirildi. Toplam 401 hastanın patoloji raporları tarandı. Bu hastalar arasından nihai patolojik tanısı PTK olan 98 hasta belirlendi. Uzun boylu hücreli varyant, anaplastik karsinom ve diğer nadir histopatolojik varyantlara sahip hastalar dışlandı ve KV-PTK veya FV-PTK tanısı alan toplam 77 hasta analize dahil edildi. Demografik veriler, klinik başvuru bulguları, cerrahi ve adjuvan tedaviler ile kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım dahil olmak üzere patolojik özellikler değerlendirildi. Tümörler AJCC/TNM 8. baskıya göre evrelendi. Sağkalım analizleri Kaplan-Meier yöntemi ile gerçekleştirildi.

Bulgular: Çalışmaya dahil edilen 77 hastanın 48'i FV-PTK grubunda, 29'u KV-PTK grubunda yer almaktaydı. Tanı yaşı FV-PTK grubunda KV-PTK grubuna kıyasla anlamlı olarak daha yüksek bulundu (51,6±12,9'a karşı 44,8±13,5 yıl; p=0,031). Klinik başvuru bulguları, cerrahi yaklaşım ve radyoaktif iyot tedavisi oranları açısından gruplar arasında anlamlı fark saptanmadı. Kapsül invazyonu KV-PTK grubunda anlamlı olarak daha sık izlendi (p=0,029). Lenfatik invazyon da KV-PTK grubunda daha yüksek oranda gözlendi (p=0,017). Ekstratiroidal uzanım KV-PTK grubunda belirgin olarak daha sık saptandı (p<0,001). Evre dağılımı ve genel sağkalım açısından gruplar arasında anlamlı fark tespit edilmedi (log-rank p=0,921).

Tartışma / Sonuç: Histopatolojik agresiflik açısından PTK'nın KV ve FV arasında belirgin farklılıklar bulunmakta olup kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım klasik varyantta daha sık gözlenmektedir. Bununla birlikte, bu farklılıklar evre dağılımı ve sağkalım sonuçları açısından anlamlı bir ayrışmaya yol açmamıştır. Bu nedenle histopatolojik varyantların, PTK'da klinik karar alma süreçlerinde diğer klinik ve patolojik risk faktörleriyle birlikte değerlendirilmesi önerilmektedir.

Anahtar Kelimeler: Klasik varyant, foliküler varyant, papiller tiroid karsinomu, klinikopatolojik özellikler, prognoz

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximately 70% of thyroid cancers, and its incidence has been increasing steadily, with epidemiological data showing a rise from 9.9 to 16.1 per 100.000 between 2003 and 2017 (1). Although the prognosis is generally favorable, certain clinical features such as a history of rapid nodule growth, invasion into surrounding tissues, new-onset hoarseness, or ipsilateral cervical lymphadenopathy are important indicators of an increased likelihood of malignancy. Surgical treatment followed by radioactive iodine (RAI) therapy is curative for the majority of patients. Nevertheless, disease recurrence may occur in approximately 10% of patients, and disease-related mortality has been reported in nearly 5% of cases; a comprehensive appraisal of recurrence risk factors has highlighted the importance of identifying high-risk patients at disease onset to guide personalized management (2,3).

The most frequently observed histopathological subtypes of PTC are the classic variant (CV) and the follicular variant (FV). These variants are referred to as the CV-PTC and the FV-PTC, respectively. In the literature, the CV has been reported to constitute approximately 55-65% of all PTC, whereas the FV accounts for 23-41% (3-5). However, it has been suggested that clinical behavior and prognosis may differ among the histopathological subtypes of PTC, with recent large-scale data indicating that extrathyroidal extension and lymph node metastasis are significantly more common in the CV compared with the FV (6). Furthermore, the introduction of the 2022 World Health Organization (WHO) classification has brought important reclassifications regarding follicular-patterned tumors, underscoring the need for updated comparative analyses between these subtypes (7). A clearer

delineation of these differences is important for prognostic assessment and for guiding patient management.

Numerous studies have aimed to identify clinical and pathological markers that may be associated with long-term adverse clinical outcomes among PTC variants (3,5). These markers include histological subtypes, tumor invasion characteristics, and genetic mutation profiles (5,6). Pathological features such as capsular invasion, lymphatic invasion, and microscopic and macroscopic extrathyroidal extension have been reported to play a critical role in predicting the biological behavior and prognosis of the disease (6,7); recent evidence further confirms that the degree and extent of these invasion parameters are independently associated with lymph node metastasis and disease recurrence (8). However, the number of studies evaluating these clinical and histopathological markers in a comparative manner between the classic and FV remains limited, and their relative prognostic significance within each variant warrants further investigation in light of contemporary classification criteria (9).

The aim of this study was to compare the classic and FV of PTC with respect to clinical and histopathological characteristics and to identify potential differences between these variants. Within this framework, the distribution of clinical and pathological parameters reported to be important for prognostic prediction was evaluated across the variants. Through this approach, our study aimed to contribute to a better understanding of variant-specific clinical and pathological features in PTC.

Materials and Methods

This retrospective study involved reviewing the medical records and final pathology reports of patients who underwent thyroid surgery in the department of general surgery of a tertiary referral center between 2012 and 2023. During the study period, pathology reports from 401 patients who underwent thyroid surgery were screened. Among these, 98 patients with a final pathological diagnosis of PTC were identified. Thyroid pathologies other than PTC were excluded from the study. Of the 98 patients diagnosed with PTC, those with the tall-cell variant, anaplastic carcinoma, and other rare histopathological variants were excluded, and a total of 77 patients diagnosed with the classic or FV of PTC who met the study criteria were included in the analysis.

Histopathological subtype classification was performed based on the diagnoses reported in the archived pathology reports. Diagnoses were based on the histopathological criteria defined in the 2017 WHO classification of tumours of endocrine organs, which was in effect during the study period. Cases were divided into two groups according to the pathology reports: the CV-PTC and the FV-PTC. Pathological evaluations were performed by the department of pathology at the same institution as part of routine diagnostic practice and based on the histopathological diagnostic criteria valid during the respective period. As the study period preceded the 2022 WHO classification, a systematic retrospective reclassification of non-invasive encapsulated FV cases (NIFTP) could not be performed. Therefore, cases were evaluated according to the terminology reported in the archived pathology reports.

Demographic data (age, sex), presenting complaints and symptoms (asymptomatic status, neck swelling, dyspnea), surgical procedures performed, pathological findings, RAI therapy, staging, and survival data were obtained retrospectively from patients' records. Preoperative thyroid functional status was classified as hyperthyroidism, hypothyroidism, or euthyroidism based on thyroid-stimulating hormone (TSH) levels measured during anesthesia preparation.

The surgical approach was planned according to preoperative evaluation and clinical indications. The surgical technique was determined on an individual basis, taking into account tumor size, location, and extent; patients underwent lobectomy, total thyroidectomy, or completion thyroidectomy as indicated. The application of neck dissection was recorded in the patients' files. Postoperative RAI therapy administration was recorded, and indications for RAI and treatment decisions were determined by the radiation oncology department.

Pathological parameters reported as prognostically significant were extracted from pathology reports. The presence of capsular invasion and lymphatic/lymphovascular invasion was classified as "present" or "absent" as reported in the pathology findings. The presence of extrathyroidal extension was recorded as reported; in cases where microscopic or macroscopic distinction was not specified in the report, extrathyroidal extension was evaluated as "present" or "absent." Tumor staging was determined according to the American Joint Committee on Cancer (AJCC)/tumor-node-metastasis (TNM) 8th edition criteria based on data obtained from medical records.

Follow-up duration and survival data were obtained from clinical records. Overall survival was defined as the time interval (months) from the date of surgery to death or last follow-up. Survival analysis was performed using the Kaplan-Meier method, and differences in survival between groups were compared using the log-rank test.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 25.0). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution were expressed as mean ± standard deviation, whereas non-normally distributed variables were expressed as median (interquartile range). Comparisons of

continuous variables between the two groups were performed using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. A two-sided p-value of <0.05 was considered statistically significant.

Ethics committee approval was obtained for the study from Çukurova University Faculty of Medicine (approval no: 26, date: 09.01.2026). Due to the retrospective study design, the requirement for individual informed consent was waived by the ethics committee.

Results

Of the 77 patients included in the study, 48 were in the FV-PTC group and 29 were in the CV-PTC group. When demographic characteristics were compared between the groups, the age at diagnosis was found to be significantly higher in the FV-PTC group compared with the CV-PTC group (51.6±12.9 vs. 44.8±13.5 years; p=0.031). No significant difference in sex distribution was observed between the two groups (Table 1).

With a focus on the clinical presentation, a similar distribution was observed between the two variants. In both groups, the most common presenting complaint was a palpable neck mass, whereas asymptomatic cases and patients presenting with dyspnea were observed less frequently. When preoperative thyroid functional status was evaluated, the majority of patients in both groups were euthyroid, and no significant difference in TSH-based classification was detected between the groups (Table 1).

Table 1. Demographic, clinical, and treatment characteristics of the patients

Variable	FV-PTC (n=48)	CV-PTC (n=29)	p-value
Age (years)	51.6±12.9	44.8±13.5	0.031
Sex			
Male	9 (18.8%)	8 (27.6%)	0.365
Female	39 (81.3%)	21 (72.4%)	
Symptomatic presentation	39 (81.2%)	26 (89.7%)	0.324
Preoperative TSH status	0.926		
Hyperthyroid	2 (4.2%)	1 (3.4%)	
Hypothyroid	1 (2.1%)	1 (3.4%)	
Euthyroid	45 (93.8%)	27 (93.1%)	
Neck dissection	6 (12.5%)	3 (10.3%)	0.775
Radioactive iodine therapy	32 (68.1%)	23 (79.3%)	0.288

Data are presented as mean ± standard deviation or n (%). P-values were calculated using the Student's t-test, chi-square test, or Fisher's exact test, as appropriate

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma, TSH: Thyroid-stimulating hormone

No marked difference was observed between the FV-PTC and CV-PTC groups with regard to surgical procedures. Neck dissection rates were similar in the two variants. Likewise, the rates of postoperative RAI therapy administration were comparable between the groups (Table 1).

When pathological features were compared, findings reflecting invasion and tumor spread were more pronounced in the CV-PTC group. Capsular invasion was significantly more frequent in the CV-PTC group than in the FV-PTC group (p=0.029). Similarly, lymphatic invasion occurred more frequently in the CV-PTC group (p=0.017), and extrathyroidal extension occurred markedly more frequently in the CV-PTC group than in the FV-PTC group (p<0.001) (Table 2).

No significant differences in stage distribution were observed between the groups. The mean overall survival was 97.3 months in the FV-PTC group and 93.6 months in the CV-PTC group. According to Kaplan-Meier analysis, no statistically significant difference in survival was detected between the groups (log-rank p=0.921). During the follow-up period, one death related to primary thyroid malignancy was recorded in the CV-PTC group, while one death due to a non-thyroid-related cause was recorded in the FV-PTC group (Table 3, Figure 1).

Table 2. Comparison of tumor and pathological characteristics

Pathological feature	FV-PTC (n=48)	CV-PTC (n=29)	p-value
Capsular invasion	13 (27.1%)	15 (51.7%)	0.029
Lymphatic/lymphovascular invasion	8 (16.7%)	12 (41.4%)	0.017
Extrathyroidal extension	10 (20.8%)	17 (58.6%)	<0.001

Data are presented as n (%). P-values were calculated using the chi-square test or Fisher's exact test, as appropriate

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma

Table 3. Staging and survival outcomes

AJCC TNM stage distribution		
AJCC stage	**FV-PTC (n=48)**	**CV-PTC (n=29)**
Stage 0	1 (2.1%)	0
Stage I	7 (14.6%)	1 (3.4%)
Stage II	27 (56.3%)	17 (58.6%)
Stage III	9 (18.8%)	8 (27.6%)
Stage IV	4 (8.3%)	3 (10.3%)

Staging was performed according to the AJCC/TNM 8th edition criteria. P-value for stage distribution comparison: p=0.478 (chi-square test). Mean overall survival: 97.3 months (FV-PTC) vs 93.6 months (CV-PTC); log-rank p=0.921

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma, AJCC: American Joint Committee on Cancer, TNM: Tumor-node-metastasis

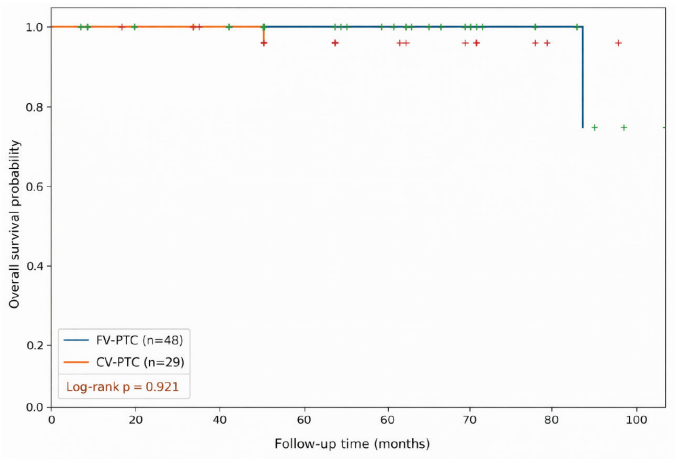

Figure 1. Survival outcomes

Kaplan-Meier overall survival curves for follicular variant papillary thyroid carcinoma (FV-PTC) and classic variant papillary thyroid carcinoma (CV-PTC). The x-axis represents follow-up time in months; the y-axis represents cumulative survival probability. No statistically significant difference in overall survival was detected between the two groups (log-rank p=0.921). One disease-specific death was recorded in the CV-PTC group and one non-thyroid-related death in the FV-PTC group during the follow-up period

Discussion

In this study, the classic and FV of PTC were compared with respect to clinical, surgical, and histopathological characteristics. Our findings demonstrated that the CV of PTC exhibited higher rates of pathological indicators of aggressiveness, including capsular invasion, lymphatic invasion, and extrathyroidal extension, compared with the FV. These findings are consistent with the existing literature suggesting that CV-PTC tends to display a more infiltrative growth pattern, potentially reflecting its BRAF-like molecular profile and associated downstream effects on tumor invasiveness (10). In contrast, no significant differences were identified between the two variants in terms of stage distribution, surgical and adjuvant treatments administered, or survival duration. Although these results suggest that the CV may, histopathologically, display a more aggressive biological behavior they indicate that this aggressiveness does not translate into a marked difference in mid- to long-term survival outcomes, a finding that has similarly been reported in other comparative series (11).

The detection of higher rates of capsular invasion, lymphatic invasion, and extrathyroidal extension in the CV of PTC suggests that this variant may exhibit more aggressive histopathological features than the FV. The CV is predominantly associated with the BRAF V600E mutation, which activates the MAPK signaling pathway and has been shown to upregulate VEGF-C expression, thereby promoting lymphangiogenesis and facilitating lymphatic invasion (12). The more frequent presence of papillary architecture in the CV, combined with its infiltrative growth pattern and associated stromal reaction, may allow tumor cells to establish earlier and more pronounced contact with stromal and lymphatic structures (10). In contrast, the FV-particularly its encapsulated form-is more commonly associated with RAS-like molecular alterations and tends to exhibit a less-infiltrative phenotype, which may account for the lower rates of invasion-related findings observed in our FV-PTC cohort (capsular invasion: 27.1% vs. 51.7%; lymphatic invasion: FV-PTC vs. CV-PTC, p=0.017; extrathyroidal extension: 20.8% vs. 58.6%, p<0.001) (7). In this context, the invasion-related pathological findings observed in the CV in our study support the presence of biologically distinct behaviors among the subtypes of PTC, consistent with their divergent molecular landscapes.

Although more pronounced features of invasion and dissemination were identified in the CV of PTC in our study, these findings did not translate into significant differences in stage distribution (stage I-II: 79.2% vs. 79.3%, p=0.478) or in survival outcomes between the two groups. This pattern is consistent with prior large-scale series demonstrating that, despite higher-risk histopathological features in CV-PTC, both variants carry similarly favorable long-term prognoses when treated according to current guidelines. Henke et al. (11) reported that even when pathologically aggressive FV-PTC tumors were selected for comparison, FV-PTC remained a more favorable diagnosis, while disease recurrence and disease-specific deaths were rare and occurred late in both subtypes. The predominance of early-stage disease in our cohort and the comparable application of total thyroidectomy and RAI treatment across groups may have attenuated the prognostic impact of histopathological differences between variants. The uniform treatment of patients, according to institutional guidelines, has been highlighted as a key factor limiting outcome divergence between CV-PTC and FV-PTC in single-institution series (11). Furthermore, the limited number of adverse events during the follow-up period-a recognized challenge in PTC outcome research given the indolent nature of the disease-reduces statistical power to detect differences in survival between subtypes. These observations collectively suggest that, while CV-PTC and FV-PTC differ in their local aggressiveness, this distinction may not independently drive survival outcomes within a uniformly treated, predominantly early-stage cohort.

In a large series by Sebastian et al. (3) evaluating the clinicopathological characteristics of histological variants, the incidence of the CV was 46%, whereas the FV accounted for 17.6%. Sparano et al. (6) also reported rates of 62% for the CV and 37% for the FV. In our center, however, 62.3% of the cases included in the study were classified as FV-PTC and 37.7% were classified as CV-PTC. This distribution differs from series in the literature that report a higher prevalence of the CV and suggests a possible influence of either the patient population at our

center or the histopathological reporting approach during the study period. In addition, the reliance of our study on pathology reports predating the 2022 WHO classification and the inability to systematically perform NIFTP differentiation should be considered factors that may complicate comparisons with the literature in the classification of follicular-patterned lesions (7).

In our study, invasion-related pathological findings were more frequently detected in the CV-PTC group. These findings are consistent with series that report that the CV is associated with higher rates of capsular invasion, lymphovascular invasion, and extrathyroidal extension than the FV (6,13). In our cohort, capsular invasion was observed in 27.1% (n=13) of FV-PTC cases and in 51.7% (n=15) of CV-PTC cases (p=0.029); lymphatic invasion was also significantly higher in the CV-PTC group, at 41.4% (n=12), compared with the FV-PTC group (p=0.017). These proportions are broadly consistent with published series of encapsulated variants, in which capsular invasion rates of 18-26% for FV-PTC and lymphovascular invasion rates of 4-17% for CV-PTC have been reported (13). Raffaelli et al. (14) reported that the CV may be associated with increased local lymph node metastasis. Because our study did not include a systematic analysis of variables related to lymph node metastasis, direct comparison of this finding is limited. Nevertheless, similar rates of neck dissection between the groups (p=0.775) suggest no marked difference in surgical approach based on clinical lymph node assessment.

Regarding prognostic factors, the literature reports that distant metastasis is the strongest predictor of disease-specific mortality in PTC, followed by extrathyroidal extension, vascular invasion, and advanced age at diagnosis (11). In our series, the significantly higher frequency of extrathyroidal extension in the CV-PTC group compared with the FV-PTC group [58.6% (n=17) vs. 20.8% (n=10); p<0.001] supports the notion that indicators of local aggressiveness may be more pronounced in the CV (4,5). Notably, the prognostic significance of extrathyroidal extension in PTC remains a subject of ongoing debate; while gross extrathyroidal extension is consistently associated with worse outcomes, the AJCC/TNM 8th edition staging system no longer incorporates minimal extrathyroidal extension into T-stage classification, reflecting uncertainty about its independent impact on survival (15). In contrast, no significant difference in staging according to the AJCC/TNM 8th edition (p=0.478) was detected between the two groups, and patients in both groups were predominantly classified as stage II. Survival analysis also revealed no significant difference between the groups (Kaplan-Meier, log-rank p=0.921). This finding may be related to the low number of events in our cohort and the similarity of treatment approaches; therefore, rather than directly confirming or refuting the recurrence and cancer-related mortality differences reported in some series, we believe our results should be validated by larger cohorts with standardized pathological classification.

Among the strengths of the study are the evaluation of a homogeneous patient population who underwent standardized surgical and pathological assessment at a single center, and the detailed comparison of clinical and histopathological features of the two variants. The findings indicate that the CV of PTC is associated with greater histopathological aggressiveness-including higher rates of capsular and lymphatic invasion and extrathyroidal extension-suggesting the need for closer postoperative surveillance and risk-based assessment in these patients. Nevertheless, these differences did not result in significant changes in stage distribution or survival when treatment approaches were comparable, implying that histopathological subtype alone may not be sufficient to determine prognosis. Accordingly, the variant should be evaluated comprehensively alongside other clinical and pathological risk factors in therapeutic decision-making.

Study Limitations

The retrospective design, single-center nature, and limited sample size represent the main limitations of this study. Histopathological classification was based on archived reports predating the 2022 WHO classification, preventing systematic reclassification of NIFTP and potentially complicating direct comparison with contemporary literature. Furthermore, the low number of oncologic events during follow-up reduced the statistical power to detect potential survival differences between variants. Prospective, multicenter studies with larger cohorts and standardized pathological classification, ideally incorporating molecular profiling, are warranted to better clarify the prognostic implications of histopathological variants in PTC.

Conclusion

This study demonstrates that there are marked differences in histopathological aggressiveness between the CV and FV of PTC, with capsular invasion, lymphatic invasion, and extrathyroidal extension being observed more frequently in the CV. However, these differences did not translate into significant disparities in stage distribution or survival outcomes between the two groups. While our findings provide important insights into the biological behavior of PTC across histopathological variants, they suggest that variant subtype alone may not independently determine prognosis. Therefore, histopathological variants should be considered holistically alongside other clinical and pathological risk factors in clinical decision-making for PTC.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from Çukurova University Faculty of Medicine (approval no: 26, date: 09.01.2026).

Informed Consent: Due to the retrospective study design, the requirement for individual informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions

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

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Clinical, Pathological, and Psychosocial Factors Influencing Patient Preference for Contralateral Prophylactic Mastectomy in Patients with Unilateral Breast Cancer

Tek Taraflı Meme Kanseri Hastalarında Kontrlateral Profilaktik Mastektomi Tercihini Etkileyen Klinik, Patolojik ve Psikososyal Faktörler

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Abstract

Objectives: Prophylactic mastectomy is an effective surgical option for reducing breast cancer risk, particularly in high-risk patients. However, the decision-making process is multifactorial and extends beyond oncologic risk alone. The aim of this study was to evaluate demographic, clinicopathological, and decision-making-related factors associated with documented patient preference among those who underwent contralateral prophylactic mastectomy for unilateral breast cancer.

Material and Methods: In this single-center retrospective observational study, 66 patients who underwent contralateral prophylactic mastectomy for breast cancer between January 2015 and January 2025 were included. Demographic and reproductive characteristics, tumor- and treatment-related variables, and decision-making parameters, including family history, genetic diagnosis, psychological fear, follow-up difficulties, aesthetic concerns, physician recommendation, and patient preference, were analyzed. The primary dependent variable was whether patient preference influenced the decision to undergo prophylactic mastectomy.

Results: Of the 66 patients, 41 (62.1%) had a documented preference for prophylactic mastectomy. Compared with those without a patient preference, this group was significantly younger and had a higher proportion of married patients. Rates of neoadjuvant systemic therapy, distant metastasis, and advanced clinical T and N stages were also higher. Family history of breast cancer, family history of other cancers, and the presence of a genetic diagnosis were strongly associated with patient preference. Fear was significantly more common in the patient preference group. No significant differences were observed in multifocality, molecular subtype, or physician recommendation, although borderline significance was noted for follow-up difficulties and aesthetic concerns. Univariable logistic regression showed that younger age, marital status, neoadjuvant therapy, psychological fear, and advanced clinical T/N stage were associated with patient preference.

Conclusion: Patient preference for prophylactic mastectomy appears to be influenced by multiple factors, including younger age, familial/genetic risk indicators, disease burden, and psychosocial factors. These findings support the importance of structured counseling and shared decision-making tailored to individual patient characteristics.

Keywords: Prophylactic mastectomy, breast neoplasms, genetic predisposition to disease, anxiety

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Öz

Giriş / Amaç: Profilaktik mastektomi, özellikle yüksek riskli hastalarda meme kanseri riskini azaltmada etkili bir cerrahi seçenektir. Ancak karar verme süreci çok faktörlüdür ve yalnızca onkolojik risk ile sınırlı değildir. Bu çalışmanın amacı, tek taraflı meme kanseri nedeniyle kontralateral profilaktik mastektomi uygulanan hastalarda dokümante edilmiş hasta tercihi ile ilişkili demografik, klinikopatolojik ve karar verme sürecine ilişkin faktörleri değerlendirmektir.

Gereç ve Yöntem: Bu tek merkezli, retrospektif gözlemsel çalışmaya, Ocak 2015-Ocak 2025 tarihleri arasında meme kanseri tanısıyla kontrlateral profilaktik mastektomi uygulanan 66 hasta dahil edildi. Demografik ve reprodüktif özellikler, tümör ve tedaviye ilişkin değişkenler ile aile öyküsü, genetik tanı, psikolojik korku, takip sürecine ilişkin güçlükler, estetik kaygı, hekim önerisi ve hasta tercihi gibi karar süreciyle ilişkili parametreler incelendi. Birincil bağımlı değişken, profilaktik mastektomi kararında hasta tercihinin varlığı olarak tanımlandı.

Bulgular: Altmış altı hastanın 41'inde (%62,1) profilaktik mastektomiye yönelik hasta tercihi saptandı. Hasta tercihi olan grup, olmayan gruba göre anlamlı olarak daha gençti ve evli hasta oranı daha yüksekti. Ayrıca bu grupta neoadjuvan sistemik tedavi alma, uzak metastaz varlığı ve ileri klinik T ve N evresi daha sıktı. Meme kanseri aile öyküsü, diğer kanserlere ait aile öyküsü ve genetik tanı varlığı hasta tercihi ile güçlü şekilde ilişkili bulundu. Psikolojik korku da hasta tercihi olan grupta anlamlı olarak daha yüksekti. Buna karşın multifokalite, moleküler alt tip, hekim önerisi ve estetik kaygı açısından anlamlı fark saptanmadı. Tek değişkenli lojistik regresyonda genç yaş, evli olma, neoadjuvan tedavi, psikolojik korku ve ileri klinik T/N evresi hasta tercihi ile ilişkiliydi.

Tartışma / Sonuç: Profilaktik mastektomiye yönelik hasta tercihi; genç yaş, ailesel/genetik risk göstergeleri, hastalık yükü ve psikososyal etkenler gibi çoklu faktörlerden etkilenmektedir. Bu nedenle karar süreci, bireysel hasta özellikleri dikkate alınarak yapılandırılmış danışmanlık ve ortak karar verme çerçevesinde ele alınmalıdır.

Anahtar Kelimeler: Profilaktik mastektomi, meme tümörleri, hastalığa genetik yatkınlık, anksiyete

Introduction

Prophylactic mastectomy is an effective surgical option for reducing the risk of breast cancer, particularly in high-risk settings such as BRCA1/2 mutations, a strong family history, and prior chest wall irradiation (1-3). Nevertheless, current consensus reports emphasize that prophylactic mastectomy is not routinely recommended for average-risk patients with unilateral breast cancer and that the decision should be based on the individual risk profile and patient-specific characteristics (1-3).

However, an increase in the rates of prophylactic mastectomy, particularly contralateral prophylactic mastectomy (CPM), has been observed in recent years (4). This trend cannot be explained solely by objective oncologic risk; in addition to genetic predisposition and family history, psychosocial factors such as fear of future cancer development, risk perception, the desire for peace of mind, and expectations regarding symmetry and cosmetic outcomes have also been reported to play a decisive role in this preference (5-7). Furthermore, the surgeon's recommendation and the quality of communication established with the patient directly influence the decision-making process (8,9).

Therefore, the aim of the present study was to evaluate demographic, clinicopathological, and decision-making factors associated with documented preference among patients who underwent CPM for unilateral breast cancer.

Materials and Methods

The study was approved by the relevant Mersin University Local Ethics Committee (approval no: 2026/027, date: 21.01.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki.

One of the author of this article (T.Ç.) is a member of the Advisory 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.

This was a single-center retrospective observational study conducted at a tertiary-care university hospital. The requirement for informed consent was waived by the ethics committee due to the retrospective design of the study. The study evaluated patients diagnosed with breast cancer who underwent CPM between January 2015 and January 2025. Patients who underwent prophylactic mastectomy during the study period and had complete clinical, pathological, and surgical data available were included. Patients with missing data, patients who underwent surgery for reasons other than prophylactic mastectomy, or patients in whom the key variables related to the decision-making process could not be assessed were excluded.

Data were obtained through a review of the hospital's electronic medical record system, operative notes, pathology reports, outpatient clinic records, and multidisciplinary tumor board evaluations. Demographic variables included age, marital status,

and menopausal status. Reproductive characteristics, such as age at menarche and age at first live birth, were also evaluated when available.

Clinical and tumor-related variables included a history of breast cancer, family history of breast cancer, family history of other cancers, presence of genetic mutations, multifocality or multicentricity of the tumor, history of neoadjuvant therapy, histopathological tumor type, tumor stage, nodal status, estrogen receptor status, progesterone receptor status, HER2 status, and the Ki-67 proliferation index. In addition, molecular subtypes were classified according to the available immunohistochemical data.

Variables related to the decision-making process included the patient's psychological fear, the burden of follow-up, aesthetic concerns, the physician's recommendation, and the patient's preference. The study's primary dependent variable was the presence of a patient preference regarding the decision to undergo prophylactic mastectomy.

Decision-making-related variables were evaluated using a predefined data collection form, derived from hospital electronic medical records, operative notes, pathology reports, outpatient clinic records, multidisciplinary tumor board evaluations, and telephone interviews with patients when additional clarification was required. Patient preference was considered present when the patient's explicit request, expressed willingness, or stated personal preference for CPM was documented in the medical records and/or confirmed during a telephone interview. A physician recommendation was considered present when the surgical decision was documented or reported as recommended by the treating surgeon or multidisciplinary team within the context of risk reduction, genetic or familial risk, surgical planning, or reconstruction-related considerations. When both patient preference and physician recommendation were identified, the variables were recorded separately based on the available information. To reduce subjectivity in the retrospective assessment, all decision-making-related variables were recorded on a predefined data collection form according to operational definitions. Unclear cases were re-evaluated by the study team and classified by consensus.

Psychological fear was defined as documented or patient-reported fear of developing contralateral breast cancer, fear of recurrence, cancer-related anxiety, or a desire to eliminate future cancer risk. This variable was assessed using predefined operational criteria based on clinical documentation and patient interviews, rather than a validated psychometric scale. Aesthetic concern was defined as documentation or a patient report indicating that symmetry, cosmetic expectations, breast appearance, or reconstruction-related aesthetic considerations influenced the decision. Difficulty with follow-up was defined as documentation or patient report of concerns about long-term surveillance, repeated imaging, hospital visits, geographic or logistical barriers, or anxiety associated with continuous follow-up.

Prophylactic mastectomy was defined as a surgical procedure performed to reduce the risk of future breast cancer, rather than to treat an existing malignant lesion.

Menopausal status was classified based on the patient's menstrual history and clinical records. Family history was recorded according to the presence of breast cancer or other malignancies in first- or second-degree relatives. Genetic diagnosis was determined based on the presence of BRCA1, BRCA2, or other pathogenic mutations. Histopathological and immunohistochemical data were recorded according to the final pathology reports.

Statistical Analysis

Continuous variables were tested for normality and were presented as median and interquartile range (IQR), whereas categorical variables were presented as number and percentage. Comparisons between patients with and without patient preference were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test, as appropriate, for categorical variables. Univariable logistic regression analysis was performed to evaluate factors associated with patient preference, and odds ratios with 95% confidence intervals were calculated. A multivariable logistic regression model was not constructed because limited sample size, a relatively small number of outcome events, and complete separation observed in several covariates collectively precluded reliable estimation using standard logistic regression. Firth-penalized logistic regression was also considered an alternative for handling sparse data and complete separation. However, because of the small sample size, the limited number of outcome events, and the presence of multiple covariates exhibiting separation, a multivariable penalized model was not constructed. Therefore, only univariable logistic regression analyses were presented, and the findings were interpreted as exploratory associations rather than as independent predictors. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 30.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value of <0.05> was considered statistically significant.

Results

A total of 66 patients were included in the study. Of these, 41 patients (62.1%) had a documented preference for prophylactic mastectomy, whereas 25 (37.9%) had no such preference.

When demographic and reproductive characteristics were evaluated, the patient preference group was found to be

significantly younger than the no preference group [median age: 37.0 years (IQR: 26.0-45.0) vs. 44.0 years (IQR: 38.0-52.0), p=0.014]. In addition, marital status was significantly associated with patient preference; the proportion of married patients was higher in the patient preference group (95.1% vs. 72.0%, p=0.021). In contrast, no significant differences were observed between the groups with respect to age at menarche, age at first live birth, breastfeeding history, multiparity, menopausal status, or hormone replacement therapy (p=0.867, p=0.171, p=0.190, p=0.359, p=0.945, and p=0.856, respectively) (Table 1).

Regarding clinicopathological and treatment-related characteristics, the proportion of patients receiving neoadjuvant systemic therapy was significantly higher in the patient preference group than in the no-preference group (87.8% vs. 36.0%, p<0.001). Distant metastasis was also more frequent in the patient preference group (22.0% vs. 0%, p=0.011). Significant differences between the groups were also identified for clinical tumor and nodal stages. Patients in the patient preference group had a higher proportion of cT3-cT4 tumors and cN2-cN3 nodal disease (both p<0.001). By contrast, no significant differences were observed in the presence of multifocal primary cancer or in the distribution of molecular subtypes (p=0.730 and p=0.164, respectively). Although the rate of nipple-sparing mastectomy was higher in the patient preference group, the difference did not reach statistical significance (70.7% vs. 44.0%, p=0.058). Similarly, no significant difference was found between the groups with respect to reconstruction status (p=0.075) (Table 2).

When risk-related, psychosocial, and decision-making variables were assessed, a family history of breast cancer was significantly more common in the patient preference group (100.0% vs. 12.0%, p<0.001). Likewise, a family history of other cancers was more frequently observed in the patient preference group (95.1% vs. 0%, p<0.001). The presence of a genetic diagnosis was strongly associated with patient preference: 90.2% of patients in the patient preference group had positive genetic tests, whereas no patient in the no-preference group did (p<0.001). The prevalence of psychological fear was significantly higher in the patient preference group (85.4% vs. 60.0%, p=0.042). In contrast, no statistically significant differences were found between the groups with respect to difficulty with follow-up, physician recommendation, or aesthetic concerns; however, borderline statistical significance was observed for difficulty with follow-up (p=0.075) and for aesthetic concerns (p=0.082) (Table 3).

In univariable logistic regression analysis, younger age, marital status, neoadjuvant systemic therapy, psychological fear, and advanced clinical T and N stages were significantly associated with patient preference for prophylactic mastectomy (Table 4).

Table 1. Demographic and reproductive characteristics according to patient preference

Variable	Overall (n=66)	No patient preference (n=25)	Patient preference (n=41)	p-value
Age, years	39.0 (31.0-47.8)	44.0 (38.0-52.0)	37.0 (26.0-45.0)	0.014
Age at menarche, years	14.0 (12.0-15.0)	14.0 (13.0-15.0)	14.0 (12.0-15.0)	0.867
Age at first live birth, years	22.0 (20.0-23.0)	21.0 (20.0-22.0)	22.0 (19.5-24.0)	0.171
Marital status				0.021
No	9 (13.6)	7 (28.0)	2 (4.9)	
Yes	57 (86.4)	18 (72.0)	39 (95.1)	
Breastfeeding history				0.190
No	6 (9.1)	4 (16.0)	2 (4.9)	
Yes	60 (90.9)	21 (84.0)	39 (95.1)	
Multiparity				0.359
No	5 (7.6)	3 (12.0)	2 (4.9)	
Yes	61 (92.4)	22 (88.0)	39 (95.1)	
Menopause				0.945
No	36 (54.5)	13 (52.0)	23 (56.1)	
Yes	30 (45.5)	12 (48.0)	18 (43.9)	
Hormone replacement therapy				0.856
No	40 (60.6)	16 (64.0)	24 (58.5)	
Yes	26 (39.4)	9 (36.0)	17 (41.5)	

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables
IQR: Interquartile range

Table 2. Clinicopathological and treatment-related characteristics according to patient preference

Variable	Overall (n=66)	No patient preference (n=25)	Patient preference (n=41)	p-value
Neoadjuvant systemic therapy				
No	21 (31.8)	16 (64.0)	5 (12.2)	<0.001
Yes	45 (68.2)	9 (36.0)	36 (87.8)	
Distant metastasis				
No	57 (86.4)	25 (100.0)	32 (78.0)	0.011
Yes	9 (13.6)	0 (0.0)	9 (22.0)	
Multifocal primary tumor				
No	56 (84.8)	22 (88.0)	34 (82.9)	0.730
Yes	10 (15.2)	3 (12.0)	7 (17.1)	
Molecular subtype				
HR-positive	12 (18.2)	7 (28.0)	5 (12.2)	0.164
HER2-positive	17 (25.8)	4 (16.0)	13 (31.7)	
TNBC	37 (56.1)	14 (56.0)	23 (56.1)	
Clinical T stage				
cT1	15 (22.7)	14 (56.0)	1 (2.4)	<0.001
cT2	14 (21.2)	9 (36.0)	5 (12.2)	
cT3	35 (53.0)	2 (8.0)	33 (80.5)	
cT4	2 (3.0)	0 (0.0)	2 (4.9)	
Clinical N stage				
cN0	11 (16.7)	11 (44.0)	0 (0.0)	<0.001
cN1	13 (19.7)	9 (36.0)	4 (9.8)	
cN2	36 (54.5)	4 (16.0)	32 (78.0)	
cN3	6 (9.1)	1 (4.0)	5 (12.2)	
Type of mastectomy				
Nipple-sparing mastectomy	40 (60.6)	11 (44.0)	29 (70.7)	0.058
Skin-sparing mastectomy	26 (39.4)	14 (56.0)	12 (29.3)	
Breast reconstruction				
No	6 (9.1)	0 (0.0)	6 (14.6)	0.075
Yes	60 (90.9)	25 (100.0)	35 (85.4)	

Data are presented as n (%) unless otherwise indicated
HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer

Discussion

In the present study, which included only patients who had undergone CPM, documented patient preference during the decision-making process could not be explained by a single variable; rather, age, family history, genetic risk, tumor burden, and psychosocial factors appeared to act in combination. Therefore, our findings should not be interpreted as identifying factors associated with undergoing CPM itself, but rather as factors associated with documented patient preference among patients who had already undergone this procedure. Our findings suggest that CPM remains an important option for selected high-risk patients, but for average-risk patients the decision is shaped not only by oncologic indicators but also by patients' perceptions and preferences. Indeed, the current literature emphasizes that although this approach reduces the risk of cancer in the contralateral breast, it should not be regarded as a routine standard, particularly in average-risk patients with unilateral breast cancer, and that the decision should be individualized within the framework of shared decision-making (10-12).

The significantly younger age observed in the patient preference group is consistent with one of the most reproducible findings in the literature. Younger patients have been reported to show a greater tendency toward CPM, which may be related to the perception of a longer lifetime risk of contralateral breast

Table 3. Risk-related, psychosocial, and decision-related characteristics according to patient preference

Variable	Overall (n=66)	No patient preference (n=25)	Patient preference (n=41)	p-value
Family history of breast cancer				
No	22 (33.3)	22 (88.0)	0 (0.0)	<0.001
Yes	44 (66.7)	3 (12.0)	41 (100.0)	
Family history of other cancers				
No	27 (40.9)	25 (100.0)	2 (4.9)	<0.001
Yes	39 (59.1)	0 (0.0)	39 (95.1)	
Genetic diagnosis				
Absent	25 (37.9)	25 (100.0)	0 (0.0)	<0.001
Present	37 (56.1)	0 (0.0)	37 (90.2)	
Unknown	4 (6.1)	0 (0.0)	4 (9.8)	
Difficulty with follow-up				
No	60 (90.9)	25 (100.0)	35 (85.4)	0.075
Yes	6 (9.1)	0 (0.0)	6 (14.6)	
Psychological fear				
No	16 (24.2)	10 (40.0)	6 (14.6)	0.042
Yes	50 (75.8)	15 (60.0)	35 (85.4)	
Physician recommendation				
No	16 (24.2)	3 (12.0)	13 (31.7)	0.129
Yes	50 (75.8)	22 (88.0)	28 (68.3)	
Aesthetic concern				
No	26 (39.4)	6 (24.0)	20 (48.8)	0.082
Yes	40 (60.6)	19 (76.0)	21 (51.2)	

Data are presented as n (%), p-values were calculated using appropriate comparative tests

Table 4. Univariable logistic regression analysis of factors associated with patient preference for prophylactic mastectomy

Variable	Comparison	Odds ratio (95% CI)	p-value
Age, years	Per 1-year increase	0.94 (0.89-0.98)	0.009
Age at menarche, years	Per 1-year increase	0.97 (0.72-1.31)	0.844
Age at first live birth, years	Per 1-year increase	1.18 (0.94-1.50)	0.160
Marital status	Yes vs. no	7.58 (1.43-40.19)	0.017
Breastfeeding history	Yes vs. no	3.71 (0.63-21.99)	0.148
Multiparity	Yes vs. no	2.66 (0.41-17.15)	0.304
Menopause	Yes vs. no	0.85 (0.31-2.30)	0.746
Hormone replacement therapy	Yes vs. no	1.26 (0.45-3.51)	0.660
Neoadjuvant systemic therapy	Yes vs. no	12.80 (3.70-44.31)	<0.001
Psychological fear	Yes vs. no	3.89 (1.20-12.64)	0.024
Multifocal primary tumor	Yes vs. no	1.51 (0.35-6.47)	0.579
Physician recommendation	Yes vs. no	0.29 (0.07-1.16)	0.081
Aesthetic concerns	Yes vs. no	0.33 (0.11-1.00)	0.050
Molecular subtype	HER2-positive vs HR-positive	4.55 (0.91-22.63)	0.064
Molecular subtype	TNBC vs HR-positive	2.30 (0.61-8.66)	0.218
Clinical T stage	Per 1-stage increase	18.61 (5.17-66.94)	<0.001
Clinical N stage	Per 1-stage increase	12.19 (3.85-38.59)	<0.001

CI: Confidence interval, HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer

cancer, a preference for more aggressive treatment, and increased anxiety about the future (11-14). In our series, a higher rate of preference among married patients was also noteworthy. Although this finding has not been demonstrated consistently across all studies, family responsibilities, concerns about children, and fear of cancer recurrence have been shown to influence surgical preferences. Yu et al. (14) demonstrated that the family context plays an important role in attitudes toward genetic testing and risk-reducing surgery, whereas Padamsee et al. (15) reported that, in some patients, the decision was shaped by the desire to choose what was perceived as the "safest option" for their children. Therefore, the more pronounced patient preference observed among younger patients and those with greater family responsibilities appears clinically understandable.

In our study, strong associations between documented patient preference and family history of breast cancer, family history of other cancers, and the presence of a genetic diagnosis were largely consistent with current recommendations and evidence. Pathogenic variants, particularly BRCA1/2, and a strong family history are well-established factors associated with an increased risk of contralateral breast cancer and may therefore provide a clinically rational basis for risk-reducing surgery in selected patients (10,11,14). Accordingly, these findings should not be interpreted solely as evidence of an independent psychosocial tendency toward CPM. They may also reflect expected and guideline-consistent clinical decision-making in patients with hereditary or familial risk. Yi et al. (13) similarly reported family history and BRCA testing as important variables associated with CPM. In this context, patient preference may emerge from the interaction among objective risk information, perceived hereditary risk, counseling, and individual risk perception. Nevertheless, the literature shows that demand for CPM may persist even in patients with negative or indeterminate genetic test results. Therefore, communication regarding genetic risk should not be limited to whether testing was performed or positive, but should instead focus on conveying the individual absolute risk in a clear and comprehensible manner (11,12,16).

The significantly higher frequency of psychological fear in the patient preference group represents one of the most important findings of our study. Numerous studies have shown that the decision to undergo prophylactic mastectomy is often not based solely on an objective risk assessment, but is also driven by fear, anxiety about recurrence, the pursuit of "peace of mind," and a tendency to choose the most aggressive treatment option (15,17,18). In particular, Padamsee et al. (15) reported that some patients perceived CPM as the "safest" and "most comprehensive" option, whereas Longfellow et al. (18) demonstrated that, in patients presenting with a strong pre-existing preference, a cautious approach by the surgeon did not always alter the final decision. In our series, the lack of a significant association with physician recommendation may also be interpreted in this context: once patient preference becomes strongly established, medical advice may no longer be the sole determinant of the decision. By contrast, the borderline significance observed for difficulty with follow-up and aesthetic concerns is consistent with the themes of "burdensome surveillance", symmetry, and cosmetic expectations that have been reported in the literature (10,12,13,17).

In patients without a documented preference, the decision to undergo CPM should also be made cautiously. In this subgroup, the absence of a documented patient preference does not necessarily indicate that the patient has no role in the decision-making process; rather, it indicates that an explicit, patient-driven request was not recorded as a primary or contributing factor. In these patients, CPM appeared to be driven more commonly by physician recommendation, multidisciplinary risk assessment, genetic or familial risk considerations, reconstruction-related planning, symmetry concerns, or other oncologic and surgical factors. Therefore, the no-preference group should not be regarded as a group in which the procedure was performed without patient involvement, but rather as a group in which the available documentation did not identify patient preference as a distinct determinant of the decision.

Another noteworthy finding was the association between documented patient preference and neoadjuvant systemic therapy, distant metastasis, and advanced clinical T/N stages. This finding should be interpreted cautiously, because current recommendations indicate that prophylactic or contralateral mastectomy should not be routinely encouraged in patients with advanced-stage or metastatic disease and should instead be considered only in highly selected circumstances (10,11). In the present cohort, this finding should not be interpreted as evidence supporting routine CPM in metastatic patients. Rather, it may reflect individualized decision-making influenced by patient preference, perceived disease burden, psychological fear, genetic or familial risk, reconstruction-related considerations, and multidisciplinary clinical judgment. The higher frequency of patients receiving neoadjuvant therapy in the CPM group reported by He et al. (12) is partly consistent with this observation. Similarly, the tendency to choose the "safest option," as described by Padamsee et al. (15), may become more pronounced in patients who perceive their disease burden as high. Therefore, in patients with advanced or metastatic disease, it is particularly important to distinguish the risk of contralateral breast cancer from the biology and prognosis of the index tumor and to ensure that decisions are based on realistic clinical benefit rather than on fear alone.

One of the most important clinical implications of these findings is the need to strengthen structured counseling and shared decision-making processes. In the systematic review

by Naaseh et al. (17), decision support tools developed for CPM were found to be feasible and capable of improving patient satisfaction and knowledge; however, standardization regarding the timing of their delivery and the balance of content remains lacking. Similarly, Sung et al. (16) reported that lower levels of shared decision-making were associated with greater decisional conflict, and that decision quality, particularly in the context of genetic risk, was influenced by the decision-making process itself. Data from Steadman et al. (11) also suggest that structured and consistent patient counseling may reduce CPM rates. Therefore, particularly for younger patients, for those with a high perceived familial/genetic risk, or for those who exhibit marked psychological fear, clear risk communication, genetic counseling, open discussion of aesthetic expectations, and a structured exploration of patient values may improve the quality of decision-making.

Study Limitations

This study has several limitations. Its single-center retrospective design and relatively small sample size may limit the generalizability of the findings. Because the study included only patients who underwent CPM, the findings do not identify factors associated with the decision to undergo CPM when compared with non-CPM patients, but rather identify factors associated with documented patient preference within the CPM cohort. Psychosocial and decision-making-related variables, including psychological fear, aesthetic concern, and difficulty with follow-up, were assessed using clinical documentation and patient interviews rather than validated psychometric scales or standardized prospective instruments. Because complete separation was observed for some variables and the number of outcome events was limited, a multivariable logistic regression model could not be constructed using standard methods. Therefore, the findings should be interpreted as associations rather than as independent predictors. Despite these limitations, a major strength of the present study is that prophylactic mastectomy decision-making was evaluated alongside pathological, genetic, psychosocial, and decision-making-related factors.

Conclusion

This study demonstrates that patient preference for prophylactic mastectomy is associated with younger age, familial/genetic risk indicators, and psychological fear. Our findings suggest that this decision is shaped not only by oncologic factors but also by the patient's risk perception, fears, and individual life context. Therefore, the decision regarding prophylactic mastectomy should be addressed within the framework of structured counseling and shared decision-making.

Ethics

Ethics Committee Approval: The study was approved by the relevant Mersin University Local Ethics Committee (approval no: 2026/027, date: 21.01.2026).

Informed Consent: The requirement for informed consent was waived by the ethics committee due to the retrospective design of the study.

Footnotes

One of the author of this article (T.Ç.) is a member of the Advisory 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.

Authorship Contributions

Concept/Design: M.Y., M.Be., T.Ç., Data Collection or Processing: M.Y., M.B., M.Be., Analysis or Interpretation: M.Y., M.Be., Literature Review: M.Y., M.B., Writing, Reviewing and Editing: M.Y., M.B., M.Be., T.Ç.

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Pancreas-preserving Surgery in Duodenal Gastrointestinal Stromal Tumors and The Role of Pancreaticoduodenectomy

Duodenal Gastrointestinal Stromal Tümörlerde Pankreas Koruyucu Cerrahi ve Pankreatikoduodenektominin Rolü

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Abstract

Objectives: Duodenal gastrointestinal stromal tumors (GISTs) are rare and surgically challenging. This study evaluated the surgical management and outcomes of duodenal GISTs, focusing on the feasibility and oncological adequacy of pancreas-preserving approaches.

Material and Methods: We retrospectively analyzed 9 patients who underwent surgical resection for duodenal GIST between January 2017 and December 2025. Clinical, operative, and pathological data, including postoperative morbidity (Clavien-Dindo), recurrence, and survival, were evaluated.

Results: Nine patients (median age 60) were included. The median operative time was 200 minutes [interquartile range (IQR), 160-270], and the median hospital stay was 9 days (IQR, 9-15). Intraoperative tumor rupture occurred in 3 patients (33.3%). R0 resection was achieved in 7 patients (77.8%), while 2 patients (22.2%) had R1 resection. Postoperative complications occurred in 4 patients (44.4%), with major complications (Clavien-Dindo ≥III) observed in two cases. During a median follow-up of 49 months (IQR, 44-74), recurrence occurred in 2 patients (22.2%), both of whom had high-risk features, such as rupture or R1 margins. At the last follow-up, 6 patients (66.7%) were alive without disease, 1 (11.1%) was alive with disease, and 2 (22.2%) had died (one disease-related death).

Conclusion: Pancreas-preserving surgery is safe for selected duodenal GISTs without compromising long-term oncological outcomes. Surgical strategy should be individualized based on tumor characteristics rather than routinely favoring radical procedures, provided that oncological principles are maintained.

Keywords: Duodenum, gastrointestinal stromal tumor, limited resection, pancreaticoduodenectomy

Öz

Giriş / Amaç: Duodenal gastrointestinal stromal tümörler (GİST) nadir görülen ve cerrahi açıdan zorlayıcı kitlelerdir. Bu çalışma, duodenal GİST'lerin cerrahi yönetimini ve sonuçlarını, özellikle pankreas koruyucu yaklaşımların uygulanabilirliği ve onkolojik yeterliliğine odaklanarak değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Ocak 2017 ile Aralık 2025 tarihleri arasında duodenal GİST nedeniyle cerrahi rezeksiyon uygulanan 9 hasta geriye dönük olarak analiz edildi. Klinik, operatif ve patolojik veriler ile postoperatif morbidite (Clavien-Dindo), nüks ve sağkalım durumları değerlendirildi.

Bulgular: Çalışmaya toplam 9 hasta (medyan yaş 60) dahil edildi. Medyan operasyon süresi 200 dakika [çeyrekler arası aralık (IQR), 160-270], medyan hastanede kalış süresi ise 9 gün (IQR, 9-15) olarak saptandı. Üç hastada (%33,3) intraoperatif tümör rüptürü meydana geldi.

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Yedi hastada (%77,8) R0 rezeksiyon sağlanırken, 2 hastada (%22,2) R1 rezeksiyon görüldü. Postoperatif komplikasyonlar 4 hastada (%44,4) gelişti; bunların ikisinde majör komplikasyonlar (Clavien-Dindo ≥III) gözlendi. Medyan 49 aylık (IQR, 44-74) takip süresince 2 hastada (%22,2) nüks gelişti; her iki nüks de rüptür veya R1 cerrahi sınır gibi yüksek riskli özelliklerle ilişkiliydi. Son takipte hastaların 6'sı (%66,7) hastalıksız hayattaydı, 1'i (%11,1) hastalıkla yaşıyordu ve 2'si (%22,2) ölmüştü (biri hastalıkla ilişkili).

Tartışma / Sonuç: Pankreas koruyucu cerrahi, uygun seçilmiş duodenal GİST hastalarında, uzun dönem onkolojik sonuçlardan ödün vermeksizin güvenle uygulanabilir. Cerrahi strateji, onkolojik prensipler korunduğu sürece, rutin olarak radikal prosedürleri tercih etmek yerine tümör özelliklerine göre bireyselleştirilmelidir.

Anahtar Kelimeler: Duodenum, gastrointestinal stromal tümör, sınırlı rezeksiyon, pankreatikoduodenektomi

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, most frequently arising in the stomach (approximately 50-60%) and small intestine (20-30%). However, only a small proportion of GISTs originate from the duodenum, accounting for approximately 3-5% of all cases, making them a rare clinical entity (1,2). Despite their low incidence, duodenal GISTs are of particular clinical importance due to their unique anatomical location and heterogeneous clinical presentation, ranging from gastrointestinal bleeding to incidental detection.

The optimal surgical approach for duodenal GISTs remains controversial due to their complex anatomical location and the need to balance oncological adequacy with surgical morbidity. While pancreaticoduodenectomy has historically been preferred for anatomically challenging tumors, it is associated with higher morbidity. In contrast, recent studies suggest that limited resection can achieve comparable oncological outcomes when negative margins are obtained, supporting a more conservative approach in appropriately selected patients (3). Similarly, oncological outcome analyses have demonstrated that the extent of resection should be tailored according to tumor characteristics rather than routine use of radical procedures (4,5)

Current management strategies for GISTs are largely guided by international consensus recommendations, including those from European Society for Medical Oncology and National Comprehensive Cancer Network which emphasize complete surgical resection with negative margins as the cornerstone of treatment. However, these guidelines provide limited specific recommendations for duodenal GISTs due to their rarity and anatomical complexity (6).

Despite an increasing number of studies on duodenal GISTs, most available data derive from retrospective series with heterogeneous patient populations and significant selection bias, particularly regarding tumor location and surgical indications. In many reports, direct comparisons between surgical techniques are limited by imbalance in baseline characteristics, making it difficult to draw definitive conclusions about the optimal operative strategy (7). Furthermore, due to the rarity of duodenal GISTs, high-quality evidence remains scarce, and individualized surgical decision-making continues to rely largely on institutional experience rather than standardized criteria (8).

This study evaluates the surgical management of duodenal GISTs through analysis of operative approaches and outcomes in our cohort, with particular emphasis on the feasibility and oncological adequacy of limited resection compared with more radical procedures.

Materials and Methods

Study Design and Patient Selection

This study was approved by the Aydın Adnan Menderes University Local Ethics Committee (approval no: 2026/88-15, date: 26.02.2026). Written informed consent was obtained from all participants.

This retrospective study included patients who underwent surgical treatment for duodenal GISTs at a single tertiary referral center between January 2017 and December 2025. All consecutive patients with histopathologically confirmed GIST originating from the duodenum were included in the analysis.

Patients who lacked definitive pathological confirmation or had incomplete clinical records were excluded. Clinical, radiological, operative, and pathological data were obtained from a prospectively maintained institutional database and electronic medical records.

Preoperative Evaluation

All patients underwent preoperative assessment with contrast-enhanced abdominal computed tomography. Endoscopic evaluation was performed when clinically indicated. Tumor location was classified by duodenal segment (D1-D4), and its relationship to the ampulla of Vater was assessed using preoperative imaging and intraoperative findings.

Preoperative diagnoses were recorded and later compared with final pathological results.

Surgical Approach

The surgical approach was determined individually based on tumor location and size, and on its relationship to adjacent structures, particularly the ampulla and the

pancreatic head. Surgical procedures included segmental duodenectomy, pancreas-preserving duodenectomy, and pancreaticoduodenectomy.

Pancreas-preserving procedures were preferred whenever oncologically feasible. Pancreaticoduodenectomy was reserved for cases in which safe resection could not be achieved due to tumor proximity to the ampulla or suspected involvement of critical structures.

Among D2-located tumors, pancreas-preserving surgery was considered feasible in selected patients in whom direct ampullary invasion was excluded by preoperative imaging and intraoperative assessment.

Pathological Evaluation

All surgical specimens were evaluated by experienced gastrointestinal pathologists. Tumor size, histological subtype, mitotic index, and immunohistochemical markers, including CD117 and DOG1, were recorded.

Resection margins were classified as R0 for negative margins and R1 for microscopically positive margins. Intraoperative tumor rupture was also documented.

Postoperative Outcomes and Follow-up

Postoperative complications were graded according to the Clavien-Dindo classification. Operative time, length of hospital stay, and intraoperative blood transfusion were recorded.

Patients were followed with regular clinical and radiological evaluations. Follow-up duration was calculated from the date of surgery to the last follow-up visit or death. Recurrence was defined as radiologically or histologically confirmed disease after curative-intent resection.

Statistical Analysis

Statistical analyses were performed using SPSS version 29 (IBM Corp., Armonk, NY, USA). Due to the limited sample size, only descriptive statistics were applied. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), as appropriate, while categorical variables were presented as frequencies and percentages. No formal comparative statistical analysis was conducted.

Results

Nine patients who underwent surgical treatment for duodenal GISTs were included in the study. The mean age was 61.8±15.9 years, and the median age was 60 years (range, 40-82). There were 5 female patients and 4 male patients. The most common presenting symptom was abdominal pain, occurring in 5 patients (55.6%), followed by incidental detection in 3 patients (33.3%), and gastrointestinal bleeding in 1 patient (11.1%) (Table 1).

Tumors were most frequently located in the second portion of the duodenum (n=4, 44.4%), followed by the fourth portion (n=3, 33.3%). One tumor was located in the first portion and another in the third. Ampullary involvement was present in 4 patients (44.4%); none had radiological or intraoperative evidence of pancreatic invasion (Table 1).

Preoperative diagnosis was consistent with GIST in 6 patients (66.7%). However, 2 patients (22.2%) were initially suspected of having pancreatic tumors, and 1 patient (11.1%) was preoperatively evaluated as having lymphoma (Table 1).

Surgical treatment included segmental duodenectomy (4 patients, 44.4%), pancreas-preserving duodenectomy (3 patients, 33.3%), and pancreaticoduodenectomy (2 patients, 22.2%). Among patients with tumors in the second portion of the duodenum, pancreas-preserving duodenectomy was performed in 3 out of 4 patients, whereas only one patient required pancreaticoduodenectomy.

Table 1: Baseline characteristics

Variable	Value
Number of patients	9
Age, years (mean ± SD)	61.8±15.9
Age, years (median, range)	60 (40-82)
Sex (female/male)	5/4
Presentation	
Abdominal pain	5 (55.6%)
Gastrointestinal bleeding	1 (11.1%)
Incidental	3 (33.3%)
Acute presentation	6 (66.7%)
Preoperative anemia	6 (66.7%)
Preoperative diagnosis	
GIST	6 (66.7%)
Pancreatic tumor	2 (22.2%)
Lymphoma	1 (11.1%)
Tumor location	
D1	1 (11.1%)
D2	4 (44.4%)
D3	1 (11.1%)
D4	3 (33.3%)
Ampullary involvement	4 (44.4%)
Pancreatic invasion	0 (0%)
Histological subtype	
Spindle	6 (66.7%)
Epithelioid	3 (33.3%)
CD117 positivity	8 (88.9%)
DOG1 positivity	8 (88.9%)

SD: Standard deviation, GIST: Gastrointestinal stromal tumor

The median operative time was 200 minutes (IQR, 160-270), and the median length of hospital stay was 9 days (IQR, 9-15). Intraoperative tumor rupture occurred in 3 patients (33.3%), and intraoperative blood transfusion was required in 5 patients (55.6%). R0 resection was achieved in 7 patients (77.8%), while 2 patients (22.2%) had microscopically positive margins (Table 2). Both patients who underwent R1 resection had tumors located in the second portion of the duodenum, which were considered surgically challenging because of their close proximity to periampullary structures. Intraoperative tumor rupture occurred in 3 patients, all of whom had large and fragile tumors. Recurrence was observed in patients with high-risk features, including tumor rupture and positive surgical margins.

Postoperative complications occurred in 4 patients (44.4%). According to the Clavien-Dindo classification, most complications were low-grade, including grade I in 2 patients (22.2%) and grade II in 1 patient (11.1%). One patient (11.1%) required radiologic intervention (grade IIIa) (Table 2).

During a median follow-up of 49 months (IQR, 44-74), recurrence was observed in 2 patients (22.2%). One patient developed liver metastasis at 24 months, and another developed peritoneal recurrence at 56 months. Both recurrences occurred in patients with high-risk features, including intraoperative tumor rupture or positive resection margins. The patients who underwent R1 resection had periampullary tumors located in D2, with technically challenging dissection planes. Adjuvant imatinib therapy was administered to 4 patients (44.4%) (Table 3).

At the last follow-up, 6 patients (66.7%) were alive without disease, 1 (11.1%) was alive with disease, 1 (11.1%) died from disease progression, and 1 (11.1%) died from non-disease-related causes (Table 3).

Table 2. Operative and postoperative outcomes

Variable	Value
Operative time, min (median, IQR)	200 (160-270)
Length of stay, days (median, IQR)	9 (9-15)
Intraoperative tumor rupture	3 (33.3%)
Intraoperative transfusion	5 (55.6%)
R0 resection	7 (77.8%)
R1 resection	2 (22.2%)
Postoperative complications	4 (44.4%)
Clavien-Dindo classification	
Grade	n (%)
I	2 (22.2%)
II	1 (11.1%)
IIIa	1 (11.1%)
IQR: Interquartile range	

Table 3. Oncological outcomes

Variable	Value
Follow-up, months (median, IQR)	49 (44-74)
Adjuvant imatinib	4 (44.4%)
Recurrence	2 (22.2%)
Time to recurrence	24 and 56 months
Recurrence site	Liver (1), peritoneum (1)
Disease-free	6 (66.7%)
Alive with disease	1 (11.1%)
Disease-related death	1 (11.1%)
Non-disease death	1 (11.1%)
IQR: Interquartile range	

Discussion

Duodenal GISTs are rare and surgically challenging due to their proximity to the pancreas, bile duct, and major vascular structures. This complexity has often led to a preference for more aggressive procedures such as pancreaticoduodenectomy, even when less extensive surgery may be feasible. However, our findings demonstrate that pancreas-preserving surgery can be safely performed in a substantial proportion of patients without compromising oncological outcomes. In our series, limited resection achieved satisfactory surgical and early oncological results, supporting a more conservative and individualized surgical approach.

The biological behavior of GISTs is a key determinant of surgical strategy. Unlike epithelial gastrointestinal malignancies, lymph node metastases are rare, and routine lymphadenectomy is not required. This allows limited resections when complete tumor removal is achievable. In our cohort, pancreas-preserving procedures predominated and resulted in successful R0 resections in nearly all patients without the need for extended surgery. These findings are consistent with studies showing that surgical extent does not independently affect long term survival (9), and that local resection is oncologically sufficient when negative margins are obtained (10).

The choice between limited resection and pancreaticoduodenectomy remains a key issue in duodenal GIST management. Limited resection is reported in approximately 60-70% of cases, while pancreaticoduodenectomy is reserved for a smaller subset of patients. Importantly, several studies have shown comparable survival outcomes between these approaches when complete resection is achieved (11,12). In our series, pancreas-preserving techniques were used in most patients, and pancreaticoduodenectomy was required in only a few cases. Despite this conservative approach, oncological

outcomes were not compromised, supporting the concept that surgical extent should be guided by tumor characteristics rather than anatomical location alone. Nevertheless, pancreas-preserving surgery requires meticulous surgical technique and careful oncological judgment, particularly in patients with friable tumors or technically challenging periampullary dissection planes. In our series, recurrence was observed in patients with high-risk features, such as intraoperative tumor rupture and positive resection margins, emphasizing the importance of careful tumor handling and complete oncological resection whenever feasible. Despite two patients with R1 resections in our series, the median follow-up of 49 months demonstrates that acceptable oncological outcomes can still be achieved. This suggests that the biological behavior of duodenal GISTs, combined with tailored adjuvant therapy, may mitigate the risks associated with microscopic positive margins in selected cases.

Pancreaticoduodenectomy remains necessary in selected patients and accounts for approximately 20-40% of cases in reported series. It is generally indicated for tumors larger than 5-10 cm, those located near the ampulla of Vater, or when there is involvement of the pancreatic head or biliary tract, where achieving negative margins with limited resection may not be feasible (13). These findings suggest that, while pancreaticoduodenectomy is an important option, it should be used selectively rather than routinely. In our cohort, intraoperative tumor rupture occurred in three patients (33.3%). Although rupture is a known risk factor for recurrence, these cases were managed with adjuvant imatinib therapy. We observed that recurrences in our series were closely associated with both high-risk features and intraoperative events.

Tumors in the second portion of the duodenum are considered more challenging due to their proximity to the ampulla of Vater and the pancreatic head, often necessitating more aggressive surgical management. However, evidence suggests that limited resection may be feasible in selected cases. When the tumor does not involve the ampulla, pancreas-preserving surgery can achieve adequate oncological outcomes (14,15). These findings indicate that anatomical location alone should not determine surgical extent, and that individualized assessment may allow less invasive approaches without compromising oncological safety.

Consistent with the literature, our study demonstrated lower morbidity in the limited-resection group. Major complications (Clavien-Dindo ≥III) were rare, occurring in only two patients, which further supports the safety of pancreas-preserving approaches over radical surgery. Pancreaticoduodenectomy is associated with higher morbidity, longer operative time, and prolonged recovery compared to limited resections, raising concerns about potential overtreatment in selected patients. Previous studies have shown that more extensive resections do not provide additional survival benefit when complete tumor removal can be achieved with limited surgery (16). Given that tumor biology and margin status are the main determinants of prognosis, unnecessarily extensive surgery should be avoided whenever feasible. Clinical presentation may also influence surgical decision making, particularly in patients presenting with bleeding or symptomatic disease requiring urgent intervention (17). In this context, an individualized approach based on tumor characteristics and intraoperative findings is essential. Although minimally invasive techniques such as laparoscopic and robotic surgery have been increasingly reported, the primary goal remains the achievement of an R0 resection rather than the choice of surgical approach (18,19).

Importantly, our findings contribute to the existing literature by demonstrating that pancreas-preserving surgery can be successfully applied even to anatomically challenging duodenal GISTs, thereby supporting a more conservative and individualized surgical strategy.

Study Limitations

This study has several limitations. First, its retrospective design may introduce selection bias. Second, the relatively small sample size reflects the rarity of duodenal GISTs and limits the generalizability of the findings. Third, the absence of a direct comparison between limited resection and pancreaticoduodenectomy precludes definitive conclusions regarding the superiority of one surgical approach over another. In addition, long-term oncological outcomes could not be fully evaluated in all patients. Despite these limitations, the study provides clinically relevant insights into surgical decision-making in a rare and challenging disease.

Conclusion

Pancreas-preserving surgery is a feasible and oncologically safe option for selected patients with duodenal GISTs. Pancreaticoduodenectomy should be reserved for cases in which negative margins cannot be achieved with limited resection. Surgical decision-making should be individualized based on tumor characteristics and anatomical relationships, rather than on anatomical location alone. These findings suggest that even selected D2-located tumors may be managed with pancreas-preserving approaches without routine pancreaticoduodenectomy.

Ethics

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Local Ethics Committee (approval no: 2026/88-15, date: 26.02.2026).

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

Footnotes

Authorship Contributions

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

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CASE REPORT / OLGU SUNUMU

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A Rare Cause of Colonic Obstruction: Endometriosis

Kolon Tıkanıklığının Nadir Bir Nedeni: Endometriozis

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Abstract

Mechanical intestinal obstruction is a surgical emergency; colonic factors account for approximately one-fourth of cases. Endometriosis, characterized by the presence of endometrial tissue outside the uterine cavity, is an extremely rare cause of colonic obstruction. A 45-year-old woman presented with a two-month history of cramping lower abdominal pain, abdominal distension, constipation, and thin, ribbon-like stools. Computed tomography showed an obstructing mass in the sigmoid colon with mildly dilated intestinal loops. Colonoscopy revealed an impassable stricture with normal mucosa located approximately 30 cm from the anal verge. During the operation, a sigmoid resection with lymph node dissection was performed. Pathological examination revealed a submucosal mass infiltrating the serosa and narrowing the lumen. The lesion was composed of endometrial gland structures that were positively stained with CK7 and CD10, indicating deep infiltrating endometrioma. Given the non-specific clinical and imaging features, endometriosis should be considered in the differential diagnosis of colonic obstruction, particularly in women of childbearing age, with or without a history of gynecological surgery.

Keywords: Colon, endometriosis, obstruction

Öz

Mekanik barsak tıkanıklığı, acil cerrahi girişim gerektiren bir durum olup olguların yaklaşık dörtte birini kolonik etkenler oluşturmaktadır. Uterus dışında endometrial dokunun varlığı ile karakterize endometriozis, kolon tıkanıklığının son derece nadir bir nedenidir. Kırk beş yaşında bir kadın, iki aydır kramp şeklinde alt karın ağrısı, şişkinlik, kabızlık ve ince dışkılama şikayetleriyle başvurdu. Bilgisayarlı tomografi, sigmoid kolonda hafif genişlemiş barsak ansları ile birlikte tıkayıcı bir kitleyi gösterdi. Kolonoskopi, anal verjden yaklaşık 30 cm uzaklıkta, normal mukozaya sahip, geçilemeyen bir darlık ortaya koydu. Ameliyatta, lenf nodu diseksiyonu ile birlikte sigmoid rezeksiyon yapıldı. Patoloji, serozayı infiltre eden ve lümeni daraltan submukozal bir kitleyi gösterdi. Lezyon, CK7 ve CD10 ile pozitif boyanan endometrial bez yapılarından oluşmaktaydı ve bu da derin infiltratif endometriomayı işaret etti. Spesifik olmayan klinik ve görüntüleme bulguları göz önüne alındığında, özellikle doğurganlık çağındaki kadınlarda jinekolojik ameliyat öyküsü olsun veya olmasın, kolon tıkanıklığının ayırıcı tanısında endometriozis de dikkate alınmalıdır.

Anahtar Kelimeler: Kalın barsak, endometriozis, tıkanıklık

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Introduction

Mechanical intestinal obstruction is a surgical emergency, and colonic factors account for approximately one-fourth of all cases (1). Cancer, volvulus, and diverticular disease are the most common causes of colonic obstruction, while other, less frequent causes include Crohn's disease, hernia, intussusception, adhesions, and endometriosis (1,2).

Endometriosis is characterized by the presence of endometrial tissue outside the uterine cavity and affects 10% of women of reproductive age. Although the exact has not been clearly demonstrated, transplantation of endometrial cells to peritoneal surfaces resulting from retrograde menstruation is the most widely accepted theory. It is mostly occurred in the pelvic region, whereas intestinal involvement is responsible for up to 12% of the cases (3). Although rare, rectum and sigmoid colon are likely to most common locations of intestinal endometriosis (4). Patients with colonic endometriosis are often asymptomatic or have mild, cyclical symptoms such as abdominal discomfort, constipation, and rectal bleeding. On the other hand, mechanical obstruction is a rare clinical presentation of colonic endometriosis, with few cases reported in the literature (2,4-6).

We present a case of colonic obstruction caused by sigmoid endometriosis presenting as the first clinical manifestation in a patient with no previous gynecological symptoms.

Case Presentation

A 45-year-old woman presented with cramping lower abdominal pain, constipation, and narrow, ribbon-like stools for two months. She was hemodynamically stable, had no history of chronic disease or abdominal or gynecological surgery, and reported a regular menstrual cycle. Physical examination revealed minimal distension and mild tenderness in the lower left abdomen, without signs of peritonism. The rectal examination was normal. Laboratory tests were all within normal limits. Ultrasonography showed normal-appearing abdominal and pelvic organs. On computed tomography, an obstructing mass in the midportion of the sigmoid colon was identified, with mildly dilated intestinal loops. No distant metastatic lesions or mesenteric lymph node metastases were observed (Figure 1). Colonoscopy revealed an impassable stricture with normal mucosa located approximately 30 cm from the anal verge (Figure 2). A biopsy was not taken because of the risk of perforation and because the mucosa was intact. During the operation, a firm, ill-defined mass was detected in the mid-sigmoid colon, invading the serosa and causing near-complete luminal obstruction. No peritoneal or visceral disease was visualised. A sigmoidectomy with lymph node dissection was performed. The patient was discharged on postoperative day 8 without complications. On pathological examination, a whitish submucosal lesion 3 cm in diameter, infiltrating the serosa and narrowing the lumen, was detected. Histopathology showed that the endometriotic lesion extended from the serosal surface to the lamina propria (Figure 3A). Surgical margins were intact, and the removed lymph nodes were all reactive. Immunohistochemically, both glands and stroma showed positive staining for estrogen (Figure 3B) and progesterone, and negative staining for CDX2 and carcinoembryonic antigen. Endometrial stroma and glandular structures were also positively stained with CD10 (Figure 3C) and CK7, respectively. Based on these findings, the lesion was diagnosed as deep infiltrating endometriosis. During the two-year follow-up, the patient was asymptomatic and recurrence-free. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

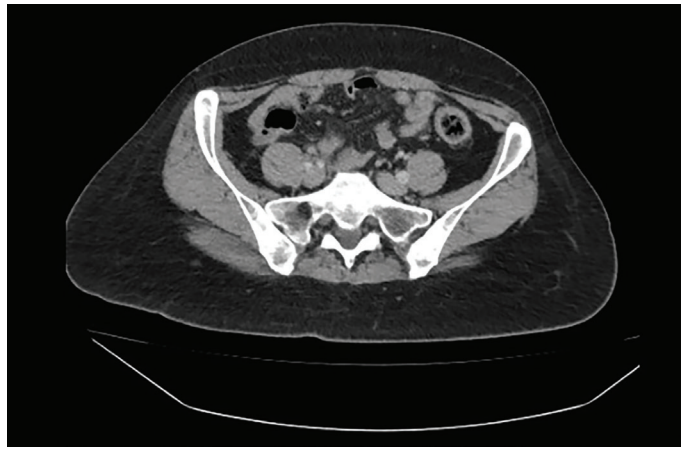

Figure 1. Tomographic view of the obstructing mass in the sigmoid colon

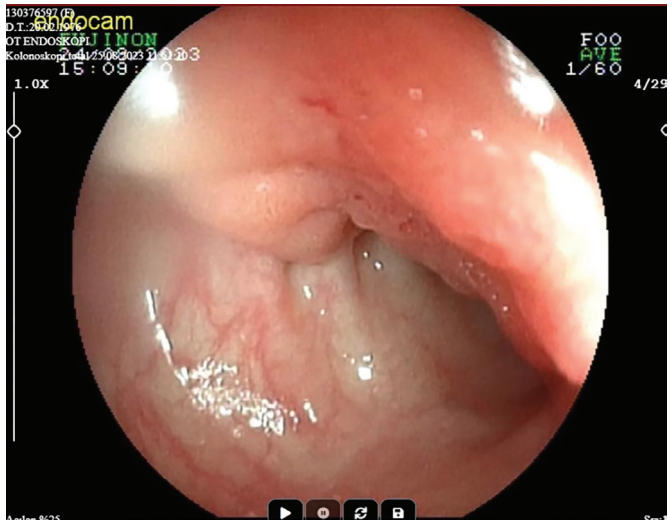

Figure 2. Colonoscopic view of the tight and non-passable stricture with normal mucosa, located approximately 30 cm from the anal verge

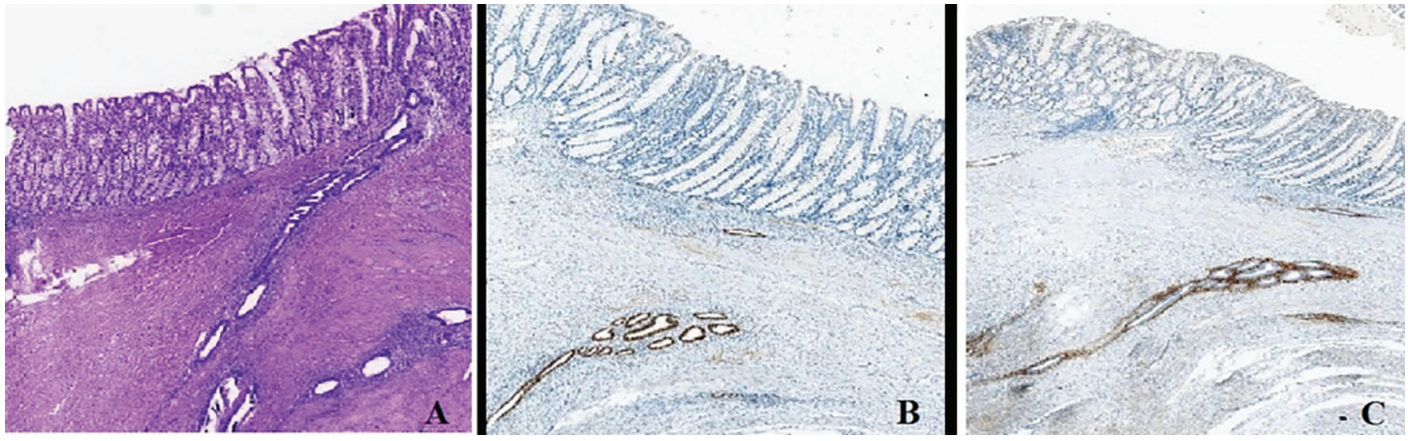

Figure 3. (A) Hemotoxilen-eosine stained colonic samples: endometriotic lesion extending from the serosa to the lamina propria (×40). (B) Estrogen-positive nuclear staining in endometrial glands (×40). (C) CD10-positive staining in endometrial stromal cells (×40)

Discussion

Endometriosis is classically categorized as superficial, peritoneal, and deep disease. Deep infiltrating endometriosis refers to the involvement of the muscularis layer or mucosa of the organ. It is more severe than superficial disease and is observed in up to 20% of patients with endometriosis. Intestinal system is the most frequently affected localization of extragenital endometriosis, among which rectum and sigmoid colon were involved more often, probably due to the proximity to the uterus (3). The clinical presentation is based on the location and depth of the lesions. Superficial lesions are usually asymptomatic or cause mild symptoms whereas infiltrative deep endometriotic lesions can lead to severe situations such as complete bowel obstruction or gastrointestinal bleeding (7). The patients with colonic endometriosis may experience a range of gastrointestinal symptoms including bloating, constipation, diarrhea, rectal bleeding, which may intensify with the menstrual cycle (8). However, a significant portion of these patients suffers from non-cyclical signs and symptoms, which poses a diagnostic challenge for physicians. Similarly, our patient had non-specific gastrointestinal symptoms not associated with her menstrual cycle. For this reason, she was misdiagnosed with irritable bowel syndrome for several weeks, until the lesion caused nearly complete obstruction.

Imaging methods, including ultrasonography and computed tomography, may be helpful for the diagnosis of colonic endometriosis, but often fail to reveal specific findings. In the present case, sonography was normal, whereas tomography showed wall thickening of the sigmoid colon, suspicious for malignancy. Endorectal ultrasonography, on the other hand, has been shown to demonstrate high sensitivity and specificity (6). The facts that it is not available in all medical centers and that it requires extensive experience are the most important factors limiting its accessibility. Colonoscopy should be included in the diagnostic workup except in urgent surgical situations because it may help establish a differential diagnosis, particularly to rule out malignancy.

Therapeutic approaches of intestinal endometriosis can be classified as medical and surgical, but have main principles including complete removal of the lesion, eliminating the pain, preserving fertility, and avoiding recurrence (7). However, there are no globally accepted treatment guidelines, and management is largely individualized. Hormonal therapy has limited effectiveness in symptomatic intestinal endometriosis, particularly in the presence of luminal obstruction. In addition, hormonal therapy has a risk of persistence of symptoms when medication is discontinued (9). Therefore, surgical resection is accepted as the most frequent therapeutic option, especially for patients with colonic obstruction and recurrent rectal bleeding. Although extremely rare, malignant transformation is an important complication of intestinal endometriosis and warrants prioritization of surgical treatment with clear margins. It should be noted here that hormonal therapy after surgery has been shown to reduce the recurrence rate (10). In our case, a complete resection with adequate lymphatic dissection was performed because of suspicion of cancer.

Endometriosis should be considered the differential diagnosis of colonic obstruction, particularly in women of childbearing age with or without a history of endometriosis or gynecological symptoms. A high clinical suspicion is essential to achieve an accurate diagnosis of intestinal endometriosis because of the non-specific clinical and imaging features.

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: M.Ö.K., Data Collection or Processing: M.Ö.K., O.K., M.F.Ç., Analysis or Interpretation: M.Ö.K., O.K., M.F.Ç., M.S.A., Literature Review: M.Ö.K., M.F.Ç., Writing, Reviewing and Editing: M.Ö.K., O.K., M.F.Ç., M.S.A.

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

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CASE REPORT / OLGU SUNUMU

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Widespread Tumor Deposit Without Lymph Node Metastasis in Colon Cancer: A Case Report Regarding the Significance of Tumor Deposit Number

Kolon Kanserinde Lenf Düğümü Metastazı Olmadan Yaygın Tümör Depoziti: Tümör Depoziti Sayısının Önemine İlişkin Bir Olgu Sunumu

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Abstract

Colon cancer is one of the most common malignancies worldwide, and tumor stage and lymph node metastasis are among the most important factors determining prognosis. Tumor deposits are defined as tumor nodules located in the pericolic or mesenteric adipose tissue that do not contain lymph node structures; in the current TNM classification, their presence in the absence of lymph node metastasis is classified as N1c. Tumor deposits are associated with adverse histopathological features such as poor differentiation, lymphovascular invasion, and advanced tumor stage, and are considered an independent poor prognostic factor affecting survival. Furthermore, it has been reported that a high tumor deposit burden may be associated with clinical outcomes similar to, or even worse than, those of lymph node-positive disease. These findings suggest that current staging systems do not adequately reflect the tumor deposit burden and that more comprehensive prognostic evaluations are needed in this patient group. This case describes the clinical condition of a patient with numerous tumor deposits in the absence of lymph node metastasis and compares this condition with cases reported in the literature.

Keywords: Colon cancer, tumor deposit, lymph node, staging

Öz

Kolon kanseri, dünya genelinde en sık görülen malignitelerden biri olup prognozu belirleyen en önemli faktörler arasında tümör evresi ve lenf nodu metastazı yer almaktadır. Tümör depozitleri, perikolik veya mezenterik yağ dokusunda yer alan, lenf nodu yapısı içermeyen tümör nodülleri olarak tanımlanmakta ve güncel TNM sınıflamasında lenf nodu metastazı olmaksızın varlığında N1c kategorisinde değerlendirilmektedir. Tümör depozitleri; kötü diferansiyasyon, lenfovasküler invazyon ve ileri tümör evresi gibi olumsuz histopatolojik özelliklerle ilişkili olup, sağkalım üzerinde bağımsız bir kötü prognostik faktör olarak kabul edilmektedir. Ayrıca, yüksek tümör depozit yükünün, lenf nodu pozitif hastalığa benzer hatta daha kötü klinik sonuçlarla ilişkili olabileceği bildirilmektedir. Bu bulgular, mevcut evreleme sistemlerinin tümör depozit yükünü yeterince yansıtmadığını ve bu hasta grubunda daha kapsamlı prognostik değerlendirmelere ihtiyaç olduğunu düşündürmektedir. Bu olgumuzda da lenf nodu metastazı olmaksızın çok sayıda tümör depoziti içeren bir hastanın klinik durumu anlatılarak literatürle karşılaştırılmıştır.

Anahtar Kelimeler: Kolon kanseri, tümör depoziti, lenf nodu, evreleme

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Introduction

Colon cancer is the 4th most common malignancy in the world. In 2018, more than 1 million new cases of colon cancer were diagnosed worldwide, and more than 500.000 people died from colon cancer (1). The spread of colon cancer is a multi-stage and heterogeneous process. The tumor can primarily advance along the intestinal wall, reach the serosa, and directly invade neighboring organs. The most common route of spread is the lymphatic pathway, where tumor cells first metastasize to the pericolic lymph nodes, then to more central lymphatic stations, which is defined as stage N in the TNM classification. Hematogenous spread occurs primarily via the venous system and most frequently results in liver metastases via the portal circulation; this process is closely related to extramural venous invasion. Furthermore, if the tumor extends beyond the serosa, it can spread to the peritoneal surfaces, leading to peritoneal carcinomatosis. Finally, tumor deposits are defined as discrete tumor nodules that do not contain lymph node structures and are located within pericolic or mesenteric adipose tissue. Although the pathogenesis of these formations has not been fully elucidated, they may be related to lymphatic, venous, or perineural spread. Cases with tumor deposits in the absence of lymph node metastasis are classified as N1c in the TNM system, suggesting alternative tumor biology beyond classical patterns of spread. The presence of tumor deposits directly affects survival (2). There are publications arguing that adjuvant chemotherapy should be considered in cases with tumor deposits without lymph node metastasis (3).

Studies focusing particularly on patients with tumor deposits without lymph node metastasis (N1c) are quite limited. The majority of existing data include heterogeneous patient groups or evaluate tumor deposits together with lymph node-positive patients (4). Therefore, this case report aims to contribute to conclusions regarding the clinical behavior and prognosis of cases that are lymph node-negative but tumor deposit-positive. In addition, there are new studies showing the relationship between the number of tumor deposits and prognosis (5). Our case, despite being N0, could contribute to the literature because of the presence of numerous tumor deposits and the associated prognosis.

This case presentation aims to discuss the current literature regarding the aggressive pathology observed in a patient with a colon tumor who presented with ileus, underwent emergency surgery, and was found to have tumor deposits without lymph node metastasis.

Case Presentation

A 75-year-old male patient presented to the emergency department with nausea, vomiting, abdominal pain, and an absence of stool for three days. Physical examination revealed mild abdominal distension and guarding. Blood tests showed elevated acute-phase reactants. An abdominal X-ray showed no pathological findings. Oral and intravenous contrast-enhanced thoracic and abdominal CT scans were performed. The CT scan revealed an obstructive mass in the proximal transverse colon. Dilatation was observed in the colon segment between the ileocecal valve and the mass (Figure 1). There were no metastases to the lungs, liver, or other organs. The patient was admitted to the ward with a diagnosis of ileus. On the following day, a relapse was observed, and elevated acute phase reactants were detected in the blood. Emergency surgery was planned. The patient gave informed consent for the surgery.

The patient underwent a right hemicolectomy and an end ileostomy because of their debilitated condition at the time of surgery. The patient was extubated and admitted to the surgical intensive care unit. After 3 days in the intensive care unit, they were transferred to the ward and discharged on the 12th postoperative day. The patient presented to the outpatient clinic with the pathology results. The pathology was consistent with T4N1C undifferentiated colon carcinoma. Subtype differentiation could not be determined due to aggressive tumor biology. There were 13 reactive lymph nodes, but numerous tumor deposits were present. Surgical margins were negative. The patient was referred to the medical oncology unit for adjuvant chemotherapy.

A computed tomography (CT) scan performed for systemic treatment planning revealed extensive metastases in the lungs and liver. These metastases were not visible on the CT scan obtained 45 days earlier (Figure 2). Adjuvant systemic chemotherapy was planned for the patient.

Discussion

Tumor deposits in colon cancer are defined as tumor nodules located within the pericolic or mesenteric adipose tissue that do not contain lymph node structures or significant vascular structures. While their biological origins are not entirely clear, mechanisms such as discontinuous lymphovascular spread, perineural invasion, or extranodal extension of microscopic nodal metastases have been proposed. Current data support the idea that the presence of tumor deposits is not only a morphological finding but also an indicator of aggressive tumor biology.

Because tumor deposits have prognostic significance, the TNM classification includes the N1c category, which refers to the presence of tumor deposits without regional lymph node metastasis. Large series in the literature have shown that overall survival is significantly worse in patients with positive tumor deposits than in patients with negative lymph nodes (N0) (2). This suggests that the presence of tumor deposits without

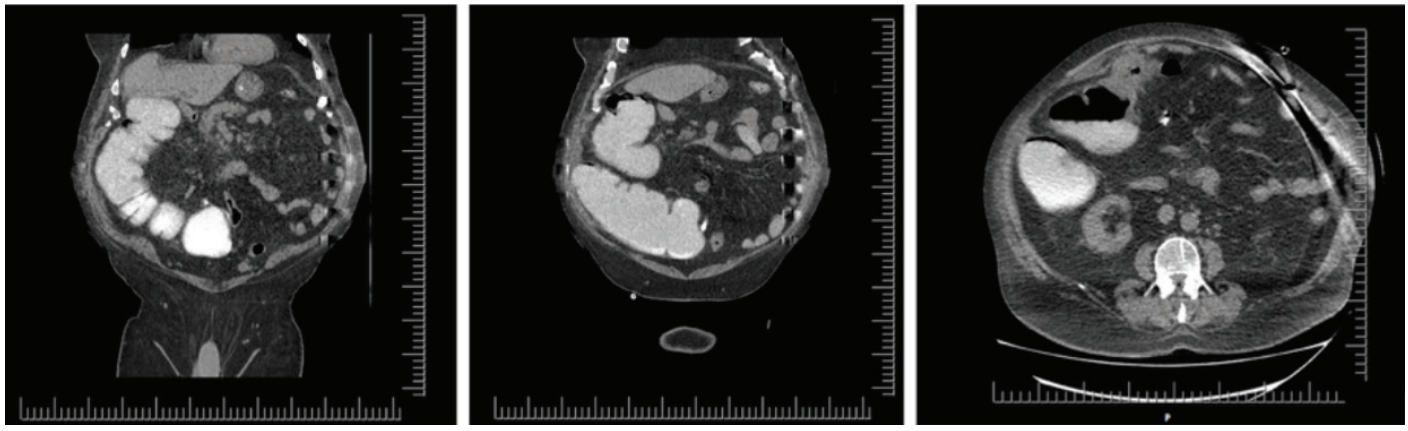

Figure 1. Preoperative CT scan images of the patient
CT: Computed tomography

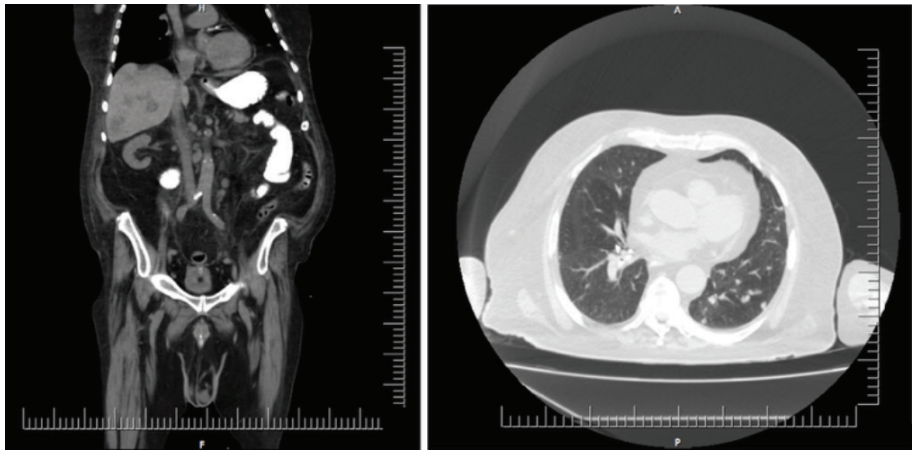

Figure 2. CT scan before adjuvant chemotherapy (liver and lung metastases)
CT: Computed tomography

lymph node involvement indicates that the disease is in a more advanced biological stage (6).

Not only the presence of tumor deposits but also their number is of prognostic importance. Various studies have reported an inverse relationship between the increase in the number of tumor deposits and survival, and that the prognosis of patients with a large number of tumor deposits can approach N2 disease (7). In line with these findings, some researchers are proposing new subclassifications (e.g., "N2c") that incorporate tumor deposit burden in addition to the parameters of the current TNM classification. In the presented case, the presence of a large tumor deposit, despite the absence of lymph node metastasis, seems consistent with the aggressive course of the disease.

Furthermore, the presence of tumor deposits is strongly associated with other unfavorable histopathological features such as poor differentiation, lymphovascular invasion, perineural invasion, and advanced T stage (6). This supports the idea that tumor deposits may be an indicator of systemic spread. Indeed, the presence of tumor deposits has been reported as an independent poor prognostic factor even in early-stage colon cancers (8). In our case, the extensive tumor deposits and the aggressiveness of the primary colon tumor are correlated.

A significant limitation of the current TNM classification is that it does not take into account the number of tumor deposits. Recent studies have shown that composite indices that evaluate the number of tumor deposits and the number of negative lymph nodes together can predict prognosis more accurately (9). This suggests that the current staging system may be insufficient, especially in patients with a high tumor deposit burden.

Clinically, the management of N1c patients remains controversial. These patients are considered stage III, and adjuvant chemotherapy is recommended; however, their prognosis is heterogeneous. Some studies show that tumor-deposit-positive patients benefit from systemic treatment similarly to lymph-node-positive patients. This suggests that tumor deposit should be evaluated as equivalent to lymph node metastasis in clinical

decision-making (10). The presented case demonstrates that the absence of lymph node metastasis does not necessarily indicate a good prognosis. The presence of dense tumor deposits is associated with rapid disease progression, consistent with the aggressive biological behavior reported in the literature.

Tumor deposits are significant prognostic factors in colon cancer and can affect the course of the disease, even without lymph node metastasis. Given the impact of the number of tumor deposits on prognosis, current staging systems should be revised to incorporate this parameter in greater detail. Undoubtedly, the prognosis for a patient with a single tumor deposit differs from that of a patient with multiple tumor deposits. More aggressive treatment approaches should be considered for patients with a high tumor-deposit burden.

Conclusion

In patients with colon cancer without lymph node metastasis, the presence of tumor deposits, especially in high numbers, indicates a biologically aggressive course of the disease. This case reveals that not only the presence but also the number of tumor deposits are determining factors in prognosis, and that the current TNM staging system may be insufficient for this patient group. More careful prognostic evaluations and aggressive treatment approaches should be considered for patients with a high tumor deposit burden.

One of the author of this article (M.A.G.) is a member of the Advisory 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.

Ethics

Informed Consent: The patient gave informed consent for the surgery.

Footnotes

One of the author of this article (M.A.G.) is a member of the Advisory 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.

Authorship Contributions

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CASE REPORT / OLGU SUNUMU

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Turk J Surg Oncol 2026;2(2):82-85

A Rare Case Report: Intra-abdominal Mass Caused by Actinomyces Infection

Nadir Bir Olgu Sunumu: Aktinomices Enfeksiyonu Kaynaklı Batın İçi Kitle

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Abstract

Human actinomycosis is an uncommon chronic infectious condition caused by bacteria of the genus *Actinomyces*. These microorganisms may become pathogenic when the integrity of the mucosal barrier is compromised due to factors such as trauma, prior surgical procedures, or other conditions affecting mucosal defenses.

In this report, we present the case of a 55-year-old man admitted with marked weight loss and abdominal distension. Imaging studies identified an intra-abdominal mass, and the patient underwent surgical debulking. Histopathological evaluation of the excised tissue confirmed the presence of an *Actinomyces* infection associated with xanthogranulomatous inflammation and abscess formation. The patient's clinical follow-up period lasted 43 days. This report outlines the clinical presentation, diagnostic evaluation, and management of the patient.

Keywords: Actinomycosis, colon, debulking, malignancy.

Öz

İnsan aktinomikozu, *Actinomyces* cinsi bakterilerin neden olduğu, nadir görülen kronik bir enfeksiyon hastalığıdır. Travma, cerrahi girişim öyküsü veya mukozal bütünlüğü bozan durumlarda, mukozal bariyeri aşarak enfeksiyon oluşturabilmektedir.

Bu olgu sunumunda, kilo kaybı ve batında şişlik şikayetleri ile başvuran 55 yaşında erkek bir hasta sunulmaktadır. Yapılan tetkiklerde batın içi kitle saptanan hasta cerrahi olarak opere edilmiş ve debulking uygulanmıştır. Rezeksiyon materyalinin histopatolojik incelemesi *Actinomyces* enfeksiyonu, ksantogranülomatöz enflamasyon ve apse formasyonu ile uyumlu olarak raporlanmıştır. Bu olgu sunumunda hastanın tanı ve tedavi süreci sunulmaktadır.

Anahtar Kelimeler: Aktinomiçes, kolon, debulking, malignite

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Introduction

Actinomycosis is a rare subacute or chronic infection caused by gram-positive, filamentous, non-acid-fast, anaerobic or microaerophilic *Actinomyces* species. The infection is typically characterized by granulomatous and suppurative inflammation; in its chronic form, it may be accompanied by multiple abscesses and granulation tissue containing sulfur granules. Approximately 70% of cases are attributed to *Actinomyces israelii* or *Actinomyces gerencseriae* (1).

The diagnosis of actinomycosis can be difficult, as identification of the causative organism necessitates prolonged incubation under anaerobic culture conditions. Moreover, the infection often follows a polymicrobial pattern, with concomitant involvement of secondary microorganisms such as *Aggregatibacter actinomycetemcomitans*, *Prevotella* species, *Streptococcus* species, members of the *Enterobacteriaceae* family, *Peptostreptococcus*, and *Staphylococcus* species (2-4).

Case Presentation

A 55-year-old male patient presented to the gastroenterology outpatient clinic with complaints of abdominal distension and an unintentional weight loss of approximately 15 kg over the previous two months. The patient had no known comorbidities and no prior abdominal surgery. On physical examination, a palpable abdominal mass was detected, and the patient was referred to our clinic for further evaluation.

Laboratory investigations at admission revealed the following results: C-reactive protein 213 mg/L, white blood cell count 12.86×10^3/µL, neutrophils 63.4%, monocytes 9.5%, hematocrit 38.2%, platelet count 261×10^3/µL, alkaline phosphatase 127 U/L, gamma-glutamyl transferase 70 U/L, aspartate aminotransferase 47 U/L, alanine aminotransferase 65 U/L, total bilirubin 0.35 mg/dL, direct bilirubin 0.04 mg/dL, calcium 8.79 mg/dL, potassium 3.8 mmol/L, sodium 146 mmol/L, creatinine 1.11 mg/dL, carbohydrate antigen 19-9 6 U/mL, and alpha-fetoprotein 3.16 ng/mL.

Computed tomography (CT) imaging demonstrated diffuse wall thickening in the sigmoid colon and upper rectum, along with a mass lesion measuring approximately 57×74 mm in the right lower quadrant, extending into adjacent anatomical structures (Figures 1 and 2). Colonoscopic evaluation revealed an area suspicious for invasion in the left colon. Histopathological examination of the biopsy specimen obtained from this region revealed focal active colitis with increased eosinophils (55 eosinophils per high-power field) in the sigmoid colon specimen. A repeat colonoscopy with biopsy demonstrated findings consistent with total active colitis, increased eosinophils, and regenerative changes in the left colon.

Positron emission tomography-CT revealed a mass with indistinct borders in the right lower quadrant involving the terminal ileum and the rectosigmoid junction, measuring approximately 83×64 mm , with markedly increased F-18 fluorodeoxyglucose uptake (SUV_{max}: 17.77) (Figure 3).

The patient subsequently underwent elective surgery. During laparotomy, a granulomatous mass lesion invading the colonic loops, distal small intestine, duodenum, ureters, and the retroperitoneal area was identified. The mass and the involved

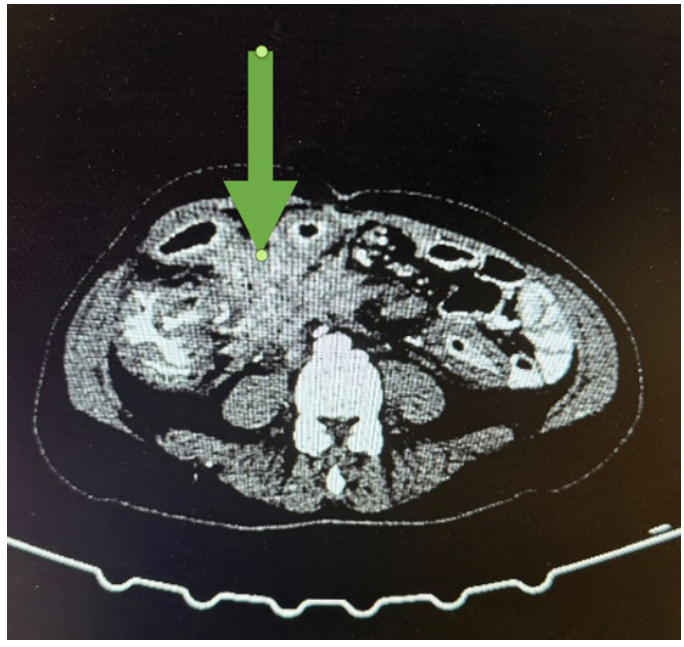

Figure 1. Mass appearance on CT (horizontal section)
CT: Computed tomography

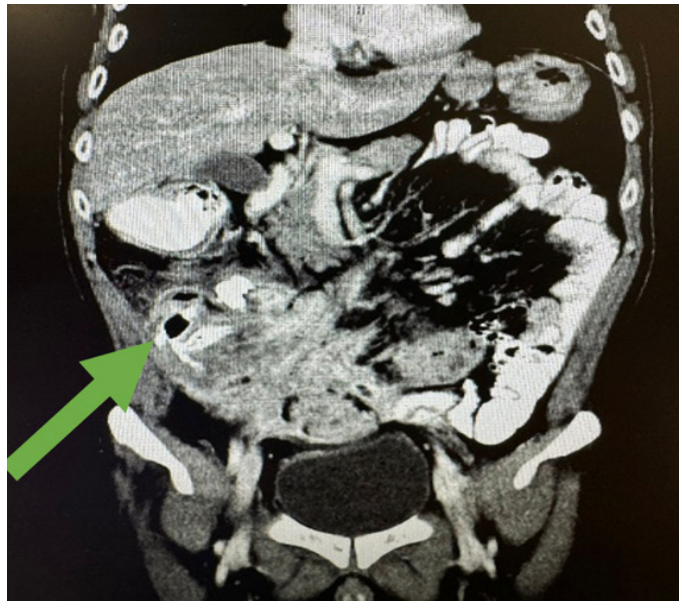

Figure 2. Mass appearance on CT (coronal section)
CT: Computed tomography

colon segment were excised, and debulking was performed. The rectum was left as a stump, and the distal small intestine was exteriorized as an end ileostomy (Figure 4).

Histopathological examination of the resection specimen of the colon revealed active chronic suppurative xanthogranulomatous inflammation with abscess formation and colonies consistent with *Actinomyces* species. The patient was subsequently seen by the infectious diseases department, and intravenous meropenem therapy was initiated. Following completion of treatment, the patient was discharged in good clinical condition. The total clinical follow-up period was 43 days. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

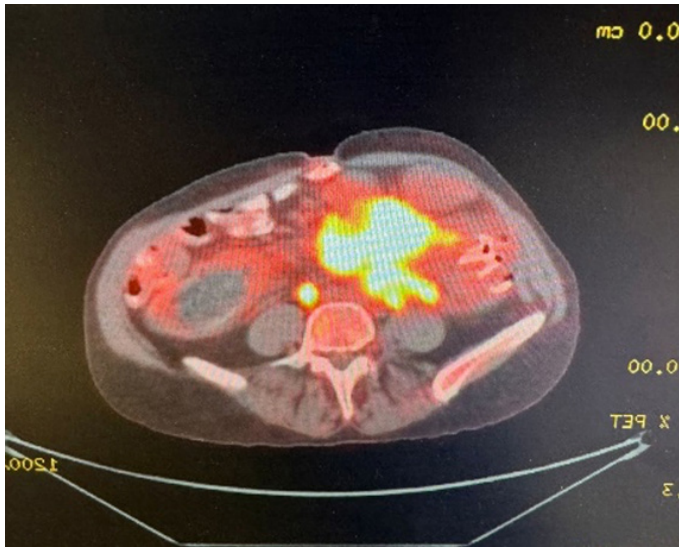

Figure 3. Metabolic uptake of the mass on PET/CT (horizontal section)
PET: Positron emission tomography, CT: Computed tomography

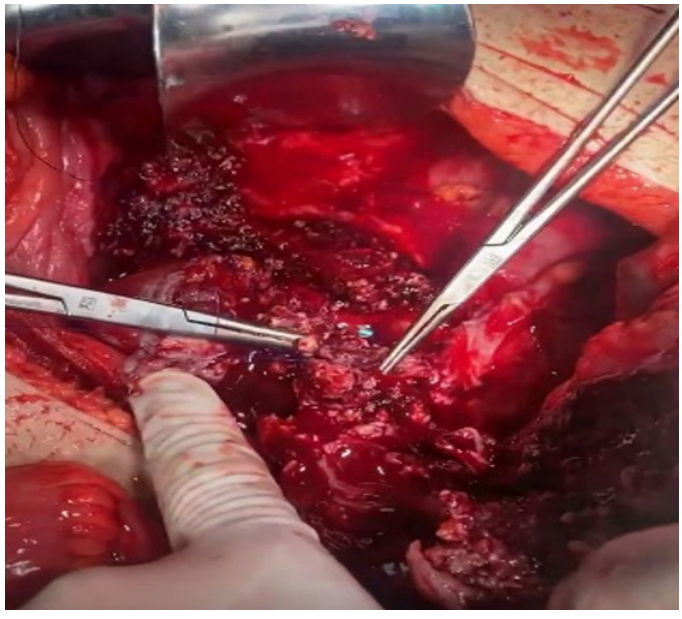

Figure 4. Post-debulking appearance

Discussion

Actinomycosis is a chronic granulomatous infectious disease caused by bacteria of the *Actinomyces* genus and is reported to affect males approximately two to four times more often than females (5). These organisms normally exist as part of the commensal microbiota of the oral cavity, gastrointestinal system, and female genital tract, and they typically remain noninvasive as long as the mucosal barrier is preserved (6-8). However, disruption of mucosal integrity resulting from trauma, surgical manipulation, invasive procedures, or systemic conditions such as diabetes mellitus may facilitate tissue invasion and subsequent infection (1). In this case, none of the known predisposing factors were present.

Actinomycosis is often difficult to diagnose. In addition to clinical and radiological findings, microbiological and histopathological examinations play an important role in establishing the diagnosis (9-10). When clinical findings are non-specific, actinomycosis may mimic intra-abdominal masses, colonic and small bowel malignancies, or mesenchymal tumors. The literature emphasizes the significant role of CT and magnetic resonance imaging in the diagnostic process (11-12). Imaging modalities are particularly valuable in differentiating neoplastic lesions from those of inflammatory origin.

In our case, the patient underwent initial CT evaluation, which revealed an intra-abdominal lesion. Subsequent colonoscopic evaluation was performed; however, biopsy specimens were non-diagnostic. Therefore, surgical exploration was preferred to establish a definitive diagnosis and provide appropriate treatment.

Conclusion

Actinomycosis is a chronic infectious disorder that is commonly associated with predisposing factors such as prior surgical procedures, trauma, or diabetes mellitus; it can present with a wide range of clinical manifestations. Nevertheless, as highlighted in this case, it may also arise in individuals without any identifiable underlying risk factors. For this reason, actinomycosis should be taken into account in the differential diagnosis of intra-abdominal masses.

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: B.A., İ.A., Analysis or Interpretation: Z.Z., G.S., Literature Review: B.Y., Writing, Reviewing and Editing: Y.K., G.S.

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LETTER TO THE EDITOR / EDİTÖRE MEKTUP

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Turk J Surg Oncol 2026;2(2):86-87

Cancer and Anesthesia: Old Friends or New Enemies?

Kanser ve Anestezi: Eski Dostlar, Yeni Düşmanlar mı?

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Cancer is the second leading cause of death worldwide after cardiovascular diseases. Despite the development of new therapeutic modalities, mortality related to recurrence and metastasis remains a significant problem.

In recent years, perioperative anesthetic management in oncologic surgery has become a topic of growing debate among oncologic surgeons and anesthesiologists. Beyond surgical resection and the perioperative stress response, factors including anesthetic agents, hypothermia, and blood transfusion may contribute to making the perioperative period a vulnerable window for tumor metastasis (1).

During tumor resection, circulating tumor cells released from the primary tumor may disseminate to distant organs through the bloodstream or lymphatic circulation, thereby contributing to metastatic spread. During tumor resection, cytokines released from immune cells-most notably interleukin-6-initiate an inflammatory cascade that enhances tumor cell motility, invasion, and proliferative potential. Concurrently, activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system increases the release of catecholamines and cortisol, leading to perioperative immunosuppression. Ischemia and tissue hypoxia induced by surgical incision activate physiological defense mechanisms aimed at tissue repair through angiogenesis, mediated by increased expression of hypoxia-inducible factor-1α and vascular endothelial growth factor. Tumor cells may utilize these same mechanisms to enhance proliferation, angiogenesis, and vascular remodeling, ultimately promoting metastatic dissemination. Thus, the triad of inflammation, immunosuppression, and angiogenesis that characterizes the perioperative period forms a fundamental basis of metastatic tumor biology (2).

Studies investigating the relationship between anesthetic technique and oncologic outcomes in cancer surgery have frequently focused on comparing the two principal anesthetic techniques: inhalational anesthesia and propofol-based total intravenous anesthesia, with survival commonly used as the primary endpoint. Until recent years, numerous retrospective and heterogeneous studies suggested that total intravenous techniques might be superior (3). However, the limited number of completed randomized controlled trials (RCTs) have not demonstrated a significant difference in survival outcomes between these approaches, and the results of several ongoing RCTs are still awaited (4).

Another important question is whether adding regional anesthetic techniques to general anesthesia, which are known to attenuate the perioperative stress response, could improve survival outcomes. In vitro studies have demonstrated that regional anesthesia may increase apoptosis and enhance the activity of natural killer (NK) cells involved in the elimination of cancer cells. Regional anesthesia is also known to reduce opioid consumption by providing effective postoperative analgesia (2). This is particularly relevant because opioids may promote tumor growth and dissemination through their effects on the immune system, including decreased neutrophil chemotaxis, reduced NK

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cell cytotoxicity, and suppression of T- and B-cell responses as well as antibody production (3). However, randomized studies have generally demonstrated no survival benefit when regional anesthesia combined with general anesthesia is compared with general anesthesia with opioid-based techniques. In a large prospective study involving more than 34.000 patients investigating the relationship between opioids and breast cancer recurrence, patients were followed for more than eight years, and no association between opioid use and cancer recurrence was found (5).

In the context of oncological outcomes, evidence from in vitro and animal studies does not fully align with results from clinical studies. Experimental models rely on artificially induced cancers and fail to adequately reflect the impact of standard oncologic treatments in humans, such as chemotherapy and radiotherapy.

Similarly, *in vitro* studies evaluating anesthetic agents typically assess the effects of a single agent under highly controlled experimental conditions. However, in clinical practice, anesthesia is performed using a combination of drugs and techniques. Consequently, in clinical studies, it is difficult to isolate and attribute oncological outcomes to any single anesthetic agent.

During the perioperative period, the recommendation best supported by evidence is to avoid unnecessary blood transfusions. Although leukocyte reduction techniques are applied to stored blood products, residual leukocytes, biologically active cytokines, and released pro-inflammatory mediators may promote tumor progression in the setting of transfusion-related immunosuppression. Large meta-analyses have demonstrated that allogeneic blood transfusion is associated with increased complications and reduced survival (2). In this context, the literature recommends focusing on restrictive transfusion strategies, preoperative anemia management, and strategies to reduce perioperative blood loss.

Although current studies indicate that the perioperative period represents a highly sensitive metastatic window influenced by both surgical and anesthetic factors, there is no definitive evidence sufficiently strong to change clinical practice. In the future, pharmacogenetic strategies tailored to tumor type may enable more individualized approaches.

Keywords: Cancer, anesthesia, surgery

Anahtar Kelimeler: Kanser, anestezi, cerrahi

Footnotes

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