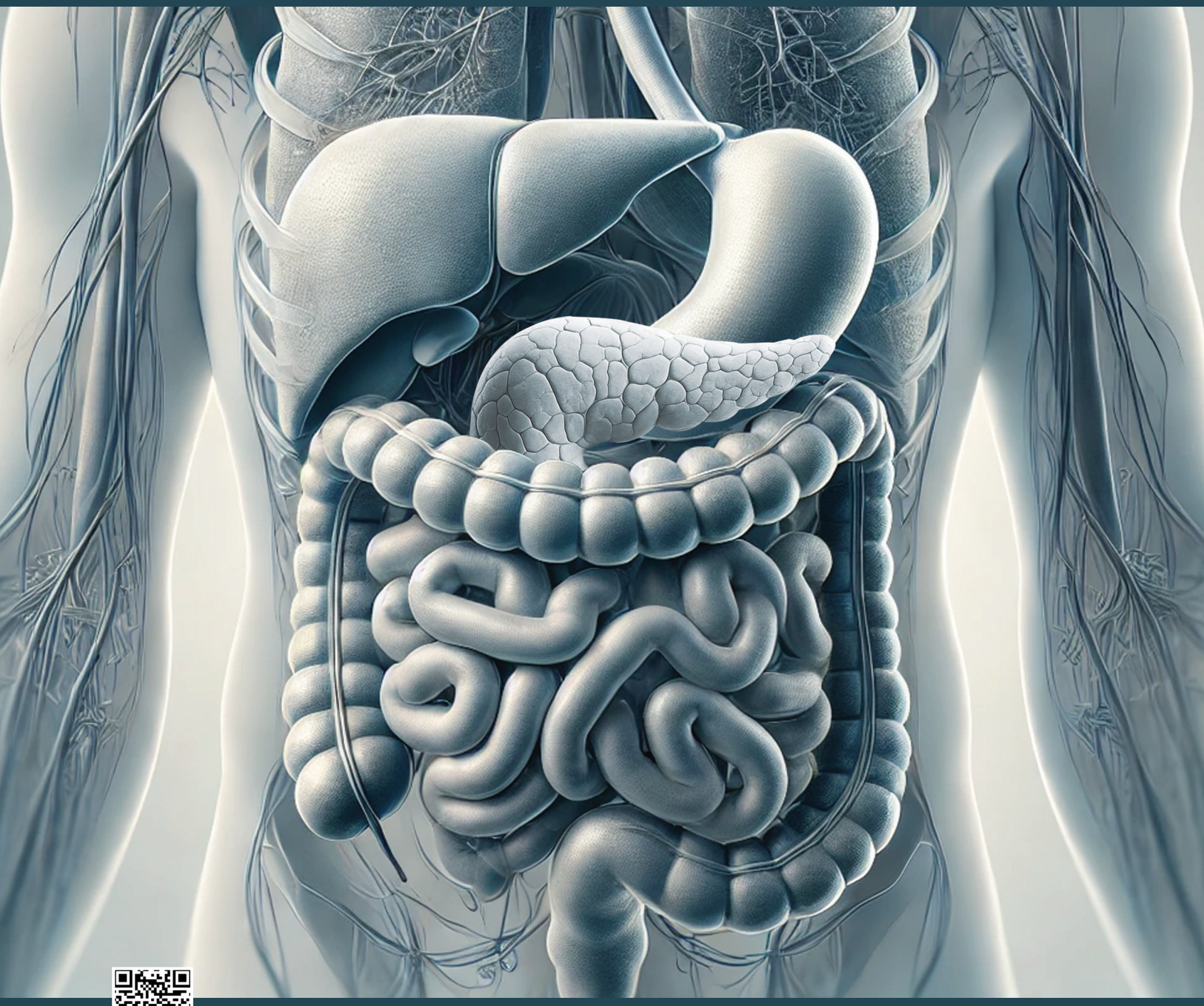
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EDITORIAL



Launching a New Era in Gastrointestinal (GI) Oncology Publishing

Dear Colleagues and Members of the Global GI Oncology Community,

It is with profound enthusiasm and a deep sense of responsibility that I welcome you to the inaugural issue of the International Journal of Gastrointestinal Cancer Research (IJGCR). This momentous launch represents not merely the establishment of another academic journal, but rather the crystallization of a collective vision-a vision shared by clinicians, researchers, and healthcare professionals worldwide who are committed to advancing the science and practice of GI oncology.

The Imperative for a Dedicated Platform

The landscape of GI cancer research has undergone a remarkable transformation over the past two decades. GI malignancies, collectively accounting for approximately one in four of all cancer cases and one in three cancer deaths globally, present an unprecedented challenge to the medical community. Yet, simultaneously, they offer unprecedented opportunities for innovation and discovery. The convergence of molecular diagnostics, precision medicine, immunotherapy, and multidisciplinary care has fundamentally altered our approach to these complex diseases.

Despite this scientific revolution, the field of GI oncology has lacked a dedicated, high-impact international journal specifically designed to serve as the primary venue for publishing cutting-edge research, clinical innovations, and translational discoveries in this domain. While excellent general oncology and specialty journals exist, they often cannot provide the focused editorial attention and specialized peer-review expertise that GI cancer research deserves. The IJGCR has been created to fill this critical gap.

Our Mission and Vision

The mission of IJGCR is to serve as the premier international platform for the dissemination of original research, clinical investigations, translational studies, and evidence-based reviews that advance our understanding and management of GI cancers. We are committed to publishing work of the highest scientific quality, rigorously peer-reviewed by experts in the field, and immediately applicable to clinical practice and future research directions.

Our vision extends beyond traditional academic publishing. IJGCR aspires to be a catalyst for international collaboration, fostering connections among researchers, clinicians, and institutions across continents. We recognize that the most significant advances in GI oncology emerge from multidisciplinary collaboration-bringing together medical oncologists, surgical oncologists, radiation oncologists, gastroenterologists, pathologists, radiologists, and basic science researchers. IJGCR will actively promote and facilitate such collaboration through our editorial policies and special initiatives.

Scope and Content

The journal will encompass the full spectrum of GI oncology, including but not limited to:

Upper GI Malignancies: Esophageal, gastric, and gastroesophageal junction cancers, with emphasis on novel therapeutic strategies, biomarker-driven approaches, and multidisciplinary management.

Colorectal Cancer: From early detection and prevention through advanced metastatic disease, including precision oncology approaches, surgical innovations, and organ-preserving strategies.

Hepatobiliary and Pancreatic Cancers: Hepatocellular carcinoma, cholangiocarcinoma, and pancreatic adenocarcinoma, with particular focus on emerging systemic therapies, regional treatment modalities, and transplantation strategies.

EDITORIAL

Rare GI Malignancies: GI stromal tumors, neuroendocrine tumors, GI lymphomas, and other uncommon entities where targeted therapy has revolutionized outcomes.

Translational Research: Molecular profiling, genomic analysis, biomarker discovery, and mechanistic studies that illuminate the biology of GI cancers and identify new therapeutic targets.

Supportive Care and Quality of Life: Palliative medicine, management of treatment-related toxicities, nutritional support, psycho-oncology, and strategies to optimize patient outcomes and quality of life.

Epidemiology and Prevention: Population-based studies, screening strategies, risk stratification, and public health approaches to reducing the burden of GI cancers globally.

Health Services Research: Health economics, healthcare delivery models, access to care, and implementation science relevant to GI oncology.

Editorial Standards and Peer-review

IJGCR is committed to the highest standards of scientific integrity and editorial excellence. All submitted manuscripts will undergo rigorous double-blind peer-review by experts in relevant subspecialties. Our editorial board comprises internationally recognized leaders in GI oncology, representing diverse geographic regions, clinical disciplines, and research expertise. This multidisciplinary composition ensures that manuscripts are evaluated not only for scientific merit but also for clinical relevance and applicability to global practice.

We adhere strictly to the principles of research ethics, including the International Committee of Medical Journal Editors guidelines. We are committed to transparency in reporting, reproducibility of findings, and the responsible communication of research results. IJGCR will maintain the highest standards of confidentiality and will not tolerate plagiarism, data fabrication, or other forms of scientific misconduct.

Global Accessibility and Impact

From its inception, IJGCR has been designed as a truly international journal. We welcome submissions from researchers and clinicians worldwide, recognizing that important advances in GI oncology emerge from institutions and healthcare systems across all continents. To ensure maximum global accessibility, IJGCR will be published in English and will be indexed in major international databases including PubMed/MEDLINE, Scopus, Web of Science, and other leading indexing services. All articles will be assigned Digital Object Identifiers to ensure permanent accessibility and accurate citation.

We are deeply committed to open science principles. IJGCR will employ an open-access model, ensuring that research findings are freely available to the global scientific community, healthcare professionals, and patients. This commitment reflects our belief that knowledge generated through scientific research should be a public good, particularly when it has the potential to improve health outcomes and save lives.

The Role of Authors, Reviewers, and Readers

The success of IJGCR will depend fundamentally on the contributions of our community. We invite researchers and clinicians to submit their best work-original investigations, clinical case reports, systematic reviews, meta-analyses, and thought-provoking commentaries that advance the field. We particularly encourage submissions from early-career researchers and from institutions in low- and middle-income countries, where GI cancer burden is often highest yet research infrastructure may be limited.

We also call upon the scientific community to serve as peer-reviewers. The peer-review process is the cornerstone of scientific publishing, and we depend upon the generosity and expertise of colleagues who volunteer their time to evaluate manuscripts. Peer-review is not merely a gatekeeping function; it is an opportunity to mentor junior researchers, to ensure scientific rigor, and to improve the quality of published work.

EDITORIAL

Finally, we invite readers to engage critically with the content published in IJGCR. Science advances through dialogue, debate, and the rigorous examination of evidence. We welcome letters to the editor, commentaries, and responses that extend the discussion initiated by published articles.

Collaboration with the International GI Cancers Conference (IGICC)

IJGCR is intimately connected with the IGICC, which has served as the premier annual gathering for GI oncology professionals since 2010. The journal will serve as an official publication venue for selected presentations and research from IGICC, and we anticipate that many of the most significant advances discussed at IGICC will find their way into the pages of IJGCR. This synergy between conference and journal will create a dynamic ecosystem for scientific exchange and knowledge dissemination.

Challenges and Opportunities

The field of GI oncology faces significant challenges. GI cancers remain among the most lethal malignancies, with 5-year survival rates for many subtypes remaining disappointingly low. Geographic disparities in cancer incidence, access to treatment, and research capacity remain profound. Many patients with GI cancers present at advanced stages, limiting the potential for curative treatment. Drug resistance and treatment-related toxicities continue to limit the efficacy of our therapeutic arsenal.

Yet these challenges also present extraordinary opportunities. The rapid pace of scientific discovery-in immunotherapy, targeted therapy, precision medicine, and surgical innovation-offers genuine hope for improved outcomes. Emerging technologies such as artificial intelligence, liquid biopsy, and advanced imaging promise to revolutionize early detection and treatment planning. The increasing recognition of the importance of multidisciplinary care, patient-centered outcomes, and health equity creates opportunities to optimize care delivery and improve quality of life for patients with GI cancers.

A Call to Action

As we launch IJGCR, I extend a heartfelt invitation to the global GI oncology community. Whether you are a basic scientist investigating the molecular biology of GI cancers, a clinical researcher conducting therapeutic trials, a practicing oncologist seeking to advance patient care, or a patient advocate working to improve outcomes for those affected by these diseases, IJGCR is your journal. This is a platform for your work, your ideas, and your voice.

I am confident that IJGCR will become an indispensable resource for the GI oncology community-a journal where the most important research is published, where rigorous science meets clinical relevance, and where the collective wisdom of the global community is brought to bear on the challenge of conquering GI cancers.

Acknowledgments

The launch of IJGCR would not have been possible without the dedication and support of many individuals and institutions. I wish to express my gratitude to the members of the editorial board, who have committed their time and expertise to ensuring the highest standards of scientific excellence. I am deeply grateful to Galenos Publishing House, whose commitment to academic publishing and whose innovative publishing platforms have made this journal possible. I also wish to acknowledge the countless researchers, clinicians, and patients whose work and experiences have inspired the creation of this journal.

Looking Forward

As we embark on this exciting journey, I am filled with optimism about the future of GI oncology. The advances we have witnessed in recent years, and those yet to come, offer genuine hope that we can improve outcomes for patients with these devastating diseases. IJGCR will serve as a beacon, illuminating the path forward and connecting the global community of researchers and clinicians who are dedicated to this mission.

I invite you to visit the journal website at https://gicancerjournal.com/ to learn more about our editorial policies, submission guidelines, and the full editorial board. I encourage you to submit your work, to serve as a peer-reviewer, and to engage as a reader and contributor to this exciting new venture in scientific publishing.

EDITORIAL

Together, we will advance the science and practice of GI oncology and ultimately, improve the lives of patients affected by these diseases.

With warm regards and best wishes for the success of IJGCR,

Editor-in-Chief: Prof., MD. Şuayib Yalçın

Hacettepe University Cancer Institute, Ankara, Türkiye

About the Editor-in-Chief

Prof., MD. Şuayib Yalçın is the Director of the Hacettepe University Cancer Institute and a leading figure in GI oncology in Türkiye and internationally. He has served as the Chairman of the IGICC and is recognized for his contributions to advancing multidisciplinary cancer care and research. Prof., Yalçın has published extensively in peer-reviewed journals and is a frequent speaker at international conferences on topics related to GI malignancies and precision oncology.

16th International Gastrointestinal Cancers Conference (IGICC 2026): Invitation, General Information and Conference Program

Invitation to 16th IGICC 2026 in Istanbul

Dear Colleagues,

On behalf of the Organizing Committee, I am pleased to invite you to the 16th IGICC 2026, to be held between December 17-20, 2026. The meeting will be held in a hybrid format, with online sessions and in-person sessions at The Marmara Taksim Hotel in İstanbul, Türkiye. However, in person sessions can be viewed live online if registered to the conference. You can get detailed information at the conference website; **www.igicc.org**

Building on the experience gained through the previous fifteen meetings, IGICC 2026 will once again provide a great forum for education, scientific exchange, and discussion of current developments in gastrointestinal cancer management. The hybrid format will make the scientific content accessible to a wider international audience while preserving the direct interaction and multidisciplinary exchange offered by an in-person meeting.

The scientific program covers the main areas of gastrointestinal oncology, including gastrointestinal, hepatobiliary, and pancreatic cancers; neuroendocrine tumors (NETs); gastrointestinal stromal tumors (GISTs); gastrointestinal lymphomas; and supportive/palliative care. The program has been developed for medical oncologists, radiation oncologists, surgeons, pathologists, gastroenterologists, nuclear medicine specialists, and other professionals involved in the care of patients with gastrointestinal cancers.

The program will include keynote lectures, educational sessions, multidisciplinary tumor board discussions, case-based presentations, and oral and poster presentations. Both online and in-person participants will be able to follow current scientific discussions, exchange experience with colleagues, and develop new professional and research connections.

We cordially invite you to join us by attending the conference either online or in person and to contribute to the scientific program by submitting your scientific work for consideration as an oral or poster presentation.

We are looking forward to welcoming you to IGICC 2026 in December 17-20 in Istanbul, where continents meet.

Sincerely,

Prof. MD. Şuayib Yalçın Chair, IGICC 2026 Hacettepe University Cancer Institute Ankara, Türkiye

16th IGICC 2026:

Introduction and Historical Background

Since its first meeting in 2011, the IGICC has grown into an established annual meeting for professionals working in gastrointestinal oncology. Over sixteen years, it has developed from a regional initiative into an international conference, bringing together thousands of participants from more than 50 countries across six continents. Throughout this period, IGICC has focused on sharing most current research and information, discussing its application in clinical practice, and supporting international collaboration.

Legacy of Previous Conferences

IGICC's development is reflected not only in increasing attendance but also in the way discussions held at the meeting have contributed to clinical practice and research priorities. Previous conferences have also supported consensus-building, encouraged international research partnerships, and provided a platform for the discussion of new treatment approaches.

IGICC 2011-2015: Foundational Years

The first meetings established IGICC as a multidisciplinary forum in gastrointestinal oncology. During this period, specialists from different fields came together to discuss clinical practice and emerging evidence. The multidisciplinary model-bringing together medical oncology, surgical oncology, radiation oncology, and supportive care-became a defining feature of the conference from the outset.

IGICC 2016-2020: The Era of Precision Oncology

As molecular diagnostics and genomic profiling became more widely available, the program increasingly addressed how molecular findings could be incorporated into clinical decision-making. Targeted therapies for specific molecular subtypes and the clinical relevance of emerging biomarkers became important areas of discussion.

IGICC 2021-2025: Immunotherapy and Personalized Care

The most recent meetings reflected the growing role of immunotherapy in gastrointestinal oncology. IGICC 2021 included presentations on checkpoint inhibitor combinations in advanced gastric cancer, while IGICC 2023 addressed neoadjuvant immunotherapy in colorectal cancer. During the same period, the program gave greater attention to patient-centered care, including palliative medicine, nutritional support, and psycho-oncology. The value of IGICC extends beyond the meeting itself. In the post-conference survey conducted after IGICC 2024, 87% of respondents reported that they had introduced new clinical strategies based on conference presentations. In addition, 64% stated that they

had started new research collaborations with colleagues they met at the conference, and 92% rated the multidisciplinary case discussions as “highly valuable” or “essential”.

Current Landscape of Gastrointestinal Cancers

Gastrointestinal cancers remain a major cause of illness and death worldwide. According to the Global Cancer Observatory, they account for approximately one in four cancer cases and one in three cancer-related deaths globally. These figures underline the continuing need to share evidence, strengthen international collaboration, and improve the transfer of current knowledge into daily practice. These priorities remain central to IGICC 2026.

Conference Objectives

IGICC 2026 aims to:
• Present clinically relevant updates across gastrointestinal oncology;
• Support multidisciplinary discussion of complex and controversial cases;
• Encourage the exchange of experience between national and international participants;
• Provide a platform for oral and poster presentations; and
• Strengthen future clinical and research collaborations.

IGICC 2026 at a Glance

December 17-20, 2026 | Hybrid format | Online and in-person sessions | The Marmara Taksim Hotel, Istanbul | Four-day multidisciplinary scientific program | Oral and poster presentations

IGICC 2026 Conference Program Overview

IGICC 2026 will offer a four-day scientific program combining online and in-person sessions. This format is intended to provide flexibility for participants while maintaining direct scientific discussion and interaction.

Conference Format and Participation Options

Virtual sessions (online): Thursday, December 17, 2026, 08:00-17:55 (GMT+3) participants can attend educational sessions remotely, ensuring global accessibility.

On-site Sessions (In-person): Thursday-Sunday, December 17-20, 2026, at The Marmara Taksim Hotel, İstanbul In-person participants benefit from direct interaction with faculty, networking opportunities, and multidisciplinary case discussions. But the sessions can be followed live online if registered, and later can be viewed at IGICC.TV at the conference website IGICC.org.

Detailed Program Schedule

Thursday, December 17, 2026-VIRTUAL SESSIONS (Online)

08:00-11:15: Update on Immunotherapy as a Standard of Care for Gastrointestinal Cancers

This three-part session reviews the transformative role of immunotherapy across the gastrointestinal cancer spectrum:

Part I (08:00-09:15): Foundational principles of immunotherapy in GI oncology, including basics and rationale for immune-oncology treatment, the impact of glucocorticoid use on immunotherapy efficacy, and management strategies for immune-related adverse events.

Part II (09:15-10:25): Disease-specific immunotherapy applications including esophageal cancer, gastroesophageal and gastric adenocarcinoma, hepatocellular cancer, and biliary tract cancers.

Part III (10:25-11:20): Additional GI malignancies including pancreatic cancer, colorectal cancer, and anal cancer, with comprehensive discussion of immunotherapy sequencing and combination strategies.

11:20-12:15: Anti-VEGF and Anti-EGFR Therapies for Metastatic Colon Cancers: Basic Principles

This session explores the fundamental mechanisms and clinical applications of vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors in metastatic colorectal cancer management, including patient selection criteria and combination strategies.

12:15-13:00: Antibody-drug Conjugates and CAR-T Cell Treatment in GI Oncology: Where Do We Stand

Emerging therapeutic modalities including antibody-drug conjugates (ADCs) and chimeric antigen receptor T-cell (CAR-T) therapies are discussed, with emphasis on current clinical evidence and future directions in gastrointestinal oncology.

13:00-16:15: Update on the Supportive and Palliative Care in GI Cancer Patients (Parts I & II)

This extended session addresses the critical supportive care needs of GI cancer patients:

Part I: Management of chemotherapy-induced neutropenia, chemotherapy-induced nausea and emesis (CINV), and survivorship issues including functional recovery, fertility, and sexual health.

Part II: Management of adverse events related to emerging targeted therapies (Claudin 18.2, ADCs, HER2, FGFR inhibitors), cancer pain management, vaccination strategies, micronutrient deficiencies (magnesium), cancer-associated fatigue and anemia, bone health in GI cancer patients, frailty assessment in older patients, and integrative oncology approaches.

16:15-16:55: Common Clinical Challenges in Daily GI Oncology Practice

Practical clinical scenarios including polypharmacy management, anticoagulation strategies, and optimal timing of surgery after neoadjuvant therapy.

16:55-17:55: Rare Tumors

Discussion of uncommon gastrointestinal malignancies including small bowel adenocarcinoma, appendiceal neoplasms and pseudomyxoma peritonei, hemangioendothelioma, and pancreatic pseudopapillary tumors.

Thursday, December 17, 2026 - ON-SITE SESSIONS (In-person)

13:00-13:45: Management of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

This session covers WHO classification updates, modern imaging and theranostic approaches, the evolving role of surgery, and treatment sequencing in advanced GEP-NETs with emphasis on precision oncology and molecular profiling (NETest).

13:00-13:45: Artificial Intelligence in GI Oncology

Parallel session exploring AI applications in medical imaging, digital pathology, clinical decision support systems, and their integration into gastrointestinal cancer management.

13:45-14:35: Peritoneal Surface Malignancies in GI Cancers

Organized in collaboration with the Turkish Peritoneal Surface Oncology Society (PYOD), this session addresses the biology of peritoneal metastases, patient selection for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), integration of systemic therapy with regional treatments, and pressurized intraperitoneal aerosol chemotherapy (PIPAC) techniques.

13:45-14:50: Rare Tumors (On-site)

Discussion of desmoid tumors, adrenocortical carcinoma, fibrolamellar hepatocellular carcinoma, and malignant peritoneal mesothelioma.

16:05-16:30: Coffee Break and Networking

16:30-16:45: Anal Cancers: Comprehensive Approach

HPV vaccination strategies, screening and early detection methods, neoadjuvant treatment approaches, and first and second-line systemic therapy for anal cancers.

17:00-18:10: Current Concepts in GIST Management

Precision pathology and molecular classification, the evolving role of surgery (neoadjuvant therapy, organ preservation, metastasectomy), adjuvant therapy patient selection, and treatment sequencing in advanced GIST based on molecular alterations.

Friday, December 18, 2026 - ON-SITE SESSIONS

08:00-09:00: Current Management of Esophageal Cancer

Coverage of localized esophageal squamous cell carcinoma, perioperative treatment of esophageal adenocarcinoma (chemotherapy vs. chemoradiotherapy vs. immunotherapy), advanced disease management in the immunotherapy era, and oligometastatic disease treatment strategies.

09:00-10:00: Advances in the Treatment of Gastroesophageal and Gastric Adenocarcinoma

Clinical characteristics of molecular subtypes (HER2, CLDN18.2, FGFR2b, MSI, PD-L1, EBV, emerging biomarkers), optimization of perioperative treatment, and first-line treatment selection for advanced disease in the precision oncology era.

10:00-10:40: Keynote Lecture: Standard and Emerging Systemic Treatment Options for Advanced GEJ and Gastric Adenocarcinoma

10:30-11:00: Industrial Symposium

11:00-11:20: Coffee Break and Networking

11:20-12:50: Early Detection, Screening and Surveillance in GI Cancers

Risk-adapted screening strategies, blood-based screening and emerging molecular technologies, upper GI cancer screening standards, colorectal cancer screening integration, and circulating tumor DNA (ctDNA) for minimal residual disease detection and surveillance.

Moderated Session (75 minutes): Discussion of gastroesophageal junction cancer management including epidemiology and diagnosis, multidisciplinary neoadjuvant care (FLOT, CROSS protocols), surgical strategy based on Siewert classification, lymphadenectomy controversies, minimally invasive and robotic techniques, and complication management with adjuvant therapy.

12:50-13:30: Lunch

13:30-14:00: Keynote Lecture: The New Era of RAS-Targeted Therapy

Review of RAS-targeted therapy evolution including spesific KRAS G12C, KRAS G12D/G12V, pan-RAS inhibitors, RAS(ON) inhibitors, resistance mechanisms, and future directions.

14:30-15:00: Industrial Symposium

15:00-16:15: Current Management of Pancreatic Cancer

Precision oncology in pancreatic cancer with biomarker-guided treatment, perioperative strategies for resectable and borderline resectable disease, evolving role of radiotherapy, and advanced pancreatic cancer management.

16:15-16:35: Coffee Break and Networking

16:35-17:35: Tissue-agnostic Pathways as Therapeutic Targets in GI Cancers

DNA damage response and repair (DDR) alterations including HRD and PARP inhibitors, gene fusion-driven cancers (RET, NTRK, NRG1/2, ALK, ROS1), and hypermutated tumors with emerging molecular targets.

16:35-17:35: Nutrition, Exercise & Cancer Cachexia Masterclass

Cancer cachexia recognition and assessment, nutrition and exercise oncology from prehabilitation to survivorship, multimodal management strategies, and case-based practical management.

17:35-18:20: Optimizing Preventive Care in GI Tumors

DPYD testing strategies, hepatitis prophylaxis, and prophylactic antibiotic use in GI cancer patients receiving systemic treatment.

Friday, December 18, 2026 - Parallel Session

11:30-13:00: Psycho-oncology & Palliative Care Integration

Early integration of palliative care in GI cancers, management of anxiety and depression, communication of difficult news, caregiver burden assessment, and supportive care strategies.

14:50-16:25: Therapeutic Role of Interventional Radiology in GI Cancers

Organized by the Turkish Interventional Oncology Society, this session covers ablative techniques (RFA, MWA, cryoablation), transarterial techniques (TACE, TARE, HAIC), portal vein embolization, interventional radiology in pain management, and vertebroplasty.

Saturday, December 19, 2026 - ON-SITE SESSIONS

08:00-09:25: Current Management of Localized Colon Cancer

Endoscopic management of early colorectal cancer, neoadjuvant treatment strategies for MSS vs. MSI-H disease, personalized adjuvant therapy, ctDNA-guided treatment, and lifestyle and metabolic interventions for recurrence prevention.

09:25-10:30: Precision Systemic Treatment for Metastatic Colorectal Cancer - Part I

Biomarker-driven first-line treatment selection, KRAS targeting in mCRC, BRAF V600E-mutant mCRC management, HER2-positive mCRC treatment, and treatment intensification strategies.

10:40-12:10: Precision Systemic Treatment for Metastatic Colorectal Cancer - Part II

Treatment sequencing and integration of local therapies, maintenance therapy optimization, second-line biomarker-guided approaches, later-line treatment strategies, oligometastatic disease management, radiotherapy and ablative therapy integration, and liver-directed therapies (TARE, HAIC).

12:10-13:15: Special Populations and Emerging Challenges in Colorectal Cancer

Early-onset colorectal cancer epidemiology and biology, treatment optimization in older adults, hereditary colorectal cancer and germline testing, gender differences in colorectal cancer, and colorectal cancer epidemiology and screening needs in Türkiye.

13:30-14:15: Lunch

14:15-14:55: Liver Transplantation in Colorectal Liver Metastases

Evidence from SECA and TRANSMET trials, patient selection criteria, multidisciplinary decision-making, and future perspectives.

14:55-15:55: Industrial Symposia

15:55-16:20: Coffee Break and Networking

16:20-17:35: Current Management of Localized Rectal Cancer

Total neoadjuvant therapy (TNT) strategies, TNT optimization (induction vs. consolidation chemotherapy), neoadjuvant immunotherapy for dMMR/MSI-H disease, organ preservation approaches (watch-and-wait, local excision), and personalized treatment selection.

17:35-18:20: Keynote Lecture: Building Regional Oncology Networks in Central & Eastern Europe

Regional collaboration, clinical trial access, and ambassadorship in advancing gastrointestinal oncology.

Sunday, December 20, 2026 - ON-SITE SESSIONS

08:00-09:15: Prevention, Early Detection and Diagnosis of Hepatocellular Carcinoma (Part I)

Prevention strategies (viral hepatitis, metabolic-associated fatty liver disease), risk stratification and surveillance protocols, imaging diagnosis (LI-RADS, MRI), HCC pathology and biomarkers, and staging systems (BCLC, TNM, Child-Pugh, ALBI).

09:15-11:00: Treatment and Multidisciplinary Management of Hepatocellular Carcinoma (Part II)

Hepatic resection techniques, liver transplantation indications, intermediate-stage HCC management, TACE and radioembolization (Y-90) strategies, radiation therapy approaches (SBRT, external beam radiotherapy), first-line therapy selection, and treatment after progression.

11:00-13:00: Current Multidisciplinary Management of Biliary Tract Cancers

Precision pathology in biliary cancers, surgical management of intrahepatic, perihilar, and distal cholangiocarcinoma, targeted therapies for FGFR2 fusions and IDH1 mutations, and systemic treatment strategies.

Target Audience and Participant Profile

The IGICC 2026 program is intended for professionals from the following specialties:

Specialty	Role and expectations at the conference
Medical oncologists	Gain current knowledge on systemic therapy algorithms, immunotherapy combinations, biomarker-guided treatment selection, and emerging drug approvals.
Radiation oncologists	Discuss advanced radiotherapy techniques (SBRT, proton therapy), neoadjuvant/adjuvant chemoradiation protocols, and organ-preserving approaches.
Surgical oncologists	Share experience on minimally invasive techniques, complex resection margins, metastasectomy indications, and perioperative complication management.
Gastroenterologists	Receive updates on early detection methods, advanced endoscopic resection techniques, and palliative endoscopic interventions.
Pathologists and geneticists	Participate in discussions on molecular profiling, biomarker analysis, precision pathology, and new WHO classifications.
Interventional radiologists	Learn about advanced ablative and transarterial techniques, theranostic approaches, and pain management strategies.
Nuclear medicine specialists	Explore advanced imaging techniques (PET/CT, PET/MRI) and theranostic applications (PRRT, radioembolization).

Registration, Accommodation, and Logistical Information

Registration Options and Fees

IGICC 2026 offers separate registration options for online and in-person participation. A 20% VAT will be added to all registration fees.

Registration type	Until August 7, 2026	August 8 - September 11, 2026	On or After September 11, 2026
Virtual registration (online only)	80 €	100 €	150 €
Physical registration (in-person)	50,000 TL	55,000 TL	60,000 TL

Note: No cancellations of conference registrations will be accepted after August 7, 2026. However, participant name substitutions will be permitted upon written notification.

Accommodation Information

Accommodation for in-person participants is available at The Marmara Taksim Hotel. The rates below are for a three-night package, with check-in on December 17 and check-out on December 20, on a bed-and-breakfast basis. A 10% VAT will be added to the accommodation fees.

Room type	Until August 7, 2026	August 8 - September 11, 2026	On or after September 11, 2026
Single room (SNG)	1,450 EURO	1,550 EURO	1,600 EURO
Double room (per person)	900 EURO	1,000 EURO	1,100 EURO

Transfer Services and Banking Information

Transfer Services: Round-trip group shuttle transfer between İstanbul Airport and the hotel is available at 200 EURO per person. Transfers will be organized for participants who have previously submitted their flight details to UNICON MICE.

Payment Information: Registration and accommodation requests become valid only after submitting your request to igicc@uniconmice.com, receiving budget approval, and sending the bank receipt evidencing payment to UNICON MICE. Payments should be made to the following VAKIFBANK accounts:

HESAP ADI: Unicon Mice Kongre Turizm Organizasyon Hiz. Tic.Ltd.Şti.

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TL IBAN: TR38 0006 2000 3950 0006 2947 20

EURO IBAN: TR03 0006 2000 3950 0009 0565 52

USD IBAN: TR14 0006 2000 3950 0009 0551 90

Conclusion

The 16th International Gastrointestinal Cancers Conference will provide an opportunity to review current developments across the rapidly changing field of gastrointestinal oncology. Through four days of online and in-person sessions, the meeting will combine scientific updates, practical discussion, and multidisciplinary exchange for professionals involved in the management of gastrointestinal cancers.

Building on the experience of the previous fifteen conferences, IGICC 2026 will continue to connect clinical practice with current research. Participants attending online or in person will be able to hear from experienced national and international faculty, discuss recent evidence, and meet colleagues working in the same field.

We look forward to welcoming you to IGICC 2026 and to your contribution to the scientific discussions in Istanbul and online.

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Not All GISTs are Gastric: A Single-center Cohort of Non-gastric GIST

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Abstract

Objectives: Non-gastric gastrointestinal stromal tumors (GIST) are less common than gastric primaries, but are often considered higher risk. Real-world cohorts focusing on non-gastric GIST with long-term follow-up remain limited.

Methods: We conducted a single-center retrospective cohort study of consecutive adults with histologically confirmed GISTs (esophagus, small intestine, and colon/rectum) treated between January 2015 and June 2025. National Institutes of Health (NIH) risk categories documented in pathology reports were recorded, and Armed Forces Institute of Pathology (AFIP) (Miettinen-Lasota) risk groups were calculated when tumor size, mitotic activity (per 5 mm2), and primary site were available. Overall survival (OS) was estimated using the Kaplan-Meier method.

Results: Among 114 patients with GIST, 41 (36.0%) had non-gastric primaries (small intestine 73.2%, rectum 19.5%, esophagus 7.3%). Median age was 55 years (range, 30-83); median tumor size was 6.0 cm (range, 0.4-26.0); and median mitotic count was 6/5 mm2 (range, 0-218). At diagnosis, 34 patients had localized disease and 7 had *de novo* metastatic disease; during follow-up, 10/34 (29.4%) patients developed recurrent metastasis, resulting in 17/41 (41.5%) patients with metastatic disease overall. NIH risk was available for 37/41 (90.2%) patients; of these, 22/37 (59.5%) were high risk. AFIP risk could be calculated in 26/41 (63.4%) patients; of these, 15/26 (57.7%) were classified as high risk. Metastatic sites most commonly involved the liver (47%) and the peritoneum (41%). After a median follow-up of 77 months, 4 of 41 (9.8%) patients had died; the 10-year OS was 86%.

Conclusion: In this real-world, non-gastric GIST cohort, high-risk disease was common, and metastases predominantly involved the liver and peritoneum. Favorable long-term survival appears achievable with high-quality surgery and guideline-consistent use of imatinib in routine practice.

Keywords: Gastrointestinal stromal tumors, survival analysis, non-gastric

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, with an annual incidence of approximately 1-1.5 per 100.000 in most series. The stomach accounts for 55-65% of primary sites and the small intestine for 20-30%, whereas colorectal and esophageal primaries are less frequent (1). Tumor size, mitotic activity, and anatomic location are the principal clinicopathologic determinants of malignant behavior, and non-gastric localization (e.g., small intestine, rectum) is widely recognized as an independent predictor of recurrence risk (1-3).

Risk stratification is commonly performed using the National Institutes of Health (NIH) consensus criteria, which integrates tumor size and mitotic count (4). After accounting for tumor size and mitotic activity, non-gastric GISTs, particularly jejuno-ileal and rectal primaries, have been associated with a higher risk of metastasis and cancer-related death than gastric GISTs (5,6). However, contemporary large databases and multicenter analyses suggest substantial outcome heterogeneity once molecular subtypes and access to effective targeted therapy are considered (7,8). Metastatic spread most frequently involves the liver and peritoneum, whereas lung and distant lymph node metastases are uncommon (9). Despite this, detailed cohorts focusing specifically on non-gastric primaries that jointly evaluate both localized and

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metastatic presentations and include long-term follow-up remain limited.

Complete surgical resection is the standard approach for localized disease, and adjuvant imatinib for up to 3 years is recommended for high-risk and selected intermediate-risk patients to reduce recurrence (2). In metastatic or unresectable disease, imatinib followed by sunitinib and regorafenib constitutes the standard sequential tyrosine kinase inhibitor (TKI) therapy and is associated with meaningful improvements in survival. Neoadjuvant imatinib is increasingly used in rectal and duodenal/jejunal GIST to facilitate organ- or sphincter-preserving surgery (10,11).

We report real-world data on non-gastric GIST, focusing on clinicopathologic features, risk stratification [NIH-reported and Armed Forces Institute of Pathology (AFIP)-calculated], metastatic patterns, and treatment trajectories in localized and *de novo* metastatic presentations.

Material and Methods

Study Design and Setting

This single-center, retrospective cohort study screened consecutive adult patients who were evaluated and/or treated for GIST between January 2015 and June 2025.

Study Population

The study population consisted of consecutive adult patients (≥18 years) with histologically confirmed GIST established on surgical or biopsy specimens and a primary non-gastric localization, including the esophagus, small intestine, colon, or rectum. Patients were required to have histologically confirmed non-gastric GIST and sufficient clinical information for baseline clinicopathologic characterization and survival follow-up. NIH risk was recorded when documented in pathology reports and was analyzed among evaluable patients. Patients were excluded if they were managed as having metastatic GIST with an unknown primary site (i.e., the primary tumor could not be identified despite diagnostic work-up) or were lost to follow-up, such that survival status could not be ascertained beyond the baseline assessment.

Data Sources and Data Collection

Clinical data were abstracted from institutional electronic medical records and pathology reports using a standardized case report form. Collected variables included sociodemographic characteristics (age at diagnosis and sex); clinical parameters (primary tumor site, date of diagnosis, treatment details, including surgery and systemic therapy, and follow-up dates); pathological features [tumor size in centimeters, margin status (R0/R1/R2) when applicable, and mitotic activity]; and disease status variables (stage at diagnosis, sites of metastasis, and recurrence/progression when applicable).

Pathological Assessment and risk Stratification

Mitotic activity was recorded as the number of mitoses per 5 mm^2. NIH risk categories reported in routine pathology records were captured according to the NIH consensus criteria (4). In addition, we independently calculated AFIP (Miettinen-Lasota) risk groups using tumor size, mitotic activity (per 5 mm^2), and primary tumor site (12). AFIP risk could be assigned only when the required parameters were available.

Outcomes

The primary outcome was overall survival (OS). OS was defined as the time from the date of diagnosis to death from any cause, or to last known follow-up (censored). The date of diagnosis was taken as the date of histopathologic confirmation. Remission/no evidence of disease (NED) was defined as the absence of radiologic and/or clinical evidence of active disease at the last evaluation, based on the treating physician's assessment and available imaging. Relapse was defined as radiologic recurrence after initial localized management or progression following a documented response or stable disease. Synchronous metastatic disease was defined as metastatic disease present at diagnosis. Metachronous metastatic disease was defined as metastatic recurrence developing during follow-up after an initially localized diagnosis.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median (min-max) depending on distribution; categorical variables were summarized as counts and percentages. OS was estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test where applicable. Two-sided p-values <0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics (version 29.0) and R (version 4.5).

Ethics

The study protocol was approved by the Dokuz Eylül University Institutional Ethics Committee of the study center (approval no: 2026/09-12, date: 02.03.2026). Given the retrospective nature of the study, the requirement for informed consent was waived in accordance with national regulations and institutional policy.

Results

Study Population and Primary Site Distribution

Among 114 patients with histologically confirmed GIST, 41 had non-gastric primary tumors, representing 36.0% of the overall cohort. The primary site distributions for the overall cohort and the non-gastric subgroup are shown in Figure 1.

Patient and Tumor Characteristics

The median age at diagnosis was 55 years (range 30-83), and 26 patients (63.4%) were male. The median tumor size was 6.0 cm (range, 0.4-26.0). The median mitotic count was 6 per 5 mm^2 (range 0-218), and Ki-67 ranged from 1% to 60%. NIH risk categories were available in 37/41 (90.2%) patients; among evaluable cases, 22/37 (59.5%) were classified as high risk. AFIP risk could be calculated in 26/41 patients (63.4%) using the available clinicopathologic parameters; among evaluable cases, 15/26 (57.7%) were classified as high risk. In localized disease, 11/22 (50.0%) evaluable patients were classified as high risk, whereas all evaluable *de novo* metastatic cases (4/4, 100%) were high risk. Baseline characteristics stratified by stage at diagnosis are presented in Table 1.

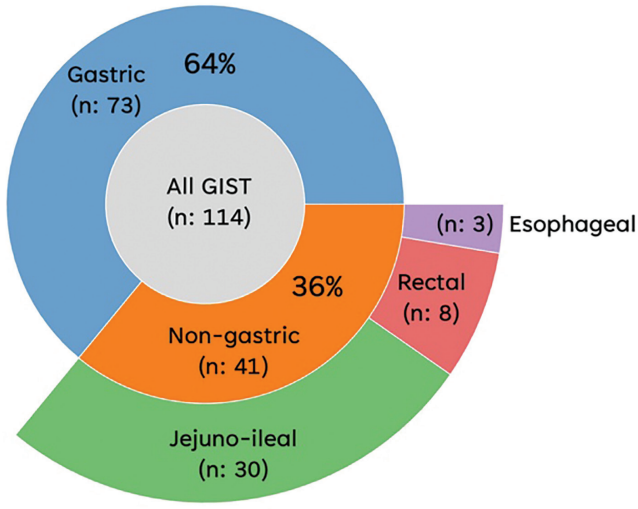


Figure 1. Distribution of primary tumor sites in the overall GIST cohort (n=114) and the non-gastric subgroup (n=41). The chart depicts the proportions of gastric GIST (n=73, 64.0%) and non-gastric GIST (n=41, 36.0%) within the total cohort. Non-gastric primary sites are further stratified into jejuno-ileal (n=30), rectal (n=8), and esophageal (n=3)

GIST: Gastrointestinal stromal tumor

Table 1. Baseline characteristics and clinical course of non-gastric GIST patients (n=41), stratified by stage at diagnosis

Characteristic	Overall (n=41)	Localized at diagnosis (n=34)	*De novo* metastatic at diagnosis (n=7)
Age, years	55 (30-83)	51.5 (30-83)	60.0 (42-68)
Sex, n (%)			
Male	26 (63.4)	20 (58.8)	6 (85.7)
Female	15 (36.6)	14 (41.2)	1 (14.3)
Primary tumor site, n (%)			
Small intestine	30 (73.2)	24 (70.6)	6 (85.7)
Rectum	8 (19.5)	7 (20.6)	1 (14.3)
Esophagus	3 (7.3)	3 (8.8)	0 (0.0)
Tumor size, cm (n=33)	6.0 (0.4-26.0)	6.0 (0.4-26.0)	7.5 (4.0-15.4)
Mitotic count, per 5 mm^2 (n=34)	6 (0-218)	5 (0-218)	18.5 (0-71)
Ki-67, % (n=33)	5 (0-60)	5 (0-60)	10 (4-45)
NIH risk group (n=37)			
Very low/no risk	4/37	4/32	-
Low	6/37	6/32	-
Intermediate	5/37	5/32	-
High	22/37	17/32	5/5 (100)
AFIP risk group (n=26)			
Very low/no risk	2/26	2/22	-
Low	5/26	5/22	-
Intermediate	4/26	4/22	-
High	15/26	11/22	4/4 (100)
Recurrent metastasis after localized diagnosis, n (% of localized)		10 (29.4)	

GIST: Gastrointestinal stromal tumor, NIH: National Institutes of Health, AFIP: Armed Forces Institute of Pathology

Disease Status and Risk Stratification

At diagnosis, 7 patients had *de novo* metastatic disease and 34 had localized disease. During follow-up, 10 of the initially localized patients developed recurrent metastatic disease, resulting in a total of 17 of 41 (41.5%) patients experiencing metastatic disease overall (*de novo* + recurrent).

Treatment Patterns

Among localized cases (n=34), 17 received adjuvant imatinib, and 1 patient received neoadjuvant imatinib followed by adjuvant imatinib.

All metastatic patients received first-line imatinib. In the second-line setting, 3 patients received high-dose imatinib and 6 received sunitinib.

Metastatic Sites and Clinical Course

Among the 17 patients who developed metastatic disease at any time, 7 had synchronous metastatic disease at diagnosis and 10 developed metachronous metastatic recurrence after initially localized disease. The most common metastatic sites were the liver (8/17, 47.1%) and the peritoneum (7/17, 41.2%). Metastatic patterns, stratified by synchronous versus metachronous presentation, are summarized in Table 2. The overall clinical trajectories are summarized in Figure 2.

Follow-up and Survival

After a median follow-up of 77 months, 4 of 41 patients (9.8%) had died. The Kaplan-Meier-estimated 10-year OS rate was 86%, and the survival curve is presented in Figure 3.

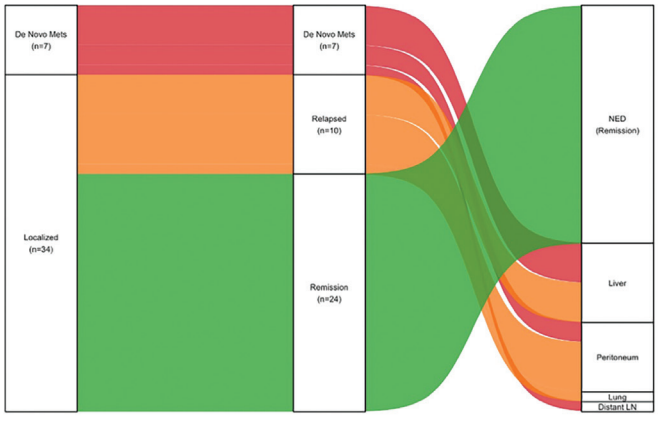


Figure 2. Clinical course and metastasis patterns in non-gastric GIST (n=41). Sankey diagram illustrating transitions from initial disease status (localized vs. *de novo* metastatic) to subsequent clinical states (remission vs. relapse) and metastatic destinations. Metastatic sites include the liver, peritoneum, lungs, and distant lymph nodes

GIST: Gastrointestinal stromal tumor, NED: No evidence of disease, LN: Lymph node

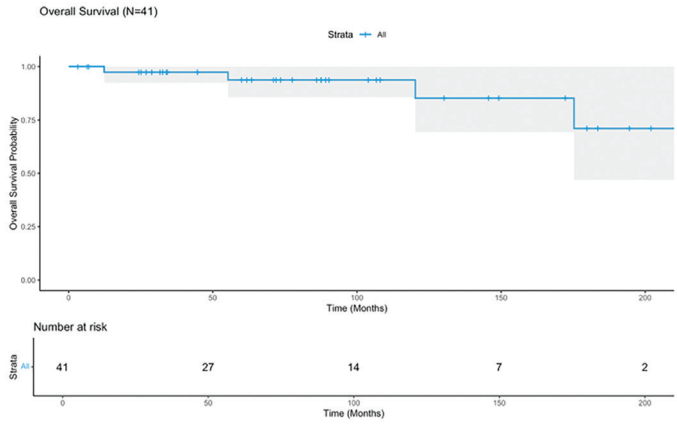


Figure 3. Overall survival in the non-gastric GIST cohort (n=41). Kaplan-Meier estimate of overall survival from date of diagnosis to death from any cause or last follow-up. Tick marks indicate censored observations. Shaded bands represent 95% confidence intervals. Numbers at risk are displayed beneath the plot

GIST: Gastrointestinal stromal tumor

Table 2. Metastatic patterns among patients with non-gastric GIST who developed metastatic disease

Metastatic characteristic	Synchronous metastatic disease (n=7)	Metachronous metastatic disease (n=10)	Overall metastatic cohort (n=17)
Liver metastasis	4 (57.1)	4 (40.0)	8 (47.1)
Peritoneal metastasis	2 (28.6)	5 (50.0)	7 (41.2)
Lung metastasis	0 (0.0)	1 (10.0)	1 (5.9)
Distant lymph node metastasis	1 (14.3)	0 (0.0)	1 (5.9)

Data are presented as n (%). Patients could have more than one metastatic site
GIST: Gastrointestinal stromal tumor

Discussion

In this real-world cohort of GIST, non-gastric tumors accounted for 36% of all GIST cases, and 17% of patients had *de novo* metastatic disease at diagnosis. Among those presenting with localized disease, NIH stratification was skewed toward high-risk categories, consistent with prior evidence that a non-gastric location confers a less favorable prognosis even after accounting for tumor size and mitotic activity.

In prior large cohorts, non-gastric primaries have comprised approximately half of all GIST cases (52-55%) (13-16) providing important national context for our observed proportion of 36%. This discrepancy may reflect differences in referral patterns, diagnostic pathways, and institutional case mix. Across published series, the most frequent non-gastric primary sites are consistently the small intestine, colon, and rectum, which align with the distribution in our cohort.

Given that risk categories were routinely documented in pathology reports using the NIH consensus criteria (4), we captured NIH risk as reported and additionally calculated AFIP (Miettinen-Lasota) groups when the required parameters were available to incorporate anatomic site into risk assessment (2,12). Because the anatomic site is a key determinant of relapse risk in GIST, incorporating site through AFIP may improve interpretability when comparing non-gastric cohorts across studies. A key observation in our cohort is the predominance of high-risk disease among evaluable cases, regardless of the risk framework applied. This risk enrichment is clinically plausible for a non-gastric-focused series, as multiple large pathological series have shown that extra-gastric primaries have a higher risk of relapse/metastasis than gastric tumors even when tumor size and mitotic activity are comparable (17,18).

Treatment patterns in this cohort largely reflect contemporary standards. Adjuvant imatinib use in localized disease tracked the high-risk burden and is supported by randomized evidence demonstrating that 3 years of adjuvant imatinib improves recurrence-free survival and OS versus 1 year in high-risk patients (19). Current guideline recommendations also endorse 3 years of adjuvant imatinib for patients with a significant risk of relapse and imatinib-sensitive genotypes (2,20). In *de novo* metastatic disease, the use of first-line imatinib for all patients is consistent with guideline-based management and reflects the central role of KIT proto-oncogene receptor tyrosine kinase/platelet-derived growth factor receptor alpha (KIT/PDGFRA) inhibition in advanced GIST.

The observed metastatic dissemination pattern, characterized by the predominance of liver and peritoneal involvement and rare lung or distant lymph node metastases, matches what has been repeatedly reported across large clinical series (21,22). This is clinically relevant because it supports surveillance focused on the liver and peritoneum in high-risk non-gastric disease while acknowledging that extra-abdominal spread, although uncommon, can occur.

Despite the unfavorable baseline risk profile expected for non-gastric primaries, the cohort's long follow-up and low number of deaths suggest that contemporary risk-adapted use of surgery and TKIs can translate into favorable long-term outcomes in real-world practice. These outcomes may, in part, reflect the routine use of a multidisciplinary tumor board at our center (medical oncology and surgery), which facilitates timely imaging review, coordinated decision-making, and consistent surgical planning. However, causal inferences cannot be made in this retrospective analysis.

Although molecular profiling was not systematically available in our cohort, the molecular landscape of GIST is highly relevant when interpreting non-gastric disease. Most GISTs are driven by activating alterations in KIT or PDGFRA, and mutational subtype has predictive as well as prognostic implications (1). KIT exon 11 mutations are the most frequent overall and are generally associated with sensitivity to standard-dose imatinib, whereas KIT exon 9 mutations are relatively enriched in small intestinal GIST and may require dose optimization in the advanced setting (2,23,24). In contrast, PDGFRA-mutant GIST is more typical of gastric primaries and shows primary resistance to imatinib, limiting its relevance to most non-gastric cohorts (25). Rectal and small intestinal GISTs may also include clinically important KIT/PDGFRA wild-type subsets, including neurofibromatosis type 1-associated, B-Raf proto-oncogene, serine/threonine kinase-mutant, or neurotrophic tyrosine receptor kinase-fusion-positive tumors, each with distinct therapeutic implications (26-28). Therefore, the lack of routine molecular annotation in the present study limits our ability to correlate anatomical site, recurrence risk, and TKI sensitivity.

Study Limitations

This observation should be interpreted cautiously; the low number of events limits robust survival modeling and subgroup inference. Moreover, the retrospective design, single-center setting, and missingness in some pathology variables, including risk classification, may introduce bias and constrain generalizability. Comprehensive molecular profiling could not be performed for every patient in routine practice, representing a real-world limitation relevant to many centers both in our country and internationally. Nonetheless, the strength of the present report lies in its granular characterization of non-gastric GIST in both

localized and metastatic presentations within routine care, thereby complementing the evidence base often dominated by mixed-site cohorts or trial-selected populations.

Conclusion

Our real-world data reinforce that non-gastric GIST constitutes a clinically heterogeneous but generally higher-risk subgroup, with metastatic spread predominantly involving the liver and peritoneum. Despite the generally more aggressive biology associated with non-gastric primaries, our findings suggest that, in routine practice, long-term outcomes can be favorable with high-quality surgery and guideline-consistent use of imatinib. Larger multicenter real-world cohorts with standardized molecular annotation are needed to refine prognostication and optimize treatment pathways.

Ethics

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Institutional Ethics Committee of the study center (approval no: 2026/09-12, date: 02.03.2026).

Informed Consent: Given the retrospective nature of the study, the requirement for informed consent was waived in accordance with national regulations and institutional policy.

Footnotes

Authorship Contributions

Surgical and Medical Practises: K.C., Ö.Y., Concept: K.C., T.Y., Design: K.C., T.Y., Data Collection or Processing: K.C., Ö.Y., Analysis or Interpretation: K.C., T.Y., Literature Search: K.C., Ö.Y., T.Y., Writing: K.C., Ö.Y., T.Y.

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

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

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Reader Questions

Based on the manuscript: "Not All GISTs are Gastric: A Single-center Cohort of Non-gastric GIST"

1. Which anatomical site was the most common non-gastric primary gastrointestinal stromal tumor (GIST) in this study?

A. Esophagus

B. Colon

C. Small intestine

D. Rectum

Correct Answer: C. Small intestine

2. Which metastatic site was observed most frequently among patients who developed metastatic disease?

A. Lung

B. Bone

C. Liver

D. Brain

Correct Answer: C. Liver

3. Which risk stratification system incorporates primary tumor location in addition to tumor size and mitotic activity?

A. AJCC TNM staging

B. NIH Consensus criteria

C. AFIP (Miettinen-Lasota) classification

D. WHO classification

Correct Answer: C. AFIP (Miettinen-Lasota) Classification

4. According to this study, what was the estimated 10-year overall survival?

A. 54%

B. 68%

C. 74%

D. 86%

Correct Answer: D. 86%

5. What was the standard first-line systemic treatment for all patients with metastatic GIST in this cohort?

A. Regorafenib

B. Sunitinib

C. Imatinib

D. Ripretinib

Correct Answer: C. Imatinib

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Epithelioid Hemangioendothelioma: Challenges in Diagnosis and Management

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Abstract

Epithelioid hemangioendothelioma (EHE) is an ultra-rare endothelial neoplasm with intermediate malignant potential and markedly variable clinical behavior. Historically regarded as within the spectrum of vascular tumors between epithelioid hemangioma and epithelioid angiosarcoma, EHE is now recognized as a distinct, molecularly defined entity, most commonly driven by *WWTR1-CAMTA1* or *YAP1-TFE3* gene fusions. The liver, lungs, and bones are the most frequently involved sites, whereas involvement of the heart, spleen, breast, and the head and neck region is uncommon. Given the frequent hepatic involvement and the clinical relevance of rare primary gastrointestinal presentations, this review synthesizes current evidence on the epidemiology, molecular pathogenesis, diagnosis, prognostic assessment, and management of EHE, with particular attention to hepatic and gastrointestinal manifestations, liver-directed strategies, and emerging therapeutic approaches.

Keywords: Epithelioid hemangioendothelioma, vascular neoplasms, gene fusion, molecular pathogenesis, immunohistochemistry

Introduction

Epithelioid hemangioendothelioma (EHE) is an ultra-rare endothelial neoplasm with intermediate malignant potential, accounting for less than 1% of all vascular tumors (1). It can arise at almost any anatomical site and shows a variable clinical course, ranging from indolent disease with prolonged periods of stability to aggressive progression. Because clinical and radiological findings are often non-specific, EHE is frequently misdiagnosed or inappropriately managed, which may adversely affect outcomes in a subset of patients. Notably, 50-76% of individuals are asymptomatic at the time of diagnosis (2). Accurate pathological confirmation is therefore essential.

Immunohistochemically, EHE typically expresses endothelial markers such as ERG and CD31, while CAMTA1 and TFE3 staining may provide additional diagnostic support. At the molecular level, the *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions are identified in approximately 90% and 10% of cases, respectively (3,4). These alterations have established EHE as a molecularly defined vascular neoplasm, and they are particularly valuable in distinguishing it from histologic mimics.

Because of its low incidence and unpredictable behavior, no universally accepted treatment strategy has been established. Complete surgical resection remains the preferred approach for localized resectable disease, whereas systemic therapy, radiotherapy, or liver-directed interventions can be used in selected clinical scenarios. Conversely, active surveillance is appropriate for some asymptomatic patients with indolent or slowly progressive disease. These management decisions are particularly relevant in hepatic EHE, one of the most common presentations, and in rare primary gastrointestinal cases that may mimic other gastrointestinal malignancies. Overall, the limited availability of prospective evidence continues to complicate therapeutic decision-making and highlights the need for individualized, multidisciplinary care (5).

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This narrative review was based on a literature search in PubMed/MEDLINE, Scopus, and Google Scholar for articles published through April 2026. Search terms included "EHE", "hepatic EHE", "gastrointestinal EHE", "*WWTR1-CAMTA1*", "*YAP1-TFE3*", "diagnosis", "systemic therapy", and "liver-directed therapy". Priority was given to consensus papers, population-based studies, real-world cohorts, and clinically relevant molecular or therapeutic reports. This review summarizes current evidence on the epidemiology, molecular pathogenesis, diagnostic evaluation, prognostic assessment, and management of EHE, with particular attention to hepatic/gastrointestinal relevance, liver-directed strategies, and emerging therapeutic approaches.

Epidemiology

A population-based analysis of U.S. National Cancer Registry data reported that malignant hemangioendothelioma is an ultra-rare vascular cancer, with an incidence of approximately 0.4 cases per million person-years (6). Although the disease is uncommon, outcomes remain poor in advanced stages, particularly among patients with metastatic disease, underscoring the need for improved therapeutic strategies (6).

EHE can occur across a wide age range, but most often presents in middle-aged adults, with a peak incidence in the fourth and fifth decades of life and a slight female predominance. Because many cases follow an indolent course and are detected incidentally, the true incidence may be underestimated. In a recent large single-center series of 115 patients, EHE showed a broad age distribution, slight female predominance, and diverse anatomical involvement, most commonly affecting the liver, lungs, and soft tissues (7). These findings indicate that EHE does not follow a uniform epidemiological pattern and may present across different patient populations and anatomical sites (7).

Clinical Presentation

EHE can arise in almost any anatomical location, but the liver, lungs, soft tissues, and bones are the most commonly affected sites. Many patients are incidentally diagnosed while asymptomatic. When symptoms occur, they are usually site-dependent and may include pain, a palpable mass, weight loss, fever, or fatigue. Pulmonary involvement can present with dyspnea, cough, hemoptysis, or chest pain, whereas osseous disease may cause pathological fractures or neurological deficits, particularly in cases with spinal involvement. Serosal disease, including pleural or peritoneal involvement, is frequently associated with effusions and a more aggressive clinical course (8,9). Hepatic EHE may be asymptomatic or present with non-specific abdominal pain, hepatomegaly, or abnormal liver function tests, whereas primary gastrointestinal involvement is rare and may mimic other gastrointestinal tumors, manifesting as bleeding, obstruction, abdominal pain, or mass-forming lesions.

A large multi-institutional retrospective study conducted by the Canadian Sarcoma Research and Clinical Collaboration (CanSaRCC) and multi-pronged Canadian research (PRO_CARE) EHE reported a median age at diagnosis of 51 years (range, 9-86), with an approximately equal sex distribution. Metastatic disease was present at diagnosis in approximately 45-47% of patients, and a substantial proportion of cases were identified incidentally. The most common primary sites were the liver (28%), the extremities (16%), and the lungs (14%) (9). Population-based analyses further indicate that EHE predominantly affects middle-aged and older adults, while pediatric cases remain rare. Tumors most commonly originate in soft tissue and skin, followed by abdominal and thoracic sites, and may present as multifocal or metastatic disease at diagnosis (10).

The clinical course ranges from prolonged stable disease to rapidly progressive and fatal outcomes. Systemic symptoms, pulmonary involvement, and serosal disease have been associated with worse prognosis (5,8). Therefore, clinical presentation should be interpreted together with disease distribution, symptom burden, and tumor kinetics when planning multidisciplinary management.

Histopathological and Molecular Features

EHE has distinctive histopathological features that support its recognition among vascular neoplasms. Histologically, it is composed of cords and nests of epithelioid endothelial cells embedded in a characteristic myxohyaline stroma. Tumor cells typically show abundant eosinophilic cytoplasm, round to mildly atypical nuclei, and hallmark intracytoplasmic vacuoles, some of which contain erythrocytes and reflect primitive vascular lumen formation. Mitotic activity is usually low; however, increased mitotic figures, nuclear pleomorphism, and necrosis may indicate more aggressive behavior. Immunohistochemically, EHE consistently expresses endothelial markers such as CD31, ERG, and FLI1, whereas CD34 expression is more variable (4,7).

At the molecular level, EHE is characterized by recurrent and highly specific gene fusions. The most common alteration is the *WWTR1-CAMTA1* fusion resulting from a t(1;3)(p36;q25) translocation, which is present in the majority of cases and represents a disease-defining event (4). A smaller subset harbors the *YAP1-TFE3* fusion, which is associated with distinct morphological features and strong nuclear TFE3 expression (3). These fusion proteins are thought to promote tumorigenesis through dysregulation of the Hippo signaling pathway and aberrant transcriptional activation (1).

The identification of these alterations has established EHE as a molecularly defined vascular neoplasm and has provided substantial diagnostic value, particularly in challenging cases. Although reverse transcription polymerase chain reaction and fluorescence *in situ* hybridization can detect these rearrangements, their limited availability in routine practice has supported the use of CAMTA1 immunohistochemistry as a practical adjunct in the diagnostic workup (1,4). The key histopathological, immunohistochemical, and molecular features used in the diagnostic evaluation of EHE are summarized in Table 1.

Imaging Features and Differential Diagnosis

Accurate staging of EHE requires comprehensive whole-body imaging because of its propensity for multifocal and systemic involvement. Cross-sectional imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), forms the basis for baseline evaluation and is often complemented by functional imaging techniques (11). Contrast-enhanced CT of the chest, abdomen, and pelvis remains the preferred initial modality because of its wide availability and utility in assessing pulmonary and abdominal disease. In suspected hepatic involvement, multiphasic liver imaging improves lesion characterization, while MRI is particularly useful for evaluating hepatic, soft tissue, and bone lesions because of its superior soft tissue contrast resolution (12). Whole-body MRI or [18F]-fluorodeoxyglucose (FDG)-PET/CT, when available, can be valuable for detecting skeletal and soft tissue involvement. Bone scintigraphy may serve as an alternative in resource-limited settings. For follow-up, imaging modality used at baseline should preferably be retained to allow reliable longitudinal comparisons (11). Functional imaging may also provide prognostic information. Although FDG uptake in EHE is typically mild to moderate, higher standardized uptake values have been associated with more aggressive disease behavior, increased risk of progression, and inferior survival outcomes (13).

Radiological findings in EHE are broad and often non-specific, with substantial overlap with other vascular, hepatic, and metastatic malignancies. Characteristic features of hepatic EHE include multifocal, coalescent nodules with a peripheral, subcapsular distribution, often accompanied by capsular retraction and a "target-like" enhancement pattern on contrast-enhanced imaging. The "lollipop sign", defined as tapering and abrupt termination of a hepatic or portal vein at the margin of a lesion, may further support the diagnosis (14). However, neither target-like enhancement nor the lollipop sign is pathognomonic. These findings should be interpreted in the clinical context, particularly because hepatic EHE can radiologically overlap with intrahepatic cholangiocarcinoma, metastatic carcinoma, and epithelioid angiosarcoma.

Thoracic involvement may manifest with diverse patterns: multiple pulmonary nodules, reticulonodular opacities, diffuse pleural thickening, or mass-like lesions with pleural invasion, which can mimic malignant pleural mesothelioma (11). In some cases, pulmonary nodules may demonstrate a surrounding ground-glass halo resembling that seen in metastatic angiosarcoma. Osseous involvement most commonly affects the axial skeleton and long bones.

Table 1. Diagnostic, immunohistochemical, and molecular features of EHE

Feature	Typical findings	Diagnostic relevance
Histological architecture	Cords and nests of epithelioid endothelial cells embedded in a characteristic myxohyaline stroma.	Supports recognition of EHE among vascular neoplasms (4,7).
Cytological features	Abundant eosinophilic cytoplasm, round to mildly atypical nuclei, and hallmark intracytoplasmic vacuoles, some containing erythrocytes.	Intracytoplasmic vacuoles reflect primitive vascular lumen formation and support endothelial differentiation (4,7).
Adverse histological features	Increased mitotic activity, nuclear pleomorphism, and necrosis.	May indicate more aggressive tumor behavior and should be integrated with clinical and radiological context (4,7).
Endothelial markers	Consistent expression of CD31, ERG, and FLI1; CD34 expression is more variable.	Confirms endothelial differentiation and helps distinguish EHE from non-vascular mimics (4,7).
Fusion-associated IHC	CAMTA1 nuclear expression in *WWTR1-CAMTA1*-associated EHE; strong nuclear TFE3 expression in the *YAP1*-TFE3 subset.	Provides a practical diagnostic adjunct, particularly when molecular testing is unavailable or limited (3,4).
Molecular alterations	*WWTR1-CAMTA1* fusion in most cases; *YAP1-TFE3* fusion in a smaller molecular subset.	Disease-defining alterations that establish EHE as a molecularly defined vascular neoplasm and support distinction from histologic mimics (3,4).
Molecular testing	RT-PCR or FISH can detect fusion rearrangements.	Useful for confirming the diagnosis in challenging cases and for resolving equivocal IHC findings (1,4).
Differential diagnosis	Epithelioid angiosarcoma, metastatic carcinoma, intrahepatic cholangiocarcinoma, malignant mesothelioma in pleural presentations, and other vascular tumors.	Requires integration of morphology, endothelial immunophenotype, molecular confirmation, and site-specific imaging findings (11,14).

EHE: Epithelioid hemangioendothelioma, IHC: Immunohistochemistry, RT-PCR: Reverse transcription polymerase chain reaction, FISH: Fluorescence *in situ* hybridization

It typically appears as poorly defined lytic lesions, occasionally exhibiting sclerotic margins or mixed expansile features. On MRI, these lesions are generally hypointense on T1-weighted images and hyperintense on T2-weighted or short tau inversion recovery sequences, reflecting their vascular and cellular composition (15).

Despite these characteristic patterns, imaging alone is insufficient to establish a definitive diagnosis. The differential diagnosis includes primary or metastatic carcinomas, epithelioid angiosarcoma, intrahepatic cholangiocarcinoma, and malignant mesothelioma in pleural presentations. This limitation is particularly important because some imaging features of EHE, although suggestive, are not specific enough to reliably distinguish it from more aggressive vascular tumors or hepatobiliary malignancies. Therefore, histopathological confirmation remains essential. Immunohistochemical and molecular analyses, including the identification of *WWTR1-CAMTA1* or *YAP1-TFE3* gene fusions, are critical for confirming the diagnosis and distinguishing EHE from its histologic mimics.

Prognosis

EHE is an intermediate-grade vascular neoplasm with an unpredictable clinical course, ranging from prolonged disease stability to rapid progression and fatal outcomes (16). Prognosis is influenced by disease distribution, tumor burden, clinical presentation, histopathological features, and disease kinetics; however, no universally accepted prognostic model has been established.

Early insights from an international patient-based registry showed that male sex and age greater than 55 years were associated with poorer survival, whereas anatomical extent alone did not consistently predict outcome (16). This study proposed a clinical classification distinguishing pattern A, defined by localized and well-demarcated lesions, from pattern B, characterized by diffuse and infiltrative disease. This distinction emphasized the prognostic relevance of tumor growth pattern rather than disease extent alone. Pleural effusion, ascites, hemoptysis, and extensive bone involvement were also identified as adverse clinical features (Table 2) (16).

Subsequent studies have supported the prognostic importance of both disease burden and clinical context. Patients with localized disease, particularly those amenable to complete surgical resection, may achieve prolonged survival. In contrast, multifocal or metastatic disease, especially when involving the liver and lungs, is generally associated with poorer outcomes (5). Systemic symptoms, weight loss, and serosal involvement have also been linked to a worse prognosis. Conversely, some asymptomatic or incidentally diagnosed patients may follow an indolent course, even in the presence of radiologically evident metastases (5).

Histopathological parameters further contribute to risk assessment. Increased mitotic activity, nuclear atypia, and necrosis have been associated with more aggressive tumor behavior, although these features alone are insufficient for reliable prognostic stratification (8). Similarly, recurrent molecular alterations, including *WWTR1-CAMTA1* and *YAP1-TFE3* fusions, define EHE biologically and diagnostically but do not fully explain its clinical variability.

More recent data have refined the understanding of prognostic determinants. In a nationwide cohort of 57 patients confirmed by molecular and immunohistochemical analyses, Tomassen et al. (17) demonstrated that tumor

Table 2. Pattern A/B classification and associated clinical implications in EHE

Feature	Pattern A	Pattern B	Clinical interpretation
Growth pattern	**Localized, well-demarcated lesions**	**Diffuse, infiltrative disease**	**Growth pattern may provide prognostic information beyond anatomical extent alone.**
Prognostic concern	Generally lower clinical concern when stable and asymptomatic	Higher clinical concern, particularly when progressive or symptomatic	Pattern B may warrant closer follow-up and earlier multidisciplinary discussion.
Role of anatomical extent	Extent of disease alone may not reliably predict prognosis	Extent of disease alone may not reliably predict prognosis	Pattern should be interpreted together with disease distribution, symptoms, and tumor kinetics.
Associated adverse features	Usually assessed in the absence or presence of additional adverse features	May coexist with adverse features such as pleural effusion, ascites, hemoptysis, or extensive bone involvement	These adverse features have been associated with poorer outcomes.
Practical use	May support observation or local treatment in selected stable patients	May support earlier active intervention when accompanied by symptoms, progression, or high-risk features	The classification should complement clinical, radiological, histopathological, and molecular assessment.

The pattern A/B classification should be used as a complementary clinical framework rather than as a standalone prognostic model
EHE: Epithelioid hemangioendothelioma

size and mitotic activity were key determinants of clinical outcome, particularly among patients with unifocal disease. These findings suggest that intrinsic tumor biology may be more relevant than anatomical extent in selected clinical contexts. Large real-world cohorts, including the CanSaRCC/PRO_CARE EHE study, further indicate that baseline disease distribution alone cannot fully predict disease behavior, supporting the need to incorporate dynamic clinical factors into prognostic assessment (9).

Multivariate analyses have identified older age, pleural effusion, ascites, primary pulmonary involvement, and metastatic disease as independent predictors of poorer survival, with pleural effusion representing the strongest adverse factor (9). These observations underscore the prognostic importance of serosal involvement and highlight the need to interpret the anatomical extent of disease together with symptoms and tumor kinetics.

In clinical practice, the pattern A/B classification should be viewed as a complementary framework rather than a standalone prognostic model. Molecular classification is essential for diagnosis, but current evidence does not support using *WWTR1-CAMTA1* or *YAP1-TFE3* status alone to guide prognosis or treatment selection. Therefore, prognostic assessment should integrate clinical presentation, growth pattern, tumor burden, histopathological risk features, molecular confirmation, and longitudinal behavior. This multidimensional approach can help identify patients suitable for active surveillance and those who require earlier local or systemic intervention.

Treatment

The management of EHE is challenging because treatment decisions must account not only for anatomical extent but also for symptoms, tumor burden, resectability, and disease kinetics (5). No universally accepted standard of care has been established, and management is therefore best individualized within a multidisciplinary framework.

Current treatment approaches combine general soft tissue sarcoma principles, as outlined in the European Society for Medical Oncology (ESMO)-European Reference Network for Rare Adult Solid Cancers (EURACAN)-European Reference Network on Genetic Tumour Risk Syndromes (GENTURIS) Clinical Practice Guidelines, with EHE-specific expert consensus recommendations, particularly those proposed by Stacchiotti et al. (8). While the ESMO guidelines provide a broad framework for sarcoma care, disease-specific consensus emphasizes a more phenotype-driven strategy, distinguishing patients with indolent disease suitable for observation from those with symptomatic, progressive, or high-risk disease requiring active intervention (8).

Localized and Unifocal Disease

For patients with localized and resectable disease, complete surgical excision with negative margins (R0 resection) remains the cornerstone of treatment and offers the greatest likelihood of long-term disease control or cure, with reported cure rates of up to 70-80% in selected cases (8). Radiotherapy can be used in selected clinical settings, including close or positive surgical margins, unresectable lesions, and symptomatic disease requiring local control. Although EHE is considered moderately radiosensitive, radiotherapy is generally used adjunctively rather than as a curative treatment (8). For patients who are not candidates for surgery, local ablative approaches such as radiofrequency ablation, microwave ablation, or stereotactic body radiotherapy (SBRT) are potential options, although supporting evidence remains limited.

Multifocal and Metastatic Disease

A substantial proportion of patients present with multifocal or metastatic disease at diagnosis, which limits curative treatment options. In this setting, management should balance the risk of overtreatment against the potential for clinically meaningful progression. Importantly, metastatic disease alone does not mandate immediate systemic therapy. In asymptomatic patients with indolent or slowly progressive disease, active surveillance (watch-and-wait) is widely accepted as the preferred initial approach (9). In contrast, symptomatic disease, rapid radiological progression, serosal involvement such as pleural effusion or ascites, and substantial tumor burden favor earlier intervention, as these features are associated with poorer outcomes (9).

Systemic Therapy

Systemic therapy is generally reserved for patients with symptomatic, progressive, unresectable, or high-burden disease. Conventional cytotoxic chemotherapy has shown limited and inconsistent efficacy, and is not routinely preferred (8). Targeted and anti-angiogenic therapies, therefore, represent the main systemic options in current practice. vascular endothelial growth factor pathway inhibitors, including tyrosine kinase inhibitors such as pazopanib and sorafenib, are commonly used and more often lead to disease stabilization than to objective tumor regression. MammalianTarget of rapamycin (mTOR) inhibitors, particularly sirolimus, have also shown activity in selected patients (9). Other agents, including interferon-alpha and thalidomide, have demonstrated modest activity, although high-level evidence remains lacking. Overall,

systemic therapy in EHE should be viewed primarily as disease-modifying rather than curative. The available clinical outcomes of commonly used systemic agents are summarized in Table 3.

Liver-directed and Locoregional Therapies

Hepatic EHE warrants particular attention because the liver is one of the most frequently involved sites, and the disease may be multifocal at presentation. Surgical resection remains the preferred option for technically resectable, liver-limited disease when complete removal is feasible (8). In carefully selected patients with unresectable liver-limited disease, liver transplantation can be considered, particularly when tumor biology appears indolent and extrahepatic disease is absent or limited (8). For patients who are not candidates for resection or transplantation, locoregional strategies such as ablative techniques, SBRT, or transarterial therapies can be considered for local control, symptom palliation, or reduction of hepatic tumor burden. However, the evidence supporting these approaches remains limited and largely retrospective. Therefore, treatment selection should be individualized by a multidisciplinary liver tumor board or sarcoma board.

Table 3. Summary of systemic therapies evaluated in advanced epithelioid hemangioendothelioma (EHE)

Study	Treatment/ agent	Study design/ population	EHE patients, n	ORR/response	PFS/TTP	OS	Main clinical interpretation
Frezza et al. (18)	Paclitaxel	Same retrospective series; advanced EHE	11	PR 1/11 (9%); SD 6/11 (55%); PD 4/11 (36%)	Median PFS 2.9 months	Median OS 18.6 months	Limited response activity; may provide disease control in selected patients.
Frezza et al. (18)	Pazopanib	Same retrospective series; advanced EHE	12	PR 0; SD 3/12 (25%); PD 9/12 (75%)	Median PFS 2.9 months	Median OS 8.5 months	Activity was variable; in this series, pazopanib mainly produced disease stabilization in a minority of patients.
Frezza et al. (18)	Interferon-alpha-2b	Same retrospective series; advanced EHE	15	PR 1/15 (7%); SD 11/15 (73%); PD 3/15 (20%)	Median PFS 8.9 months	Median OS 64.3 months	Occasional durable disease control was observed, but evidence remains retrospective.
Stacchiotti et al. (24)	Sirolimus	Retrospective case-series; advanced/ progressive EHE treated within the Italian Rare Cancer Network	18 total; 17 EHE and 1 retiform HE	In EHE: PR 1; SD 12; PD 3; retiform HE also achieved PR	Median PFS 12 months	Median OS 16 months	Sirolimus demonstrated disease control in selected patients; activity appeared lower in patients with pleural/peritoneal effusions.
Chevreau et al. (25)	Sorafenib	Multicenter single-arm phase 2 trial; progressive EHE	15 enrolled	Two partial responses; 9-month progression-free rate 30.7%	2-, 4-, and 6-month progression-free rates: 84.6%, 46.4%, and 38.4%	NR	Sorafenib showed modest activity, with limited response rates and occasional clinical benefit.
Agulnik et al. (26)	Bevacizumab	Open-label multicenter phase 2 trial in angiosarcoma and EHE	7 EHE among 30 evaluable patients	In EHE: PR 2/7 (29%); SD 4/7 (57%); PD 1/7 (14%)	Median PFS 39.1 weeks in EHE	Median OS 142.6 weeks in EHE	Bevacizumab showed activity in a small EHE subset, but interpretation is limited by the mixed-histology design and small sample size.
Schuetze et al. (21)	Trametinib	Single-arm phase 2 trial; locally advanced or metastatic EHE	44 enrolled; 42 started treatment	ORR 3.7%	Median PFS 10.4 months	2-year OS 33.3%	Trametinib did not meet the ORR goal but was associated with reduction in EHE-related pain, suggesting palliative benefit in selected patients.
IAG933/IK-930 studies (22,23)	TEAD inhibitors	Early-phase trials in advanced solid tumors, including EHE or Hippo pathway alterations	EHE-specific efficacy not yet mature	NR	NR	NR	Biologically rational investigational strategy; clinical efficacy in EHE remains to be defined.

HE: Hemangioendothelioma, ORR: Objective response rate, PR: Partial response, SD: Stable disease, PD: Progressive disease, PFS: Progression-free survival, TTP: Time to progression, OS: Overall survival, NR: Not reported

Real-world Evidence and Treatment Heterogeneity

Real-world cohorts demonstrate substantial variability in the management of EHE. Surgical resection is most commonly used for localized disease, whereas systemic therapy is applied selectively in advanced cases and is generally associated with modest benefit (9). Observational strategies are also frequently used in asymptomatic or slowly progressive disease, including in some patients with metastatic lesions, indicating that radiological extent alone is insufficient to define treatment urgency.

In a large retrospective series from the World Sarcoma Network, Frezza et al. (18) reported that conventional chemotherapy had limited activity in advanced EHE, with low objective response rates and disease stabilization as the most common outcomes. Anti-angiogenic agents and targeted therapies, including pazopanib, sorafenib, and mTOR inhibitors, produced variable but occasionally durable disease control, supporting their use in selected patients with progressive or symptomatic disease. However, no systemic agent has demonstrated consistent superiority across all subgroups (18).

The nationwide NETSARC cohort of 267 patients, followed over 12 years, further illustrated the longitudinal nature of EHE management. Many patients were initially managed without systemic therapy, and treatment strategies were frequently modified over time according to evolving tumor behavior (19). Sequential use of systemic, surgical, and locoregional approaches was common in advanced disease, supporting a dynamic treatment model based on repeated clinical reassessments rather than a fixed upfront algorithm (19).

Guideline-practice Gap

Although ESMO-EURACAN-GENTURIS guidelines provide a broad framework for soft tissue sarcoma management, EHE-specific decision-making remains constrained by the absence of prospective evidence and validated treatment algorithms (8). This gap is most evident in three practical areas: the duration and intensity of active surveillance, the threshold for initiating systemic therapy, and the selection or sequencing of local, liver-directed, and systemic treatments in advanced disease.

In clinical practice, patients with asymptomatic metastatic EHE may remain under observation for prolonged periods, yet guidelines do not define optimal imaging intervals, surveillance duration, or radiological progression thresholds that should trigger treatment. Similarly, systemic therapy is often initiated for symptomatic, progressive, or high-burden disease, but no standardized criteria exist to determine the optimal timing for initiating treatment (9,19). Local and locoregional therapies are also used variably, particularly in hepatic-predominant disease, where resection, transplantation, ablative approaches, or transarterial strategies may be discussed according to disease distribution, tumor biology, and institutional expertise.

Another important gap concerns treatment goals. In real-world practice, systemic therapy is frequently used to delay progression or maintain disease control rather than to achieve objective tumor regression, reflecting the cytostatic activity of many available agents (18,19). These discrepancies highlight the need for a more disease-specific framework that integrates guideline principles with real-world evidence. Until stronger prospective data are available, management should preferably be conducted at specialized sarcoma centers or by multidisciplinary boards, with treatment decisions reassessed over time according to symptoms, tumor kinetics, anatomical involvement, and patient-specific factors.

Future Therapeutic Approaches in EHE

Future therapeutic development in EHE is increasingly focused on disease-defining molecular drivers, particularly the *WWTR1-CAMTA1* and *YAP1-TFE3* fusions and their interaction with TEAD transcription factors. Because TAZ and YAP are key mediators of Hippo pathway signaling and cancer progression, small molecules designed to disrupt YAP/TAZ-TEAD-dependent transcription represent a biologically rational strategy. Verteporfin, a porphyrin derivative, has been proposed as a potential inhibitor of the YAP/TAZ-TEAD interaction, thereby impairing downstream transcriptional programs. Similarly, stabilization of angiomotin family proteins through tankyrase inhibition has been suggested as an indirect approach to reduce nuclear localization and transcriptional activity of these fusion-driven proteins. However, these strategies remain largely preclinical and should be interpreted as hypothesis-generating rather than clinically established therapeutic options.

The potential sensitivity of fusion-driven signaling to upstream regulatory pathways has also generated interest in alternative approaches. Inhibition of mevalonate synthesis (for example, through statins) or modulation of extracellular matrix stiffness (with agents such as losartan) could theoretically suppress YAP/TAZ activity if these pathways are confirmed to be relevant in human EHE. Similarly, modulation of phosphoinositide 3-kinase/protein kinase B (AKT serine/threonine kinase) signaling may influence the glycogen synthase kinase-3-mediated phosphorylation of the phosphodegron motif, thereby promoting proteasomal degradation of fusion-

related proteins. These approaches aim to target oncogenic signaling at the protein or microenvironmental levels, but their clinical relevance remains unproven and requires validation in EHE-specific experimental models.

Biological therapies and immunotherapy are also areas of ongoing interest. The observation that TAZ and YAP can promote programmed death-ligand 1 expression and immune evasion in several cancers provides a rationale for exploring immune checkpoint inhibition in EHE. In addition, monoclonal antibodies such as TRC105, which targets endoglin, an endothelial cell surface marker highly expressed in EHE cells, have been evaluated as targeted biological therapies. In the longer term, small interfering RNAs (siRNA) directed against fusion transcripts or clustered regularly interspaced short palindromic repeats (CRISPR)-based gene-editing strategies may offer a theoretical means of suppressing or eliminating the oncogenic driver. At present, however, siRNA, CRISPR, and microenvironment-targeted strategies remain investigational and preclinical. Their successful development will depend on robust EHE-specific cell lines, genetically engineered mouse models, and improved characterization of downstream target genes (20).

Recent and Ongoing Clinical Trials

Recent and ongoing studies in EHE increasingly focus on pathway-directed therapies, reflecting the biological importance of WWTR1-CAMTA1 and *YAP1-TFE3* fusions in Hippo/YAP-TAZ signaling (20). However, most available evidence comes from early-phase or retrospective studies or from small patient subsets, and no systemic therapy has yet been established as a uniformly effective standard.

Trametinib, a MEK inhibitor, was evaluated in a single-arm phase 2 trial in patients with locally advanced or metastatic EHE. Although the objective response rate was low, treatment was associated with a reduction in EHE-related pain and a median progression-free survival of approximately 10 months, suggesting a potential palliative role rather than strong cytoreductive activity (21).

TEAD inhibitors are an important investigational strategy because TEAD transcription factors function as downstream effectors of YAP/TAZ-driven oncogenic signaling. Early-phase trials are evaluating oral TEAD inhibitors in advanced solid tumors, including EHE. IAG933 is being studied in a phase 1, first-in-human trial, while IK-930 has also been evaluated in a phase 1 study in advanced solid tumors with Hippo pathway alterations (22,23). These studies are biologically relevant, but their clinical efficacy in EHE remains to be defined.

Among established systemic options, sirolimus and pazopanib remain the most commonly used agents in clinical practice, although supporting evidence is largely retrospective. Sirolimus has demonstrated disease control in selected patients with slowly progressive EHE (24). Pazopanib and other anti-angiogenic agents have shown variable activity, generally leading to disease stabilization rather than objective tumor shrinkage (18). Earlier prospective studies also evaluated sorafenib and bevacizumab in vascular sarcomas, including EHE, and reported limited response rates with occasional clinical benefit (25,26).

Taken together, current and emerging data suggest that systemic therapy in EHE is most relevant for patients with progressive, symptomatic, or unresectable disease. Future trials should aim to define predictive biomarkers, clarify optimal treatment sequencing, and determine whether pathway-directed agents can improve outcomes beyond disease stabilization.

Conclusion

EHE is an ultra-rare endothelial neoplasm with distinctive molecular alterations and a broad clinical spectrum. Accurate diagnosis requires integration of histopathological findings, endothelial immunophenotype, molecular confirmation, and site-specific radiological assessment. Although *WWTR1-CAMTA1* and *YAP1-TFE3* fusions have substantially improved diagnostic precision, prognostic assessment remains challenging and should incorporate clinical presentation, disease distribution, tumor kinetics, histopathological risk features, and serosal involvement.

Management should be individualized within a multidisciplinary framework. Complete surgical resection remains the preferred approach for localized resectable disease, whereas active surveillance is appropriate for selected asymptomatic patients with indolent or slowly progressive disease. In hepatic EHE, liver-directed strategies, including resection, transplantation, or locoregional approaches, may be relevant in carefully selected cases. For progressive, symptomatic, unresectable, or high-burden disease, systemic therapies such as anti-angiogenic agents, mTOR inhibitors, and investigational pathway-directed agents can provide disease control, although objective responses remain uncommon and no standard systemic regimen has been established.

Future progress will depend on prospective registries, international collaboration, improved risk stratification, and biomarker-driven clinical trials. In particular, better integration of molecular classification with clinical behavior may help refine treatment selection and clarify the role of emerging targeted approaches in this rare and biologically distinctive malignancy.

Footnotes

Authorship Contributions

Concept: G.Ö., S.T., Design: G.Ö., S.T., Data Collection or Processing: A.F.A., Analysis or Interpretation: G.Ö., S.T., Literature Search: G.Ö., A.F.A., S.T., Writing: G.Ö., A.F.A., S.T.

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Reader Questions

Based on the manuscript: "Epithelioid Hemangioendothelioma: Challenges in Diagnosis and Management"

1. Which gene fusion is identified in the majority of epithelioid hemangioendothelioma (EHE) cases?

A. EWSR1-FLI1

B. WWTR1-CAMTA1

C. SS18-SSX

D. NAB2-STAT6

Correct Answer: B. WWTR1-CAMTA1

2. Which immunohistochemical marker is most consistently expressed in EHE?

A. CK20

B. CD31

C. S100

D. Desmin

Correct Answer: B. CD31

3. According to current expert recommendations, which strategy is appropriate for selected asymptomatic patients with slowly progressive metastatic EHE?

A. Immediate chemotherapy

B. Immediate radiotherapy

C. Active surveillance ("watch-and-wait")

D. Liver transplantation

Correct Answer: C. Active surveillance ("watch-and-wait")

4. Which organ is one of the most common primary sites or sites of involvement in EHE?

A. Pancreas

B. Liver

C. Thyroid

D. Prostate

Correct Answer: B. Liver

5. Which class of targeted agents is most commonly used for progressive or symptomatic advanced EHE?

A. EGFR inhibitors

B. VEGF pathway inhibitors (e.g., pazopanib, sorafenib)

C. PARP inhibitors

D. BRAF inhibitors

Correct Answer: B. VEGF pathway inhibitors (e.g., pazopanib, sorafenib)

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Changes in Serum Tryptophan Levels and Chemotherapy-related Cognitive Impairment in Older Patients with Colon Cancer: A Prospective Pilot Study

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Abstract

Objectives: Chemotherapy-related cognitive impairment (CRCI) significantly affects quality of life among older adults with cancer. Despite its prevalence, reliable biomarkers for CRCI risk assessment and monitoring are lacking. This study proposes and evaluates the hypothesis that alterations in serum tryptophan levels, influenced by systemic inflammation, may be associated with CRCI in older patients with colon cancer undergoing chemotherapy.

Methods: A prospective pilot study was conducted involving older patients with stage II-III colon adenocarcinoma who received adjuvant mFOLFOX6 chemotherapy. Serum tryptophan and C-reactive protein (CRP) levels were measured at baseline, after six cycles of chemotherapy, and at the three-month post-chemotherapy follow-up. Cognitive function was assessed using the mini-mental state examination (MMSE), and patients were classified according to the presence of CRCI.

Results: Baseline tryptophan levels were significantly lower in cancer patients than in healthy controls ($p<0.001$). However, no significant baseline differences were found between CRCI and non-CRCI subgroups. Notably, follow-up tryptophan levels were significantly lower in the CRCI group, with a marked decrease in Δ tryptophan ($p<0.001$). Receiver operating characteristic analysis demonstrated promising discriminatory performance for follow-up and Δ tryptophan levels (area under the curve=0.874 and 0.904, respectively). These findings are exploratory and require external validation. Follow-up tryptophan levels were inversely correlated with CRP and positively correlated with MMSE scores.

Conclusion: Declining serum tryptophan levels during chemotherapy, especially in the context of systemic inflammation, may reflect increased vulnerability to CRCI. These findings support the potential utility of tryptophan as a non-invasive candidate biomarker associated with CRCI. Further large-scale studies are warranted to validate its clinical application and explore preventive interventions.

Keywords: Chemotherapy-related cognitive impairment, tryptophan metabolism, inflammation, older cancer patients, biomarker, cognitive dysfunction, neuroinflammation, colon cancer

Introduction

Chemotherapy-related cognitive impairment (CRCI), colloquially known as “chemo brain”, encompasses a range of cognitive deficits including impairments in memory, attention, processing speed, and executive function (1). It is especially prevalent among older cancer patients and survivors (2). Despite the growing recognition of CRCI in clinical oncology, its mechanisms remain insufficiently understood, and a robust, accessible biomarker is lacking (1-3).

Current hypotheses implicate neuroinflammation, oxidative stress, cytokine dysregulation, and neurotransmitter imbalances (4-6). One emerging candidate that intersects these pathways is tryptophan; an essential amino acid involved in both serotonin and kynurenine metabolic pathways (7-9). The balance between these pathways is influenced by

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inflammatory stimuli, notably cytokines such as interferon-γ and tumor necrosis factor-α, which drive tryptophan metabolism away from serotonin production toward the kynurenine pathway, yielding neurotoxic metabolites (10). This biochemical shift is believed to affect neuroplasticity, mood, and cognition (10,11).

Furthermore, aging and systemic inflammation, both prevalent in oncology populations, may exacerbate this shift (2,12-14). Thus, evaluating serum tryptophan as a peripheral indicator of cognitive vulnerability during chemotherapy is a timely and potentially transformative approach.

This study aimed to investigate whether changes in serum tryptophan levels were associated with CRCI in older patients with colon cancer undergoing adjuvant chemotherapy.

Material and Methods

Patients and Methods Study Design

This prospective observational pilot study with a matched control group was conducted after approval by the Muğla Sıtkı Koçman University Institutional Ethics Committee (approval no: 14/X, date: 24.08.2022) and in accordance with the Declaration of Helsinki. Data were collected in the Department of Medical Oncology at a tertiary oncology center between September 6, 2022, and August 2, 2024. Prior to enrollment, all participants were provided with comprehensive verbal and written information about the study, and written informed consent was obtained from each individual who voluntarily agreed to participate.

Study Population

The study group consisted of male and female patients aged 65 years and older who had undergone surgical resection for stage II or stage III colon adenocarcinoma and who were deemed eligible to receive adjuvant chemotherapy with the modified FOLFOX6 (mFOLFOX6) regimen administered biweekly. Only patients with preserved cognitive function, as demonstrated by a mini-mental state examination (MMSE) score of 25 or higher, were included in the study.

Patients were excluded if they had prior systemic anticancer therapy for other malignancies; previous neurosurgery or cranial radiotherapy; psychiatric disorders requiring ongoing treatment or follow-up (including psychosis, major depression, or personality disorders); neurodegenerative or cerebrovascular diseases; diabetes mellitus; myocardial infarction within the past six months; significant renal dysfunction or the need for dialysis; decompensated chronic liver disease; neurological involvement in rheumatologic or connective tissue disorders; clinical hypothyroidism; megaloblastic anemia due to vitamin B12 or folic acid deficiency; chronic alcoholism; substance dependence; alcohol withdrawal syndrome; significant electrolyte disturbances (such as hyponatremia, hypokalemia, hypercalcemia, or hyperkalemia); insufficient proficiency in reading and understanding Turkish; significant hearing impairment; or a history of symptomatic, polymerase chain reaction (PCR)-confirmed coronavirus disease-2019 (COVID-19) requiring hospitalization or home-based treatment.

Patients in the study group were scheduled to receive a total of 12 cycles of adjuvant chemotherapy every two weeks, according to the mFOLFOX6 regimen, which consisted of 5-fluorouracil (400 mg/m^2 bolus plus 2400 mg/m^2 46-hour continuous infusion), leucovorin (400 mg/m^2 infusion), and oxaliplatin (85 mg/m^2 infusion). After completion of six cycles of chemotherapy, computed tomography scans were performed to assess recurrence or metastasis.

Patients without evidence of disease progression continued treatment up to the planned 12 cycles. Following treatment completion, patients were monitored every three months for two to three years for disease surveillance. During the study, patients who developed significant clinical complications precluding further participation were excluded, and additional eligible patients were enrolled to achieve the planned sample size. Ultimately, the study group included 30 patients who completed the planned treatment protocol and were confirmed to be free of recurrence or metastasis at the three-month follow-up after completion of chemotherapy.

Control Group

The control group was recruited after completion of patient enrollment and comprised healthy volunteers who were matched to the study group in terms of age and sex. Volunteers were primarily selected from healthy caregivers of patients under follow-up in the oncology department. Exclusion criteria for the control group were inadequate proficiency in reading and understanding Turkish and a history of symptomatic, PCR-confirmed COVID-19 requiring hospitalization or home-based care.

Data Collection Tools

Data collection was conducted using a specifically developed case follow-up form alongside validated instruments, including the MMSE and the functional assessment of cancer therapy-general (FACT-G) questionnaire.

The case follow-up form captured demographic and personal information, such as age, sex, occupation, education level, marital status, socioeconomic status, smoking status, height,

weight, body mass index (BMI), and body surface area (BSA). For the study group, additional clinical information was recorded, including details of the colon cancer diagnosis, the chemotherapy regimen, and chemotherapy-related adverse events, which were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Laboratory evaluations were conducted at three time points for the study group: prior to the initiation of chemotherapy, after the completion of the sixth cycle, and three months after the completion of all twelve chemotherapy cycles. Parameters measured included complete blood count, C-reactive protein (CRP) levels (reference range: 0-2 mg/L), and serum tryptophan concentrations. For the control group, these measurements were collected only at baseline.

MMSE

Cognitive function was assessed using the MMSE, which has been validated for use in the Turkish population. An MMSE score of 25 or higher was considered indicative of normal cognitive function, while scores between 19 and 24 suggested mild impairment, scores between 10 and 19 indicated moderate impairment, and scores below 10 reflected severe cognitive decline (15). For the purposes of this study, CRCI was defined as a decline of total MMSE score to below the normal-range threshold (<25) at the post-chemotherapy assessment in a patient who had scored within the normal range (≥25) at baseline. Although the MMSE is a widely used and validated screening instrument, it is primarily designed to detect global cognitive impairment and may have limited sensitivity for the subtle deficits in executive function, attention, processing speed, and working memory that characterize CRCI. This limitation is further addressed in the discussion section.

FACT-G

Quality of life was evaluated using the FACT-G, a 27-item questionnaire validated in Turkish, encompassing four domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. Higher scores on the FACT-G correspond to better perceived quality of life (16).

Data Collection Process for the Study Group

Eligible patients were enrolled following screening based on inclusion and exclusion criteria. Participants who provided informed consent and scored within the normal range on the MMSE were scheduled to begin the study assessments on the first day of chemotherapy.

On the initial day of chemotherapy, fasting blood samples were collected to measure serum tryptophan and CRP levels and promptly transported to the biochemistry laboratory for processing and storage. The FACT-G was administered prior to chemotherapy to assess baseline quality of life.

Assessments performed after six cycles of chemotherapy included clinical evaluations, imaging studies to detect metastasis or recurrence, repeat administration of the MMSE and FACT-G, and collection of additional blood samples for serum tryptophan and CRP measurements. Patients without evidence of disease progression proceeded to complete the full chemotherapy regimen.

At the three-month post-chemotherapy follow-up, patients underwent imaging, MMSE and FACT-G assessments, and further blood sampling for tryptophan and CRP levels.

Data Collection Process for the Control Group

Recruitment of the control group commenced after enrollment of the patient group had been finalized. A matching process ensured demographic and clinical comparability between groups, that smoking status was not included in the matching criteria because the controls were healthy.

Healthy volunteers underwent cognitive screening using the MMSE, and only individuals with scores of 25 or higher were included. Fasting blood samples were collected once to measure serum tryptophan and CRP levels and stored until batch analysis.

Measurement of Blood Samples

All collected blood samples were analyzed in batches at the medical biochemistry research laboratory after completion of data collection. Fasting venous blood samples were drawn into red-top biochemistry tubes, centrifuged at 1500×g for 15 minutes to separate serum, and transferred into Eppendorf tubes for storage at -80 °C until analysis. Serum tryptophan levels were measured using a commercially available enzyme-linked immunosorbent assay kit, with all analyses performed in duplicate according to the manufacturer's instructions. The procedure involved incubation of samples in antibody-coated wells, followed by sequential steps including incubation with biotinylated antibody, addition of enzyme conjugate, chromogenic substrate reaction, and measurement of optical density at 450 nm using a microplate reader. Sample concentrations were determined from a standard calibration curve.

Serum CRP levels were measured by a high-sensitivity nephelometric method on an automated analyzer, and results were expressed in mg/L.

Statistical Analysis

Sample size calculations were performed using G*Power software, based on an assumed effect size of 0.5, a significance level of 0.05, and a power of 0.80, yielding a target sample size of 30 patients and 30 controls.

To reduce potential confounding between the study and control groups, frequency matching was applied during recruitment of the control group to ensure comparable group-level distributions of the matching variables across the two groups. Patients and controls were matched on age and sex; smoking status was not included among the matching variables, given the health status of the control group. Standardized mean differences were calculated for each matching variable, with values <0.1 considered acceptable. Statistical comparisons employed independent samples t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, and chi-square or Fisher's exact tests for categorical variables. Longitudinal changes in variables such as serum tryptophan levels, MMSE scores, and FACT-G scores were analyzed using paired-sample t-tests or appropriate non-parametric alternatives, with Bonferroni correction applied to account for multiple repeated-measures comparisons across the three assessment time points.

Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of serum tryptophan levels to discriminate CRCI. The resulting cut-off values are reported as exploratory findings derived from this pilot cohort and require external validation. All statistical analyses were conducted using SPSS v24, with significance set at $p<0.05$.

Results

Comparison Between Study and Control Groups

A total of 30 patients with stage II-III colon adenocarcinoma and 30 age- and sex-matched healthy controls were included (Supplementary Figure 1). Demographic characteristics such as educational level, marital status, economic status, occupation, body weight, height, BMI, and BSA did not differ significantly between groups (all $p>0.05$).

However: a higher proportion of active smokers was observed in the patient group than in controls (50% vs. 20%, $p=0.014$; Supplementary Table 1).

Baseline cognitive function, assessed by the MMSE total score, was slightly lower in patients than in controls (28.59±1.02 vs. 28.69±1.01), although this difference did not reach statistical significance ($p=0.492$). However, baseline serum tryptophan levels were significantly reduced in the patient group (49.37±28.62 ng/mL) compared with controls (97.97±47.75 ng/mL; $p<0.001$) (Supplementary Table 2).

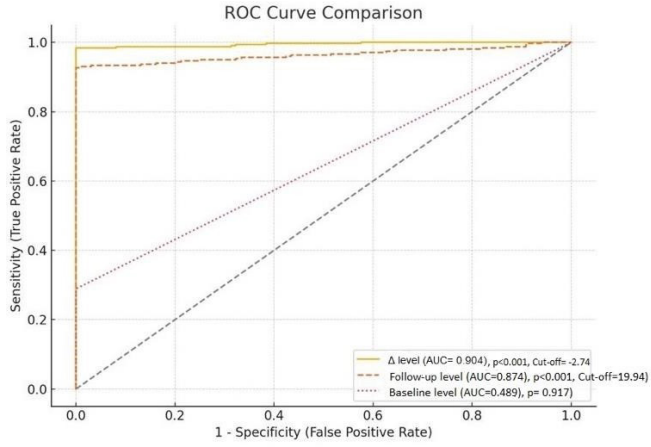


Figure 1. ROC curve for CRCI of tryptophan levels during the study period

ROC: Receiver operating characteristic, CRCI: Chemotherapy-related cognitive impairment, AUC: Area under the curve

Cognitive Changes during Chemotherapy

Among patients, MMSE subscale scores showed significant declines over the course of chemotherapy. From baseline to the final assessment, three months after completing 12 chemotherapy cycles, significant reductions were observed in orientation ($p<0.001$), registration memory ($p<0.001$), recall ($p<0.001$), language ($p<0.001$), and attention-calculation ($p<0.001$) subdomains. The MMSE total score also significantly decreased from baseline (26.91±1.02) to follow-up (23.67±2.78; $p<0.001$) (Supplementary Table 2).

Quality of Life Changes

FACT-G total scores declined significantly during chemotherapy, dropping from 88.8±2.45 at baseline to 73.2±1.76 after six cycles ($p<0.001$). However, by the three-month post-chemotherapy follow-up, FACT-G total scores recovered to baseline levels (88.7±2.41, $p=0.618$ compared to baseline). A similar pattern of temporary decline and subsequent recovery was observed across all FACT-G subdomains, including physical, social/family, emotional, and functional well-being (all $p<0.001$ for decline during treatment and all $p>0.05$ for recovery at follow-up) (Supplementary Table 3).

Tryptophan Levels and Cognitive Impairment

Within the study group, 16 patients developed cognitive impairment based on MMSE scores, whereas 14 maintained normal cognitive function. Patients with cognitive impairment exhibited significantly lower hemoglobin levels at both baseline and follow-up ($p<0.001$) and higher CRP levels at follow-up ($p=0.033$) (Table 1).

Table 1. Comparison of demographic, clinical, laboratory, and chemotherapy side effects between patients with and without cognitive impairment in the study group

Characteristics	Patients with cognitive impairment	Patients without cognitive impairment	p-value[α]
n	**(n=16)**	**(n=14)**	
Qualitative variables			
Gender; n (%) Male Female	11 (69) 5 (31)	8 (57) 6 (43)	0.345
Educational status; n (%) Primary or middle school High school Undergraduate or above	7 (44) 6 (37) 3 (19)	4 (29) 3 (21) 7 (50)	0.137
Economic level; n (%) Lower income Middle income Higher income	4 (25) 7 (44) 5 (31)	4 (29) 6 (42) 4 (29)	0.616
Occupation; n (%) Housewife Retired worker Retired officer	3 (19) 6 (37) 7 (44)	4 (29) 6 (42) 4 (29)	0.314
Marital status; n (%) Married Single	11 (69) 5 (31)	9 (64) 5 (36)	0.469
Smoking habits; n (%) Never smoking Quit smoking (>10 years) Active smoker	2 (12) 4 (25) 10 (63)	4 (28) 5 (36) 5 (36)	**0.037**
Disease stage; n (%) Stage 2 Stage 3	5 (31) 11 (69)	4 (29) 10 (71)	0.433
Chemotherapy-related oral mucositis; n (%) Absent Grade 1 Grade 2	4 (25) 8 (50) 4 (25)	5 (36) 7 (50) 2 (14)	0.494
Chemotherapy-related fatigue; n (%) Absent Grade 1 Grade 2	2 (13) 9 (56) 5 (31)	1 (7) 8 (57) 5 (36)	0.174
Chemotherapy-related diarrhea; n (%) Absent Grade 1 Grade 2	8 (50) 8 (50) 0	7 (50) 6 (43) 1 (7)	0.396
Chemotherapy-related chronic neuropathy; n (%) Absent Grade 1 Grade 2	7 (44) 9 (56) 0	4 (29) 8 (57) 2 (14)	0.096
Chemotherapy-induced anemia; n (%) Absent Grade 1 Grade 2	0 13 (81) 3 (19)	6 (43) 7 (50) 1 (7)	**<0.001**
Chemotherapy-induced neutropenia; n (%) Absent Grade 1 Grade 2	2 (13) 12 (74) 2 (13)	2 (14) 11 (79) 1 (7)	0.348
Chemotherapy-induced thrombocytopenia; n (%) Absent Grade 1 Grade 2	6 (38) 9 (56) 1 (6)	5 (36) 8 (57) 1 (7)	0.597

Table 1. Continued

Characteristics	Patients with cognitive impairment	Patients without cognitive impairment	p-value[α]
n	**(n=16)**	**(n=14)**	
Quantitative variables			
Weight (kg); median (min-max)	72 (52-82)	77 (56-88)	0.324
Height (cm); median (min-max)	167 (148-178)	168 (148-178)	0.245
BMI (kg/m²); median (min-max)	**20.1 (17.2-24.4)**	21.9 (18.4-24.2)	0.316
BSA (m²); median (min-max)	1.74 (1.54-2.01)	1.76 (1.54-2.21)	0.654
Leukocyte count (µL); median (min-max) Baseline Follow-up*	 9137 (6974-11241) 6937 (5374-8766)	 8648 (5474-8335) 6344 (4274-7037)	**<0.001** 0.412
Neutrophil count (µL); median (min-max) Baseline Follow-up*	 7964 (4837-9474) 4169 (3433-6274)	 6219 (3798-5964) 4296 (3374-5974)	**<0.001** 0.374
Lymphocyte count (µL); median (min-max) Baseline Follow-up*	 2954 (975-4125) 1978 (742-3148)	 2845 (918-3945) 2055 (908-3214)	0.245 0.494
Platelet count (x10³/µL); median (min-max) Baseline Follow-up*	 496 (337-674) 248 (137-407)	 414 (294-537) 234 (137-407)	**<0.001** 0.415
Hemoglobin level (g/dL); median (min-max) Baseline Follow-up*	 9.2 (8.9-10.6) 8.9 (8.6-9.4)	 10.4 (8.4-12.7) 9.6 (9.1-12.1)	**<0.001** **<0.001**
Serum CRP level (mg/L); median (min-max) Baseline Follow-up*	 3.7 (2.8-5.7) 2.9 (1.9-3.6)	 3.3 (1.9-4.2) 2.6 (1.4-3.4)	<0.001 0.033
Serum tryptophan level (ng/mL); mean ± SD Baseline Follow-up* Difference	 41.19±33.92 36.64±24.51 -4.55±9.81	 43.37±32.21 42.19±32.62 -1.22±0.41	0.496 <0.001 <0.001
Δ Baseline-follow-up FACT-G scores (mean ± SD)			
Physical score			
Baseline Follow-up* Difference	13.19±1.17 21.75±3.26	13.78±1.12 15.21±1.76	0.165 <0.001
Social-family support			
Baseline Follow-up* Difference	24.37±1.02 23.68±0.87	24.93±1.07 23.57±1.16	0.160 0.757
Emotional			
Baseline Follow-up* Difference	19.31±1.53 14.44±1.51	19.14±1.46 14.21±1.31	0.760 0.670
Functional			
Baseline Follow-up* Difference	19.44±1.86 24.56±0.89	20.21±1.76 24.07±1.38	0.252 0.252
Total score			
Baseline Follow-up* Difference	76.32±1.58 84.44±3.83	78.07±2.37 77.07±2.76	0.22 <0.001

*: Follow-up: at control after 3 months completed 12-cycles treatment, α: Statistical significance is indicated by p-values in bold. Chi-square test and Fisher's exact test were used for comparing categorical variables, and Mann-Whitney U test were used for continuous variables with non-normal distributions. The Student's t-test was used for normally distributed variables. Mean and standard deviations were presented for normally distributed variables, and medians and ranges were given for non-normally distributed variables, Δ: Difference between, BMI: Body mass index, BSA: Body surface area, FACT-G: Functional assessment of cancer therapy-general, CRP: C-reactive protein, SD: Standard deviation

Serum tryptophan levels declined significantly in patients with cognitive impairment, decreasing from 41.19±33.92 ng/mL at baseline to 36.64±24.51 ng/mL at follow-up (p<0.001).

In contrast, patients without cognitive impairment showed no significant change in serum tryptophan levels over time (43.37±32.21 ng/mL at baseline vs. 42.19±32.62 ng/mL at follow-up; p=0.496) (Table 1).

Factors Associated with Cognitive Impairment

In univariate logistic regression analysis, baseline BMI below 22 kg/m^2, elevated CRP levels at follow-up, and follow-up serum tryptophan levels below 19.94 ng/mL were each significantly associated with cognitive impairment (all p<0.001). In multivariate analysis, low baseline BMI [odds ratio (OR): 2.96; 95% confidence interval (CI): 1.656-3.274], elevated follow-up CRP levels (OR: 1.89; 95% CI: 1.578-3.148), and low follow-up serum tryptophan levels (OR: 1.83; 95% CI: 1.637-3.513) remained associated with cognitive impairment (p<0.001) (Table 2). Given the limited sample size and number of cognitive impairment events relative to the number of covariates, these multivariate findings should be interpreted with caution, as the model may be susceptible to overfitting; this limitation is further discussed below.

ROC analysis was performed to evaluate the diagnostic performance of serum tryptophan levels in predicting CRCI. The analysis identified a follow-up serum tryptophan cut-off value of 19.94 ng/mL, which yielded an area under the curve (AUC) of 0.874 (p<0.001). These exploratory findings require external validation. At the follow-up cut-off of 19.94 ng/mL, the sensitivity and specificity were 86% and 74%, respectively. These cut-off values should be regarded as exploratory findings derived from a pilot cohort and therefore require external validation in larger samples before clinical application. Additionally, changes in serum tryptophan levels (Δ level) demonstrated even higher discriminative performance, with an AUC of 0.904 (p<0.001) and an exploratory cut-off of -2.74 ng/mL. In contrast, baseline serum tryptophan levels showed no significant discriminatory ability (AUC=0.489, p=0.917). These results are illustrated in Figure 1.

Correlation Analyses

Correlation analysis revealed a significant inverse relationship between the reduction in serum tryptophan levels and the decline in MMSE total scores over the course of treatment (r=-0.654, p<0.001), suggesting that greater decreases in serum tryptophan levels were associated with more pronounced cognitive decline. No significant correlations were observed between changes in tryptophan levels and other clinical or laboratory parameters, including leukocyte, neutrophil, lymphocyte, or platelet counts (all p>0.05). Although both MMSE and FACT-G scores declined during chemotherapy, their recovery patterns diverged: FACT-G scores returned to baseline by the three-month follow-up, whereas MMSE scores remained reduced. This dissociation suggests that the transient decline in FACT-G largely reflects treatment-related physical and emotional burden, while the persistent MMSE decline is more specifically related to cognitive impairment; no significant correlation was observed between changes in MMSE and FACT-G scores (Supplementary Table 3).

Discussion

This study suggests that reductions in serum tryptophan levels during chemotherapy may represent a candidate biomarker for CRCI in older patients with colon cancer. While baseline tryptophan levels were significantly lower in patients than in healthy controls, this baseline difference cannot be causally attributed to chemotherapy exposure, nor was it the primary focus of this study; rather, our findings indicate that the trajectory of tryptophan levels over the course of treatment, rather than baseline levels alone, better reflects CRCI risk. Notably, patients who developed cognitive impairment experienced greater declines in serum tryptophan and had elevated CRP levels, supporting a link between systemic inflammation and cognitive vulnerability.

Table 2. Factors associated with the presence of cognitive impairment

Variables	Univariate analysis				Multivariate analysis			
	p-value	OR	95% CI lower	95% CI upper	p-value$^{\alpha}$	OR	95% CI lower	95% CI upper
Baseline low BMI* (<cut-off)	<0.001	2.74	1.768	3.749	<0.001	2.96	1.656	3.274
Follow-up** CRP (>UNL vs. other)	<0.001	1.94	1.592	3.137	<0.001	1.89	1.578	3.148
Follow-up** tryptophan (<cut-off)*	<0.001	1.91	1.673	2.969	<0.001	1.83	1.637	3.513

*: Cut-off for BMI=22 kg/m^2 (AUC=0.764, p<0.001). Cut-off for follow-up tryptophan=19.94 ng/mL (AUC=0.874, p<0.001). **: Follow-up: at control after 3 months completed 12-cycles treatment, $^{\alpha}$: These models included multiple ordinal and nominal variables. Initially, the probability of predicting cognitive impairment was 59.6%, but with the developed model, this rate increased to 82.9% (p<0.001, the Nagelkerke R^2=0.719), OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, UNL: Upper normal limit, AUC: Area under the curve, BMI: Body mass index

These results align with existing evidence that systemic inflammation can alter tryptophan metabolism through activation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase, shifting tryptophan away from serotonin synthesis toward the kynurenine pathway. This metabolic diversion increases neurotoxic metabolites, such as quinolinic acid, while reducing neuroprotective compounds, contributing to neuroinflammation and cognitive dysfunction (13,17). Similar metabolic disturbances have been implicated in neurocognitive disorders such as depression and Alzheimer's disease, which share clinical features with CRCI (18,19).

Our data extend this mechanistic hypothesis by demonstrating an inverse correlation between declining tryptophan levels and worsening MMSE scores. This supports the notion that tryptophan may be a candidate biomarker for CRCI. Previous studies have shown that cancer patients, particularly those undergoing chemotherapy, frequently display sustained disruptions in tryptophan metabolism, especially in the presence of elevated inflammatory markers like CRP (20-24). In this context, CRP is best regarded as an inflammatory biomarker associated with both CRCI and alterations in tryptophan metabolism, rather than as evidence of a direct causal pathway linking inflammation, tryptophan, and cognitive decline.

Study Limitations

Nevertheless, limitations exist. Not all studies have reported significant associations between baseline tryptophan levels and CRCI (25-27), highlighting the limited utility of single-point measurements. As a pilot investigation, this study was limited by a modest sample size that constrained statistical power, generalizability, and causal inference; the observational design further precludes conclusions about causality. Cognitive assessments relied on the MMSE, which, despite its widespread clinical use and validation in the Turkish population, may not detect subtle deficits, particularly in executive functions, attention, processing speed, and working memory. Future studies should consider more sensitive instruments such as the Montreal Cognitive Assessment and comprehensive neuropsychological batteries. Moreover, serum tryptophan levels may not perfectly reflect central nervous system availability due to blood-brain barrier dynamics and competition with other amino acids. Additionally, factors such as dietary intake, nutritional status, circadian variation, and medications, as well as hepatic and renal function, were not systematically controlled (2,10,22). The control group was not followed longitudinally and was assessed only at a single baseline time point, precluding comparison of within-group changes over time. In addition, smoking status differed significantly between the study and control groups and was not included among the matching variables. Because smoking can influence systemic inflammation and tryptophan metabolism, this imbalance may have confounded comparisons between groups. Finally, although Bonferroni correction was applied to the repeated-measures analyses, multiple comparisons across variables and time points may still increase the risk of type I error, and our regression findings in particular should be interpreted with caution given the limited number of events relative to the number of covariates examined.

If validated in larger cohorts, monitoring serum tryptophan levels may facilitate early identification of patients at high risk of CRCI, enabling timely interventions. Strategies such as anti-inflammatory therapies, lifestyle modifications, or direct modulation of the kynurenine pathway (e.g., IDO or kynurenine 3-monooxygenase inhibitors) are potential avenues for future research (28-31). Given mechanistic overlaps with neurodegenerative conditions, oncology may benefit from biomarker models established in neuropsychiatric disorders (32-35).

Importantly, our findings revealed that, even before chemotherapy, cancer patients had significantly lower serum tryptophan levels than controls. This suggests that cancer-related metabolic stress, inflammation, or malnutrition may predispose patients to lower tryptophan reserves, potentially increasing vulnerability to cognitive decline once chemotherapy is initiated (36). Early nutritional or metabolic interventions might help mitigate this risk (37).

Future studies should include larger, multicenter cohorts and more sensitive neurocognitive assessments. Investigating sex differences, microbiome interactions, and neuroimaging correlates may further clarify the role of tryptophan in CRCI and improve biomarker specificity (2,10,22). Additionally, exploring cerebrospinal fluid metabolites could help link peripheral changes to central neurobiology.

Conclusion

Serum tryptophan emerges as a biologically plausible candidate biomarker associated with CRCI and requires validation in larger prospective studies. Our findings suggest that decreases in tryptophan levels during chemotherapy are associated with cognitive decline and systemic inflammation. Integrating tryptophan monitoring into oncology care could enable earlier detection of cognitive risks and inform preventive strategies.

Beyond its diagnostic potential, maintaining tryptophan levels during chemotherapy might help protect against neuroinflammation and cognitive impairment. Preclinical data and our pilot results support investigating tryptophan supplementation or modulation of its metabolic pathways as a topic for future research. Future randomized clinical trials are needed to determine whether preserving physiological tryptophan levels can reduce CRCI incidence and severity and potentially improve quality of life and survivorship outcomes.

In summary, serum tryptophan offers promise as a candidate biomarker associated with CRCI, meriting further rigorous clinical evaluation.

Ethics

Ethics Committee Approval: This study with a matched control group was conducted after approval by the Muğla Sıtkı Koçman University Institutional Ethics Committee (approval no: 14/X, date: 24.08.2022) and in accordance with the Declaration of Helsinki.

Informed Consent: Prospective observational pilot study.

Footnotes

Authorship Contributions

Surgical and Medical Practises: Ö.T., Concept: Ö.T., Ü.Ö.T., Design: Ö.T., Data Collection or Processing: Ö.T., Analysis or Interpretation: Ö.T., Ü.Ö.T., Literature Search: Ö.T., Ü.Ö.T., Writing: Ö.T., Ü.Ö.T.

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

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Supplementary Figure 1: https://d2v96fxpocvxx.cloudfront.net/e3bb5c55-588b-4d9b-90a5-1da04e1a25d8/content-images/47c7ec28-4640-404b-998b-a07010f2c879.pdf

Supplementary Tables 1-3: https://d2v96fxpocvxx.cloudfront.net/e3bb5c55-588b-4d9b-90a5-1da04e1a25d8/content-images/2cced50b-4ca6-4bcd-9cde-2895776ac590.pdf

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Reader Questions

Based on the manuscript: "Changes in Serum Tryptophan Levels and Chemotherapy-related Cognitive Impairment in Older Patients with Colon Cancer: A Prospective Pilot Study"

1. Which chemotherapy regimen was administered to all patients in this study?

A. CAPOX

B. FOLFIRI

C. mFOLFOX6

D. FOLFIRINOX

Correct Answer: C. mFOLFOX6

2. Which biomarker showed the strongest association with chemotherapy-related cognitive impairment during follow-up?

A. Baseline CRP

B. Baseline tryptophan

C. Follow-up serum tryptophan level

D. White blood cell count

Correct Answer: C. Follow-up serum tryptophan level

3. Which cognitive assessment tool was used to evaluate chemotherapy-related cognitive impairment in this study?

A. Montreal cognitive assessment (MoCA)

B. FACT-Cog

C. Mini-mental state examination (MMSE)

D. Trail making test

Correct Answer: C. Mini-Mental State Examination (MMSE)

4. According to the proposed biological mechanism, inflammatory activation shifts tryptophan metabolism toward which pathway?

A. Dopamine pathway

B. Glutamate pathway

C. Kynurenine pathway

D. GABA pathway

Correct Answer: C. Kynurenine pathway

5. What was the primary conclusion of this pilot study?

A. Baseline serum tryptophan predicts CRCI with high accuracy.

B. Declining serum tryptophan during chemotherapy may serve as a candidate biomarker associated with CRCI.

C. CRP alone is sufficient to diagnose CRCI.

D. Tryptophan supplementation prevents CRCI.

Correct Answer: Correct Answer: B. Declining serum tryptophan during chemotherapy may serve as a candidate biomarker associated with CRCI.

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Evaluation of the Relationship Between Prognostic Nutritional Index and Survival in Operated Stage II and III Colorectal Cancer Patients Receiving Adjuvant Chemotherapy

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Abstract

Objectives: The prognostic nutritional index (PNI) is an important parameter that reflects nutritional and immunological status and serves as a prognostic marker for many types of gastrointestinal cancer. In this study, we aimed to evaluate the relationship between PNI and survival outcomes among patients with colorectal cancer (CRC) who underwent surgery and received adjuvant chemotherapy.

Methods: Demographic, clinical, and pathological data; treatments received; inflammatory and nutritional prognostic markers, including PNI, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR); and survival outcomes of 314 patients diagnosed with stage II and III CRC were examined retrospectively. Pre- and post-chemotherapy values of PNI, NLR, and PLR, and their associations with 5-year overall survival (OS) and disease-free survival (DFS), were analyzed. Patients were divided into two groups based on median values of each biomarker.

Results: The median pre-chemotherapy PNI, NLR, and PLR were 38.01, 3.85, and 197.15, respectively; the post-chemotherapy medians were 41.31, 2.47, and 143.80. In stage II CRC, pre-chemotherapy PNI ≤38.01 significantly decreased OS (p=0.022) and DFS (p=0.033) compared to PNI >38.01. In stage III CRC, PNI did not significantly affect OS (p=0.746) or DFS (p=0.438). In multivariate Cox regression analysis for 5-year DFS, pre-chemotherapy NLR, pre-chemotherapy PNI, post-chemotherapy PNI, and body mass index were independent prognostic factors (p=0.010, p=0.018, p=0.008, and p=0.005, respectively).

Conclusion: Pre-chemotherapy PNI was significantly associated with OS in univariate analysis of stage II CRC; however, it was not retained as an independent predictor in the multivariate OS model. Both pre- and post-chemotherapy PNI values were independent predictors of 5-year DFS. These findings suggest that PNI may serve as a valuable and easily accessible prognostic marker, particularly for disease recurrence in early-stage CRC.

Keywords: Colorectal cancer, prognostic nutritional index, overall survival, disease-free survival, prognostic factors, platelet-to-lymphocyte ratio

Introduction

Cancer is a major global public health problem. In the United States, lung, prostate, and colorectal cancer (CRC) in men and lung, breast, and CRC in women are the leading causes of cancer-related death (1). CRC is the second leading cause of death when both sexes are combined (2). It is estimated that there were a total of 151.030 new CRC cases in the United States in 2022 (1).

Survival outcomes of CRC patients are mainly predicted by tumor-related factors such as tumor, node, metastasis (TNM) staging, tumor grade, and tumor location. However, studies have demonstrated that prognosis is also related to host factors (3,4).

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The preoperative nutritional status of the host and the systemic inflammatory response play a crucial role in the progression and metastasis of many cancer types. Accordingly, the importance of prognostic markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the prognostic nutritional index (PNI) has been investigated in various malignancies (5-8). PNI is a prognostic marker that reflects both immunological and nutritional status and is calculated from the serum albumin level and peripheral lymphocyte count.

In the literature, a study of stage II and III patients undergoing curative resection investigated whether nutritional scores [PNI and controlling nutritional status (CONUT) score] and inflammatory scores were independent prognostic factors for overall survival (OS) and found that nutritional scores were superior (9). Another study examining preoperative and postoperative PNI values in operated stage II and III patients found that the combination of preoperative and postoperative PNI was an independent predictor of poor OS (10).

In this study, we aimed to determine the prognostic significance of PNI and its relationship with clinicopathological and other prognostic factors in surgically treated CRC patients receiving adjuvant chemotherapy.

Material and Methods

A total of 314 patients diagnosed with early-stage CRC who were admitted to the Medical Oncology Department of Necmettin Erbakan University between January 2010 and December 2021 were included in this study. The cohort included patients with both colon and rectal cancer. Patients with rectal cancer who received radiotherapy (n=62, 19.7%) were treated in accordance with contemporary National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology Guideline recommendations. Pelvic radiotherapy is indicated for stage II (T3-T4, N0) and stage III (any T, N1-2) rectal cancer because of the elevated risk of local recurrence after surgery alone. Radiation was administered either as neoadjuvant chemoradiotherapy prior to total mesorectal excision or as adjuvant postoperative chemoradiotherapy at the discretion of the multidisciplinary tumor board. Patient data were retrospectively analyzed. Patients with missing pathology results, those who did not receive or could not complete adjuvant chemotherapy, or those who had incomplete laboratory data were excluded from the study. Patient data were obtained retrospectively from the hospital's electronic databases, the prescription system, and the national health system network. Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University for Non-Pharmaceutical and Non-Medical Device Research (approval no: 2021/3430, date: 01.10.2021). The research was conducted in accordance with the principles of the Declaration of Helsinki.

All stage II patients in this cohort were classified as high-risk and received adjuvant chemotherapy accordingly. High-risk stage II disease was defined based on the presence of one or more of the following clinicopathological features, in accordance with NCCN Clinical Practice Guidelines (version 2.2025, colon cancer): T4 disease, poorly differentiated or undifferentiated histology [exclusive of microsatellite instability-high (MSI-H) tumors], lymphovascular invasion, perineural invasion, fewer than 12 lymph nodes examined, tumor presentation with bowel obstruction or localized perforation, and close, indeterminate, or positive surgical margins. The decision to administer adjuvant chemotherapy for stage II patients was made by the treating oncologist based on the individual risk profile of each patient.

Patient demographics [age, sex, height, weight, body mass index (BMI)], comorbidities, date of diagnosis, date of operation, history of emergency surgery, primary tumor location, history of radiotherapy and chemotherapy, tumor histopathology (histological type, stage, grade, lymphovascular invasion, T4 disease), MSI (evaluated by immunohistochemistry for MLH1, MSH2, MSH6, and PMS2), genetic mutation analysis (K-RAS, N-RAS, BRAF), carcinoembryonic antigen (CEA) level, and laboratory values measured preoperatively and after adjuvant chemotherapy [neutrophil count, lymphocyte count, platelet count, albumin, NLR, PLR, C-reactive protein (CRP), and PNI] were recorded.

NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. PNI was calculated using the formula: PNI=10×serum albumin (g/dL) +0.005×total lymphocyte count (/mm^3), as originally described by Onodera et al. (11). Since no consensus cut-off values for NLR, PLR, and PNI have been established in the literature, median values were used as cut-off points to divide patients into two groups. This approach has been widely adopted in comparable exploratory retrospective studies (9,10,12). However, using population-specific median values may limit reproducibility across populations; receiver operating characteristic (ROC)-based or externally validated thresholds should therefore be explored in future studies.

Post-chemotherapy laboratory values (PNI, NLR, and PLR) were obtained from blood samples collected during the first scheduled follow-up visit, approximately one month after completion of adjuvant chemotherapy.

Patients were divided into two groups based on the median PNI value before and after chemotherapy. The effects of PNI on 5-year OS and disease-free survival (DFS) were evaluated.

Statistical Analysis

Data were analyzed using SPSS 18.0. Descriptive analyses included frequency (n, %), mean ± standard deviation, median (interquartile range), relative risk, and 95% confidence interval (CI). Categorical data were compared using chi-square and Fisher's exact tests. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent samples t-test and Mann-Whitney U test were used as appropriate. Kaplan-Meier survival analysis was performed, and univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors. For multivariate Cox regression, all clinically relevant prognostic variables were entered into the model using the forced entry method, regardless of their significance in univariate analysis, to account for potential confounding effects. Results were evaluated at the 95% confidence level, and significance was set at $p<0.05$.

Results

Patients were divided into two groups based on the pre-chemotherapy PNI median value: ≤38.01 and >38.01. The mean age of the patients in the low PNI group was higher than that in the high PNI group ($p<0.001$). No significant differences were found between the two groups with respect to other sociodemographic characteristics (BMI, sex, comorbidity, Eastern Cooperative Oncology Group). There were no significant differences between the two groups tumor location, lymph node count, T4 disease, lymphovascular invasion, MSI, and mutations (Table 1).

As adjuvant chemotherapy, 134 patients (42.7%) received 5-fluorouracil, leucovorin, oxaliplatin, 67 (21.3%) received 5-fluorouracil/leucovorin, 60 (19.1%) received capecitabine, and 53 (16.9%) received capecitabine, oxaliplatin. No significant difference in survival was observed between chemotherapy groups.

Among the patients, 66 (21.0%) were MSI-H/deficient mismatch repair (dMMR) and 61 (19.4%) were microsatellite stable (MSS)/pMMR.

Among pre-chemotherapy laboratory values, the mean albumin was lower in the low PNI group than in the high PNI group ($p<0.001$). CRP, neutrophil count, and NLR were higher in the low PNI group than in the high PNI group ($p<0.001$, $p=0.002$, and $p=0.002$, respectively). No significant differences were observed between the two groups with respect to pre-chemotherapy platelet counts, lymphocyte counts, and PLR values. Post-chemotherapy PNI was also lower in the group with low pre-chemotherapy PNI ($p<0.001$). Post-chemotherapy albumin levels were lower in the low PNI group than in the high PNI group ($p<0.001$). No significant differences were observed between the two groups in post-chemotherapy CRP, neutrophil, platelet, and lymphocyte counts, NLR, and PLR (Table 2).

The effects of pre-chemotherapy PNI, NLR, and PLR values on OS in patients with stage II and stage III CRC were analyzed by grouping patients according to median values. In patients with stage II CRC, the mean OS was 97.29 months (CI: 81.05-112.78) in the group with pre-chemotherapy PNI ≤38.01, and 117.31 months (CI: 108.34-126.27) in the group with PNI >38.01. In patients with stage II CRC, a PNI level of ≤38.01 at initial diagnosis significantly decreased OS compared to PNI >38.01 ($p=0.022$) (Figure 1).

The effect of pre-chemotherapy PNI on OS in patients with stage III CRC was not statistically significant ($p=0.746$). In patients with stage II and III CRC, the effects of pre-chemotherapy NLR and PLR levels on survival were not statistically significant (NLR: $p=0.106$ for stage II and $p=0.845$ for stage III; PLR: $p=0.522$ for stage II and $p=0.706$ for stage III).

Post-chemotherapy PNI, NLR, and PLR values were grouped based on their median levels and their effects on OS were analyzed. In patients with stage II CRC, the mean OS was 98.69 months (CI: 86.89-110.50) in the group with post-chemotherapy PNI ≤42.00, and 125.64 months (CI: 118.51-132.77) in the group with PNI >42.00. A post-chemotherapy PNI level of ≤42.00 significantly decreased survival compared to PNI >42.00 ($p=0.002$) (Figure 2).

The effect of post-chemotherapy PNI on survival in patients with stage III CRC was not statistically significant ($p=0.462$). The effect of post-chemotherapy NLR on survival in patients with stage II and III CRC was not statistically significant ($p=0.054$ and $p=0.706$, respectively). In patients with stage II CRC, the mean OS was 126.32 months (CI: 118.80-133.85) in the group with post-chemotherapy PLR ≤111.36, and 101.44 months (CI: 90.51-112.37) in the group with PLR >111.36. A post-chemotherapy PLR ≤111.36 significantly increased OS compared to PLR >111.36 ($p=0.007$) (Figure 3). In patients with stage III CRC, the effect of post-chemotherapy PLR on survival was not statistically significant ($p=0.804$).

Univariate analysis examined the effects of independent prognostic factors on 5-year OS. Among these, the effects of pre-chemotherapy NLR and PNI, and of post-chemotherapy NLR and BMI, on 5-year OS were statistically significant ($p=0.017$, $p=0.042$, $p=0.009$, and $p=0.015$, respectively). In

Table 1. General characteristics of patients			
	Pre-chemotherapy PNI		
	≤38.01 (n=127)	**>38.01 (n=187)**	**p-value**
Age (years)	70.00 (63.00-75.00)	65.00 (56.00-72.00)	**<0.001***
BMI (kg/m²)	26.36 (22.85-29.38)	26.66 (23.83-30.09)	0.208*
Gender Female Male	48 (37.80) 79 (62.20)	80 (42.80) 107 (57.20)	0.378**
Comorbidity Yes None	60 (47.20) 67 (52.80)	103 (55.10) 84 (44.90)	0.173**
ECOG PS ECOG 0 ECOG 1 ECOG 2	19 (15.00) 94 (74.00) 14 (11.00)	41 (21.90) 137 (73.30) 9 (4.80)	0.052**
Tumor location Left colon Right colon	92 (72.40) 35 (27.60)	130 (70.70) 54 (29.30)	0.732*
Number of lymph nodes removed ≥12 <12	95 (74.80) 32 (25.20)	140 (74.90) 47 (25.10)	0.990*
Histological type Adenocarcinoma Mucinous adenocarcinoma	115 (92.00) 10 (8.00)	157 (84.00) 30 (16.00)	**0.037***
Lymphovascular invasion Yes None	60 (47.20) 67 (52.80)	72 (38.50) 115 (61.50)	0.124*
MSI MSI high (dMMR) (n=66) MSS (n=61)	30 (56.60) 23 (43.40)	36 (48.60) 38 (51.40)	0.376*
K-RAS mutation Yes (n=33) None (n=46)	17 (45.90) 20 (54.10)	16 (38.10) 26 (61.90)	0.480*
N-RAS mutation Yes (n=3) None (n=68)	1 (3.10) 31 (96.90)	2 (5.10) 37 (94.90)	1.000**
BRAF mutation Yes (n=1) None (n=67)	0 (0.00) 31 (100.00)	1 (2.70) 36 (97.30)	1.000**
Radiotherapy Yes None	29 (22.80) 98 (77.20)	33 (17.60) 154 (82.40)	0.257**
Adjuvant CTx protocol FOLFOX 5-FU/LV Capecitabine XELOX	58 (45.70) 22 (17.30) 26 (20.50) 21 (16.50)	76 (40.60) 45 (24.10) 34 (18.20) 32 (17.10)	0.516**
Progression Yes None	31 (24.40) 96 (75.60)	40 (21.40) 147 (78.60)	0.530*
Latest status Alive-disease-free Alive-diseased Deceased	87 (68.50) 8 (6.30) 32 (25.20)	140 (74.90) 13 (7.00) 34 (18.20)	0.326*

PNI: Prognostic nutritional index, BMI: Body mass index, ECOG-PS: Eastern cooperative oncology group- performance status, MSI: Microsatellite instability, dMMR: Deficient mismatch repair, MSS: Microsatellite stable, CTx: Chemotherapy, FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin, 5-FU/LV: 5-fluorouracil/leucovorin, XELOX: Capecitabine, oxaliplatin

Table 2. Comparison of laboratory parameters of pre-chemotherapy PNI groups

	Pre-chemotherapy PNI		
	≤38.01 (n=127)	**>38.01 (n=187)**	**p-value**
CEA	1.92 (1.20-3.80)	2.20 (1.37-3.97)	0.312*
Before chemotherapy			
Albumin	3.40 (3.10-3.60)	4.10 (4.00-4.30)	**<0.001***
CRP	23.50 (3.10-104.00)	5.20 (2.00-25.00)	**<0.001***
Neutrophil	6.00 (4.30-8.40)	5.10 (3.90-6.84)	**0.002***
Platelets	324.00 (261.00-410.00)	307.00 (253.50-378.75)	0.188*
Lymphocyte	1.80 (1.40-2.40)	1.90 (1.40-2.60)	0.282*
NLR	3.30 (2.16-5.50)	2.61 (1.72-4.55)	**0.002***
PLR	180.19 (133.75-248.75)	169.05 (120.21-227.47)	0.059*
After chemotherapy			
PNI	41.00 (38.00-43.00)	42.00 (40.01-44.01)	**<0.001***
Albumin	4.10 (3.80-4.30)	4.20 (4.00-4.40)	**<0.001***
CRP	2.70 (2.00-7.30)	2.30 (1.70-6.70)	0.275*
Neutrophil	3.30 (2.50-4.60)	3.40 (2.42-4.40)	0.323*
Platelets	240.00 (180.00-300.00)	252.00 (180.00-320.00)	0.370*
Lymphocyte	1.86±0.83	1.95±0.90	0.363**
NLR	1.94 (1.30-3.00)	1.92 (1.36-2.88)	0.245*
PLR	111.30 (80.00-187.33)	116.54 (87.06-177.86)	0.900*

*: Mann Whitney U-Test, **: Independent samples t-test, PNI: Prognostic nutritional index, CEA: Carcinoembryonic antigen, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

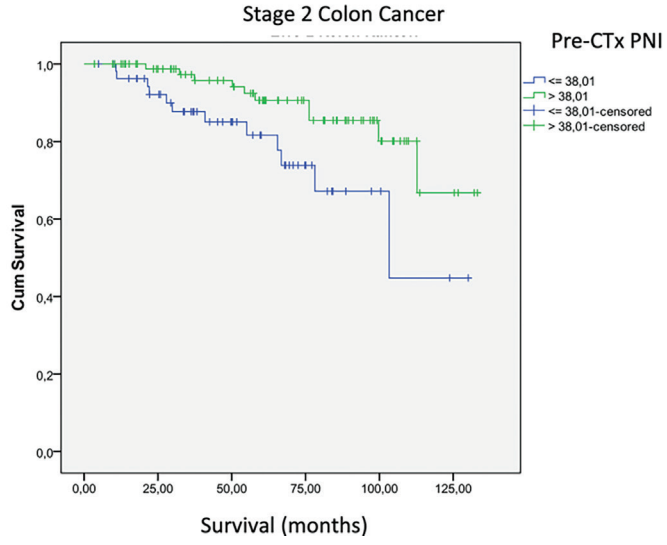


Figure 1. The effect of pre-chemotherapy PNI levels on overall survival in patients with stage 2 colon cancer

PNI: Prognostic nutritional index, CTx: Chemotherapy

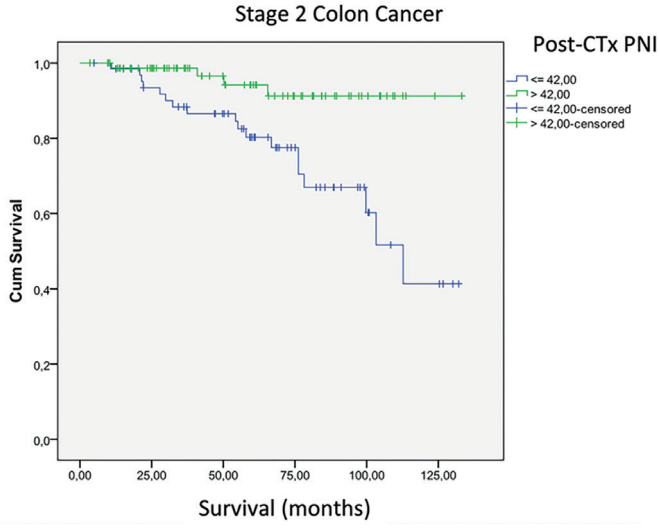


Figure 2. The effect of post-chemotherapy PNI levels on overall survival in patients with stage 2 colon cancer

PNI: Prognostic nutritional index, CTx: Chemotherapy

the multivariate Cox regression analysis for 5-year OS, the effects of pre-chemotherapy NLR and PLR values, and of post-chemotherapy NLR and BMI values, were statistically significant (p=0.010, p=0.006, p=0.010, and p=0.010, respectively) (Table 3).

Univariate analysis was performed to assess the effects of independent prognostic factors on 5-year DFS. The effects of pre-chemotherapy NLR and PNI and of post-chemotherapy NLR, PLR, PNI, and BMI on 5-year DFS were statistically significant (p=0.004, p=0.002, p=0.003, p=0.048, p=0.016, and p=0.008, respectively). In the multivariate Cox regression

analysis for 5-year DFS, the effects of pre-chemotherapy NLR and PNI, and of post-chemotherapy PNI and BMI, were statistically significant (p=0.010, p=0.018, p=0.008, and p=0.005, respectively) (Table 4).

Discussion

In this study, we investigated the prognostic significance of PNI in patients with early-stage CRC and whether it was superior to other prognostic markers such as NLR and PLR.

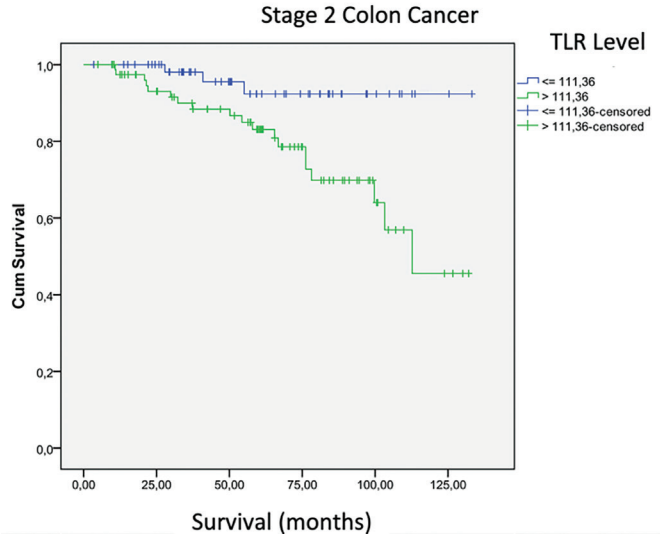


Figure 3. The effect of post-chemotherapy TLR levels on overall survival in patients with stage 2 colon cancer

TLR: Trombosit-lenfosit ratio

Surgical resection is the main treatment for stage I-III CRC. A significant proportion of patients develop recurrence or metastases within 5 years of surgical resection. Disease prognosis can vary greatly even among patients with the same stage. Therefore, new parameters are needed to predict survival and prognosis accurately. Molecular parameters such as MSI and RAS/RAF mutations have been associated with prognosis; however, complex and expensive laboratory techniques are required to measure these parameters.

Survival outcomes of CRC patients are mainly predicted by tumor-related factors, including TNM staging, tumor grade, and tumor location (3,4). Studies have reported that prognosis is related to host and tumor factors.

The preoperative nutritional status of the host and the systemic inflammatory response play a crucial role in triggering progression and metastasis in many types of cancer. The inflammatory response is indicated by the levels of neutrophils, lymphocytes, platelets, and acute phase proteins such as CRP (4). One of the indicators of nutritional status is albumin level. Hypoalbuminemia and malnutrition are common among cancer patients. Based on this, the importance of prognostic markers (such as NLR, PLR, PNI) has been investigated in many oncological malignancies (5-8). However, there is no consensus on which marker is more useful.

While the prognostic significance of PNI in CRC has been reported in several studies, the present study offers several distinct contributions. First, to our knowledge, this is one of the few studies to evaluate both pre- and post-

Table 3. Cox-regression analysis of independent prognostic factors on 5-year overall survival

5-year overall survival				
	Univariate Cox-regression		**Multivariate Cox-regression**	
	RR (CI)	**p-value**	**RR (CI)**	**p-value**
NLR (pre-chemotherapy)	**1.523 (1.079-2.148)**	**0.017**	**1.730 (1.199-2.497)**	**0.010**
PLR (pre-chemotherapy)	0.940 (0.670-1.320)	0.721	**0.998 (0.997-1.000)**	**0.006**
PNI (pre-chemotherapy)	**0.694 (0.488-0.987)**	**0.042**	-	-
NLR (post-chemotherapy)	**1.601 (1.126-2.276)**	**0.009**	**1.605 (1.121-2.300)**	**0.010**
PLR (post-chemotherapy)	1.293 (0.917-1.823)	0.143	-	-
PNI (post-chemotherapy)	0.711 (0.505-1.000)	0.050	-	-
BMI	**0.645 (0.454-0.919)**	**0.015**	**0.619 (0.430-0.890)**	**0.010**
Comorbidity	0.945 (0.670-1.333)	0.746	-	-
Lymph node count	0.797 (0.546-1.163)	0.240	-	-
T4 disease	1.202 (0.847-1.705)	0.303	-	-
MSI	0.588 (0.201-1.719)	0.332	-	-
CEA	1.084 (0.772-1.522)	0.641	-	-
K-RAS mutation	1.104 (0.458-2.663)	0.826	-	-

RR: Relative risk, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, BMI: Body mass index, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen

chemotherapy PNI values in a cohort in which all patients completed adjuvant chemotherapy, thereby allowing a more homogeneous assessment of treatment-related nutritional changes. Second, the combined analysis of PNI, NLR, and PLR at two time points provides a more comprehensive inflammatory-nutritional prognostic profile than those from most existing single-time-point studies. Third, the finding that post-chemotherapy PNI was an independent predictor of DFS highlights the potential clinical utility of serial PNI monitoring during adjuvant treatment, an area that remains underexplored in CRC.

In our study, the mean age of patients in the low PNI group was higher, which is consistent with the results of previous studies (13,14). The findings support the conclusion that malnutrition and immunosuppression have become more prevalent among elderly patients with cancer.

In our study, the cut-off values for pre-chemotherapy PNI, NLR, and PLR were 38.01, 3.85, and 197.15, respectively. In patients with stage II CRC, a PNI level of ≤38.01 at initial diagnosis significantly decreased OS and DFS compared to PNI >38.01. In patients with stage III CRC, the effect of PNI on OS and DFS was not statistically significant. NLR and PLR levels did not have a significant effect on OS or DFS in either stage II or stage III CRC.

On review of the literature, a study of 197 patients diagnosed with stage IIA colon cancer who underwent curative resection between 2006 and 2016 found that low PNI (<44.8) was the only independent predictor of DFS. The effects of NLR and PLR on DFS were not significant. In this study, 37 patients received adjuvant chemotherapy. The results for PNI were similar to our findings (13).

In a study involving 1.035 patients with stage IIA disease who underwent surgery, the prognostic effects of PNI, NLR, PLR, and serum fibrinogen levels on OS and DFS were analyzed. Patients in the poor prognosis group (NLR ≥2.4, PLR ≥150.8, fibrinogen ≥339.5 mg/dL, and PNI <45.5) had higher-grade histology, older age, and lower BMI. While patients with low PNI and high NLR had a worse prognosis, no significant results were obtained for PLR in 5-year survival analysis (15). Unlike these studies, our study made no subgroup distinction among stage II patients. However, all patients received adjuvant chemotherapy and were high-risk stage II patients. The results for PNI in our study were consistent with the literature and demonstrated that PNI is an important prognostic marker in stage II CRC.

In the study by Peng et al. (14) involving 274 patients with stage III colon cancer, a low PNI (≤49.22) was significantly related to short OS and DFS in patients with stage IIIC, but not in patients with stage IIIA/IIIB. In our study, the number of stage III patients was 171. The differences between the studies may be due to the unknown number of patients with stage IIIC and the relatively small number of patients (14).

The effect of independent prognostic factors (PNI, NLR, PLR, BMI, comorbidity, number of lymph nodes, T4 disease, MSI, CEA, K-RAS mutation) on 5-year OS was analyzed (Table 3). Among these, the effects of pre-chemotherapy NLR and PNI

Table 4. Cox-regression analysis of independent prognostic factors on 5-year disease-free survival

5 years disease-free survival				
	Univariate Cox-regression		Multivariate Cox-regression	
	RR (CI)	p-value	RR (CI)	p-value
NLR (Pre-chemotherapy)	**1.715 (1.182-2.489)**	**0.004**	**1.638 (1.125-2.384)**	**0.010**
PLR (Pre-chemotherapy)	0.933 (0.649-1.341)	0.706	-	-
PNI (Pre-chemotherapy)	**0.535 (0.362-0.791)**	**0.002**	**0.615 (0.412-0.918)**	**0.018**
NLR (Post-chemotherapy)	**1.774 (1.214-2.592)**	**0.003**	**-**	**-**
PLR (Post-chemotherapy)	**1.452 (1.004-2.099)**	**0.048**	**-**	**-**
PNI (Post-chemotherapy)	**0.637 (0.441-0.920)**	**0.016**	**0.588 (0.396-0.873)**	**0.008**
BMI	**0.592 (0.403-0.870)**	**0.008**	**0.562 (0.374-0.844)**	**0.005**
Comorbidity	0.931 (0.642-1.349)	0.704	-	-
Lymph node count	1.009 (0.673-1.512)	0.966	-	-
T4 Disease	1.241 (0.855-1.801)	0.256	-	-
MSI	0.684 (0.215-2.177)	0.521	-	-
CEA	1.076 (0.746-1.550)	0.696	-	-
K-RAS mutation	2.390 (0.473-12.081)	0.292	-	-

RR: Relative risk, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PNI: Prognostic nutritional index, BMI: Body mass index, MSI: Microsatellite instability, CEA: Carcinoembryonic antigen

and of post-chemotherapy NLR and BMI on 5-year OS were statistically significant.

When the effects of independent prognostic factors on 5-year DFS were analyzed, pre-chemotherapy NLR and PNI, and post-chemotherapy NLR, PLR, PNI, and BMI were statistically significant. In the multivariate Cox regression analysis of 5-year DFS, pre-chemotherapy NLR and PNI, and post-chemotherapy PNI and BMI, were significant (Table 4).

In a study of 1.880 patients with stage II and III CRC who underwent curative resection, Ahiko et al. (9) investigated whether two nutritional scores (PNI and CONUT) and four inflammatory scores (modified Glasgow prognostic score, NLR, PLR, and CRP/albumin ratio) are independent prognostic factors for OS. Two nutritional and two inflammatory scores were independent prognostic factors for OS; however, PNI and CONUT were superior to the inflammatory scores. PLR was not a significant independent prognostic factor. This finding is similar to our findings (9). In this study, 715 patients received adjuvant chemotherapy, while all patients in our study did so. Although our study included fewer patients, the results were similar.

In a study evaluating 1.014 CRC patients who underwent surgery in China, PNI was found to be an independent risk factor for 1-5 year OS and DFS and could be used together with TNM staging (16). Similarly, a Japanese study the PNI values of patients with stage II and III CRC. Although the preoperative PNI value was low, the prognosis of patients with increased PNI value after adjuvant treatment was reported to be better (12). Providing adequate energy and protein intake for patients with low PNI values may improve PNI and contribute positively to prognosis and OS.

In a meta-analysis of studies on BMI and survival in CRC, it was found that being underweight (BMI <18.5 kg/m^2) or class II/III obese (BMI >35 kg/m^2) during CRC surgery may lead to worse long-term survival results, while being slightly overweight (BMI 25-30 kg/m^2) may improve survival (17).

We have not found any study in the literature that investigates the prognostic role of post-chemotherapy PNI in CRC or examines its combined analysis with pretreatment PNI. In the study of Küçükarda et al. (18) with 107 patients with non-metastatic nasopharyngeal cancer, PNI values were analyzed both before and after treatment, and PNI was found to be an independent prognostic marker for OS both before and after treatment. In our study, the effect of post-treatment PNI (mean value of 41.31) on 5-year DFS was significant.

Shibutani et al. (10) examined the effect of preoperative and postoperative PNI values on OS. The study included 218 stage II and III patients, 141 of whom received chemotherapy. The median preoperative PNI was 47.90 and the median postoperative PNI was 48.69. The combination of pre- and postoperative PNI was an independent predictor of poor OS. These results demonstrate the importance of preoperative, postoperative, and post-chemotherapy PNI as prognostic markers.

In most studies, a cut-off value for PNI was determined, and groups were compared. In the study by Luvián-Morales et al. (19), patients were divided into four groups according to PNI values (>47.1; 47.0-43.5; 43.4-34.2; and <34.2) and the effect on prognosis was analyzed. Lower PNI values were associated with poorer 5-year survival. Although a different method was used for PNI evaluation, the findings are consistent with ours.

A summary of key studies evaluating PNI as a prognostic factor in CRC is presented in Table 5. Among these studies, cut-off determination methods varied considerably, including ROC curve analysis (13,15), median-based cut-offs (9,10,12), the X-tile program, and quartile-based divisions (19). This heterogeneity highlights the need for consensus-driven or externally validated PNI thresholds. In the present study, median values were used, consistent with several prior reports; however, we acknowledge that this approach may limit external reproducibility.

Regarding molecular subgroup analyses, MSI-H/dMMR status is a well-established favorable prognostic factor in stage II CRC and is known to influence treatment decisions. In our cohort, MSI/MMR data were available for only 127 patients (66 with MSI-H/dMMR and 61 with MSS/pMMR), and MSI status was not a significant predictor in univariate analysis of either OS (p=0.332) or DFS (p=0.521). The potential interaction between MSI-H/dMMR status and PNI is of clinical interest, as both may reflect aspects of the host immune response. However, the limited sample size for this subgroup precluded meaningful interaction analysis. Future studies with larger cohorts should explore whether PNI retains its prognostic value across MSI-defined subgroups.

A potentially important area for future investigation is the dynamic change in PNI values from pre- to post-chemotherapy. Categorizing patients based on the direction of PNI change (e.g., sustained high, sustained low, improving, or declining) may provide additional prognostic information beyond single time-point measurements. Such an approach could help identify patients whose nutritional and immunological status deteriorates during adjuvant treatment, enabling timely nutritional interventions. Prospective studies with larger sample sizes are warranted to further explore this transitional analysis.

Table 5. Summary of studies evaluating PNI as a prognostic factor in colorectal cancer

Author, year	n	Stage	PNI cut-off	Cut-off method	Adj CTx, n (%)	Main PNI findings
Maruyama et al. (13)	197	IIA	44.8	ROC curve	37 (19%)	Low PNI was the only independent predictor of DFS
Park et al. (15)	1.035	IIA	45.5	ROC curve	NR	Low PNI and high NLR predicted worse OS; PLR was not significant
Peng et al. (14)	274	III	49.22	ROC curve	All	Low PNI predicted short OS and DFS in stage IIIC only
Ahiko et al. (9)	1.880	II-III	NR	Median	715 (38%)	PNI and CONUT were superior to inflammatory scores for OS prediction
Xie et al. (16)	1.014	I-IV	Continuous	Per-unit HR	NR	PNI was an independent risk factor for 1-5 year OS and DFS
Tamai et al. (12)	218	II-III	47.90/48.69	Median	141 (65%)	Pre/postoperative PNI combination was an independent predictor of poor OS
Shibutani et al. (10)	218	II-III	47.90	Median	141 (65%)	Combination of pre- and postoperative PNI predicted poor OS independently
Luvián-Morales et al. (19)	NR	I-IV	4 groups*	Quartile-based	NR	Lower PNI groups showed progressively worse 5-year OS
Present study	314	II-III	38.01/42.00†	Median	All (100%)	Pre- and post-chemotherapy PNI independently predicted DFS; pre-CTx PNI significant for OS in stage II

*: PNI groups: >47.1, 47.0-43.5, 43.4-34.2, and <34.2, †: 38.01 (pre-chemotherapy median) and 42.00 (post-chemotherapy median), PNI: Prognostic nutritional index, Adj CTx: Adjuvant chemotherapy, ROC: Receiver operating characteristic, DFS: Disease-free survival, OS: Overall survival, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CONUT: Controlling nutritional status, NR: Not reported, HR: Hazard ratio

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective single-center design and the relatively limited sample size are inherent limitations.

Second, the exclusion of patients who did not initiate or complete adjuvant chemotherapy may have introduced selection bias, as these patients may represent a frailer subgroup with an inherently worse prognosis. This limits the generalizability of our findings to the broader population of patients with stage II and III CRC who underwent surgery.

Third, median-based cut-off values for PNI, NLR, and PLR were used rather than ROC-derived thresholds. Although the sample size (n=314) would have been suitable for ROC analysis, median values were chosen for consistency with comparable studies in the literature. Future studies should employ ROC-derived or externally validated cut-off values.

Fourth, low PNI values may partly reflect underlying confounding factors such as advanced age, frailty, chronic inflammation, comorbidities, or poor treatment tolerance, rather than representing an independent biological mechanism driving worse survival outcomes. Although we adjusted for age, comorbidity, and BMI in our analyses, residual confounding cannot be entirely excluded.

Fifth, the multivariate Cox regression model was constructed using forced entry of clinically relevant variables; however, major clinicopathological confounders such as age, stage, T stage, MSI status, and performance status were not uniformly pre-specified as mandatory covariates. The unexpected significance of pre-chemotherapy PLR in the multivariate OS model, despite non-significance in univariate analysis, may reflect a suppressor effect and should be interpreted cautiously, given the minimal effect size (hazard ratio: 0.998).

Sixth, potential collinearity among nutritionally and immunologically related variables warrants consideration. PNI is derived from serum albumin and the lymphocyte count, thereby creating an inherent mathematical relationship with these components. Similarly, NLR and PLR share lymphocyte count as a common denominator, and BMI may correlate with albumin levels as a reflection of nutritional status. Formal collinearity diagnostics (e.g., variance inflation factor analysis) were not performed, which may have influenced the multivariate regression estimates.

Seventh, MSI/MMR and molecular mutation data were not available for all patients, which limited subgroup analyses. Future studies with comprehensive molecular profiling are warranted.

Nevertheless, results consistent with the literature were obtained in the majority of analyses.

Conclusion

Pre-chemotherapy PNI was significantly associated with OS on univariate analysis, particularly in stage II CRC patients; however, it was not retained as an independent predictor in the multivariate model for OS. In contrast, both pre- and post-chemotherapy PNI were independent predictors of 5-year DFS in multivariate analysis. These findings suggest that PNI, which can be easily calculated from routine laboratory parameters (serum albumin and lymphocyte count), may serve as a valuable and accessible prognostic marker for disease recurrence in early-stage CRC. Prospective studies with larger sample sizes, ROC-derived cut-off values, and comprehensive molecular profiling are needed to validate these findings and establish standardized PNI thresholds for clinical use.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Necmettin Erbakan University for Non-Pharmaceutical and Non-Medical Device Research (approval no: 2021/3430, date: 01.10.2021).

Informed Consent: Patient data were obtained retrospectively from the hospital's electronic databases, the prescription system, and the national health system network.

Footnotes

Authorship Contributions

Surgical and Medical Practises: M.U., M.Z.K., M.K.E., M.A., Me.A., Concept: S.Ç., Ş.B.A., M.Z.K., M.K.E., M.A., Design: S.Ç., M.U., Me.A., Data Collection or Processing: M.U., Ş.B.A., M.Z.K., M.K.E., M.A., Me.A., Analysis or Interpretation: S.Ç., M.U., M.Z.K., Me.A., Literature Search: S.Ç., M.U., M.Z.K., Me.A., Writing: S.Ç., M.U., M.Z.K., Me.A.

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Reader Questions

Based on the manuscript: "Evaluation of the Relationship Between Prognostic Nutritional Index and Survival in Operated Stage II and III Colorectal Cancer Patients Receiving Adjuvant Chemotherapy"

1. What formula is used to calculate the prognostic nutritional index (PNI)?

A. Albumin×neutrophil count

B. 10×serum albumin (g/dL)+0.005×total lymphocyte count (/mm3)

C. Platelet count÷lymphocyte count

D. CRP×BMI

Correct Answer: B. 10×serum albumin (g/dL)+0.005×total lymphocyte count (/mm^3)

2. Which survival outcome remained independently associated with both pre- and post-chemotherapy PNI in multivariate analysis?

A. Overall survival (OS)

B. Progression-free survival (PFS)

C. Disease-free survival (DFS)

D. Cancer-specific survival (CSS)

Correct Answer: C. Disease-free survival (DFS)

3. In which patient subgroup did pre-chemotherapy PNI significantly predict overall survival in univariate analysis?

A. Stage I colorectal cancer

B. Stage II colorectal cancer

C. Stage III colorectal cancer

D. Metastatic colorectal cancer

Correct Answer: B. Stage II colorectal cancer

4. Which inflammatory biomarker is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count?

A. PNI

B. PLR

C. NLR

D. CONUT

Correct Answer: C. NLR

5. What was the principal conclusion of this study?

A. PNI replaced TNM staging for prognosis.

B. PNI may serve as a simple and accessible prognostic marker, particularly for disease recurrence in early-stage colorectal cancer.

C. PLR was superior to all other biomarkers.

D. BMI was the strongest predictor of overall survival.

Correct Answer: B. PNI may serve as a simple and accessible prognostic marker, particularly for disease recurrence in early-stage colorectal cancer.

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Int J Gastrointest Cancer Res 2026;1:41-46

SMARCB1 (INI1)-deficient Rhabdoid Pancreatic Carcinoma: A Rare Subtype of Pancreatic Cancer

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Abstract

Rhabdoid pancreatic carcinoma (RPC) is a rare and highly aggressive subtype of undifferentiated pancreatic carcinoma characterized by rhabdoid morphology and frequent loss of SWItch/sucrose non-fermentable chromatin-remodeling complex-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1), integrase interactor 1 (INI1) expression. Due to its rarity, its clinicopathological characteristics and optimal management remain poorly defined. A 56-year-old woman with an Eastern Cooperative Oncology Group performance status of 1 presented with a one-month history of abdominal and back pain. Contrast-enhanced computed tomography revealed an infiltrative pancreatic head mass measuring 125×52×75 mm, with vascular involvement and multiple metastatic lymph nodes. Histopathological examination demonstrated RPC, with complete loss of nuclear SMARCB1 (INI1) expression by immunohistochemistry. Comprehensive next-generation sequencing showed KRAS wild-type status. The patient received modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) chemotherapy and achieved partial regression of metastatic abdominal lymph nodes after six cycles. Treatment was continued for a total of 12 cycles before disease progression was documented. This case highlights the aggressive clinical behavior and distinctive molecular profile of SMARCB1 (INI1)-deficient RPC. The observed partial response to mFOLFIRINOX suggests that selected patients may derive temporary benefit from systemic chemotherapy; however, durable disease control remains challenging. Increased recognition of this rare entity and further investigation of molecularly targeted and immunotherapeutic strategies are needed to improve outcomes.

Keywords: Rhabdoid pancreatic carcinoma, SMARCB1 deficiency, INI1 loss, KRAS wild-type, mFOLFIRINOX

Introduction

Pancreatic cancer (PC) remains one of the leading causes of cancer-related mortality worldwide. In 2026, the United States alone is projected to have an estimated 67.530 new cases and 52.740 deaths, underscoring its disproportionately high mortality relative to incidence. Despite advances in systemic therapy, the 5-year relative survival rate remains approximately 13%, reflecting its aggressive biology and frequent late-stage presentation (1). While pancreatic ductal adenocarcinoma (PDAC) constitutes the majority of pancreatic malignancies, a small subset comprises undifferentiated pancreatic carcinomas (UPC), which are characterized by high-grade morphology and an aggressive clinical course. UPC accounts for approximately 2-7% of PC and includes anaplastic, sarcomatoid, rhabdoid, and carcinosarcoma subtypes (2). Within this heterogeneous group, rhabdoid pancreatic carcinoma (RPC) represents a rare histologic subtype distinguished by prominent rhabdoid morphology.

RPC is frequently associated with alterations in the SWItch/sucrose non-fermentable chromatin-remodeling complex, most notably the loss of matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1), integrase interactor 1 (INI1) expression. Histologically, these tumors demonstrate sheets of poorly differentiated cells with abundant eosinophilic cytoplasm and eccentrically placed nuclei; they are often diagnosed at advanced stages and present with rapidly progressive disease. The designation "rhabdoid" in PC reflects its histopathologic resemblance to rhabdomyosarcoma (3).

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Given its rarity and the limited clinical experience, the clinicopathologic spectrum and optimal management strategies for RPC remain incompletely defined. Herein, we present a case of metastatic SMARCB1 (INI1)-deficient RPC, which adds to the limited body of evidence and helps to further clarify the diagnostic and clinicopathologic features of this aggressive entity.

Case Presentation

A 56-year-old woman presented with a one-month history of abdominal and back pain. At presentation, the patient had an Eastern Cooperative Oncology Group performance status of 1. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis revealed a 38×29 mm lesion in the gallbladder fundus and a 125×52×75 mm infiltrative mass centered in the pancreatic head, encasing the common bile duct and extending into the paraaortic and paracaval regions. The lesion was in close contact with the celiac trunk, superior mesenteric artery, and portal vein. Multiple metastatic lymph nodes forming conglomerates were identified in the abdomen.

Serum tumor markers were within normal limits. Laboratory evaluation demonstrated elevated levels of liver enzymes, including aspartate aminotransferase (78 U/L), alanine aminotransferase (170 U/L), alkaline phosphatase (239 U/L), and gamma-glutamyl transferase (215 U/L). Thoracic CT showed multiple enlarged mediastinal lymph nodes, the largest measuring 2.5 cm in the left upper paratracheal region.

Histopathological examination of the pancreatic head mass revealed findings consistent with SMARCB1 (INI1)-deficient RPC. Immunohistochemical analysis demonstrated complete loss of nuclear SMARCB1 (INI1) expression, confirming the diagnosis. Comprehensive next-generation sequencing (NGS) of tumor tissue did not reveal a KRAS mutation.

The patient was initiated on modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX), administered every 14 days, at standard dosing (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus followed by 2400 mg/m^2 continuous infusion). After six cycles, partial regression of the abdominal lymph nodes was observed (Figures 1A and 1B). Treatment was continued for a total of 12 cycles. At the end of therapy, disease progression was documented in several lymph nodes, while the primary pancreatic lesion remained radiologically stable.

Second-line chemotherapy with gemcitabine (900 mg/m^2 on days 1 and 8) and docetaxel (100 mg/m^2 on day 8), administered every 21 days, was initiated. However, the patient died one month after initiation of second-line therapy from progressive disease.

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

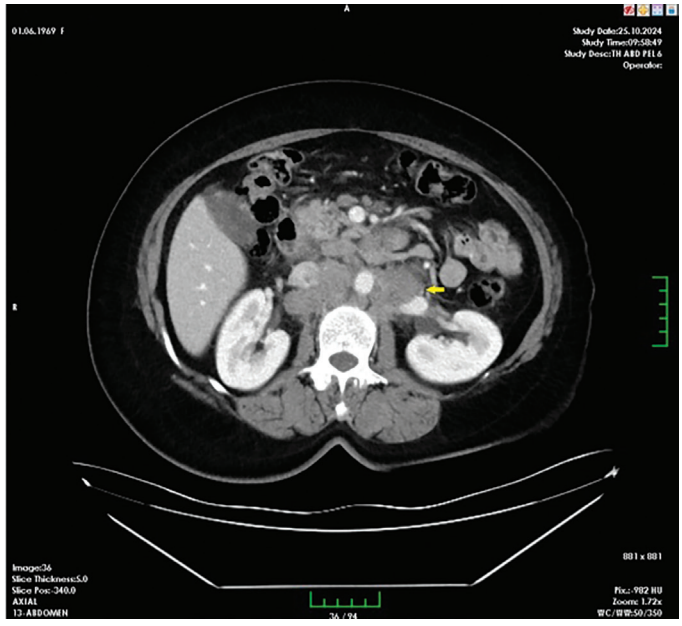


Figure 1A. Baseline CT before initiation of mFOLFIRINOX (cycle 0)

CT: Computed tomography, mFOLFIRINOX: Modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin

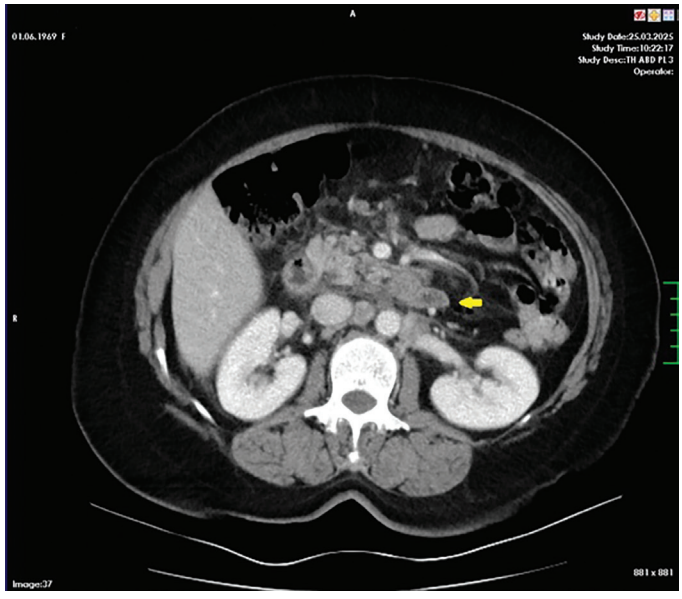


Figure 1B. CT after completion of six cycles of mFOLFIRINOX demonstrating partial radiologic response

CT: Computed tomography, mFOLFIRINOX: Modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin

Discussion

UPC represents a rare and biologically aggressive subset of exocrine pancreatic malignancies, comprising approximately 2-7% of all PC (2,4). Within the current World Health Organization 5th edition classification, these tumors are subcategorized into anaplastic, sarcomatoid, and rhabdoid types, as well as undifferentiated carcinomas (UC) with osteoclast-like giant cells (5).

RPC is a particularly infrequent and lethal variant defined by its characteristic histomorphology, which mimics malignant rhabdoid tumors of childhood (6). This case, a 56-year-old woman with a markedly enlarged (125 mm) metastatic pancreatic head mass and KRAS wild-type status, highlights the distinctive clinical and molecular profile associated with this entity. This case contributes to the emerging evidence that RPC is not merely a high-grade variant of PDAC but a unique clinicopathologic entity often driven by alterations in the SWI/SNF chromatin-remodeling complex (7).

The clinicopathologic correlations observed in this case align with the aggressive parameters reported in the limited RPC literature. While conventional PDAC typically presents with smaller masses, UCs, especially the rhabdoid subtype, are characterized by larger tumor dimensions at diagnosis, with reported median sizes ranging from 4.6 cm to over 9.0 cm (7). In the present case, the tumor reached a maximum dimension of 12.5 cm, exceeding previously reported averages and highlighting the aggressive growth kinetics of this tumor type. Demographic data for RPC show a slight male predominance and a median age of onset in the 6th or 7th decade, though cases have been reported in patients as young as 13 years old (7,8).

In the present case, the patient's falls within the relatively younger age range reported for SWI/SNF-deficient tumors compared with conventional PDAC. Furthermore, the localization of the primary tumor in the pancreatic head in this case is consistent with recent large-scale reviews showing a predilection for the head (68%) in SWI/SNF-deficient undifferentiated variants, whereas other UC subtypes are more evenly distributed (7).

The molecular landscape of RPC is increasingly understood through the paradigm of SWI/SNF complex alterations, most notably the loss of SMARCB1 (INI1) expression (9,10,11). A seminal analysis by Agaimy et al. (9) proposed a binary classification of RPC based on KRAS and SMARCB1 (INI1) status: a pleomorphic giant cell subtype characterized by KRAS alterations and intact SMARCB1 (INI1), and a monomorphic anaplastic subtype defined by the loss of SMARCB1 (INI1) and the absence of KRAS mutations. The present case, in which comprehensive NGS did not identify a KRAS mutation, appears to align with the latter molecular pathway. Recent genomic data from Yavas et al. (7) support this association, noting that carcinomas with SMARCB1 (INI1) deletions frequently lack canonical PDAC driver mutations such as KRAS, TP53, and SMAD family member 4. The loss of SMARCB1 (INI1) function leads to global epigenetic dysregulation, stimulating the MYC proto-oncogene network and promoting mesenchymal reprogramming in a KRAS-independent manner (12). This molecular transition is often accompanied by the loss of cellular adhesion molecules like E-cadherin and β-catenin, contributing to the discohesive, infiltrative growth pattern observed in RPC (13).

Diagnostic challenges are a hallmark of RPC due to its nonspecific clinical presentation and the lack of reliable biomarkers. Similar to the present case, patients frequently present with non-specific abdominal or back pain, while serum tumor markers such as cancer antigen 19-9 and the carcinoembryonic antigen are often within normal limits, in contrast to conventional PDAC (10,14,15). Radiologically, RPC often presents as a large, hypovascular mass with extensive internal necrosis or hemorrhage (16). Pathological diagnosis is therefore mandatory and relies on endoscopic ultrasound-guided fine-needle aspiration or biopsy (14). Immunohistochemically, RPC must demonstrate at least focal positivity for epithelial markers such as cytokeratins to distinguish it from true sarcomas (6). The integration of SMARCB1 (INI1) staining is now considered essential when rhabdoid cells are identified, as its loss is highly specific for the SMARCB1 (INI1)-deficient subtype (7,17).

Management strategies for RPC remain unstandardized, and clinical outcomes are generally suboptimal. Radical surgical resection remains the only curative treatment option, but its utility is often limited by the frequent presence of metastatic disease at the time of diagnosis, as seen in our case (10,14). Pooled analyses indicate that even with surgery, median survival is often restricted to approximately three months, with over 77% of patients dying within one year (17). For metastatic or unresectable RPC, systemic therapy is the primary treatment modality, yet responses to standard PDAC regimens are inconsistent. Our case showed a partial regression of abdominal lymph nodes after six cycles of mFOLFIRINOX, which is a noteworthy outcome given that many reports describe immediate progression on this regimen (17,18). However, the subsequent disease progression in several lymph nodes underscores the transient nature of such responses. Evidence is mounting that gemcitabine plus nab-paclitaxel may offer more sustained responses in some

patients with undifferentiated variants; some case reports have even shown complete responses. The ongoing phase II clinical trial (jRCTs031220099) investigating this combination in UC may provide more definitive guidance (14).

The prognostic implications of RPC are profound, with median overall survival typically ranging from three to six months (14). Our case illustrates the biological aggressiveness of the tumor, which progressed despite twelve cycles of intensive combination chemotherapy. This aggressive behavior is likely mediated by the loss of SWI/SNF function and the concomitant activation of epithelial-mesenchymal transition pathways (14,17). Emerging data suggest that PD-L1 enrichment is common in UPC, potentially providing a rationale for the use of immune checkpoint inhibitors in a subset of patients (7,14,15). Although a previously reported case of SMARCB1 (INI1)-deficient PC achieved a complete response to pembrolizumab, RPC was not specifically described (19). The response to immunotherapy in the present case therefore remains to be elucidated in future investigations (20). PD-L1 expression was not evaluated in the present case.

This case of metastatic SMARCB1 (INI1)-deficient RPC reinforces the need to consider this rare entity in the differential diagnosis of large, rapidly enlarging pancreatic masses, particularly when tumor markers are normal and KRAS is wild-type. Our case contributes to the limited literature by documenting a partial clinical response to mFOLFIRINOX before eventual disease progression and by adding detail to the scant evidence regarding the systemic management of metastatic RPC. Given the aggressive biology and poor prognosis, early identification by immunohistochemical evaluation of SWI/SNF subunits is critical. Future progress in managing RPC will require multi-institutional collaboration to evaluate targeted strategies, such as immunotherapy, in the context of specific molecular subtypes. Maintaining this index case as a central reference highlights that, while RPC is highly aggressive, a deeper understanding of its unique molecular drivers may eventually pave the way for precision oncology in this challenging patient population.

Ethics

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

Footnotes

Authorship Contributions

Concept: M.D., Design: M.Y., M.B., Data Collection or Processing: M.Y., D.B.G., B.Y., M.D., Analysis or Interpretation: M.Y., D.B.G., B.Y., Literature Search: M.Y., M.B., Writing: M.Y., M.D.

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

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Reader Questions

Based on the manuscript: "SMARCB1-deficient Rhabdoid Pancreatic Carcinoma: A Case Report"

1. Which molecular alteration is most commonly associated with rhabdoid pancreatic carcinoma?

A. KRAS amplification

B. SMARCB1 (INI1) loss

C. HER2 amplification

D. BRAF V600E mutation

Correct Answer: B. SMARCB1 (INI1) loss

2. Which chemotherapy regimen was used as first-line treatment in this case?

A. Gemcitabine plus nab-paclitaxel

B. FOLFIRI

C. Modified FOLFIRINOX

D. Gemcitabine monotherapy

Correct Answer: C. Modified FOLFIRINOX

3. What was the patient's best radiologic response after six cycles of first-line chemotherapy?

A. Complete response

B. Partial regression of abdominal lymph nodes

C. Stable disease in all lesions

D. Progressive disease

Correct Answer: B. Partial regression of abdominal lymph nodes

4. Which molecular feature supported the diagnosis of the monomorphic SMARCB1-deficient subtype?

A. KRAS mutation

B. TP53 mutation

C. Loss of SMARCB1 (INI1) expression with KRAS wild-type status

D. EGFR amplification

Correct Answer: C. Loss of SMARCB1 (INI1) expression with KRAS wild-type status

5. According to the discussion, which emerging therapeutic approach may have potential in selected SMARCB1-deficient pancreatic tumors?

A. Anti-EGFR therapy

B. Immune checkpoint inhibition

C. Anti-HER2 therapy

D. PARP inhibition

Correct Answer: B. Immune checkpoint inhibition

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Primary Tumor Site Modifies the Prognostic Impact of Mucinous Histology in Non-metastatic Colorectal Cancer: An Interaction Analysis of the SEER Database

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Abstract

Objectives: The prognostic value of mucinous adenocarcinoma (MAC) in colorectal cancer (CRC) remains controversial, with conflicting reports regarding its impact on survival. We hypothesized that the primary tumor location would modify the prognostic significance of mucinous histology in patients with non-metastatic CRC.

Methods: We analyzed 286.046 adult patients with non-metastatic CRC, identified in the surveillance, epidemiology, and end results database (2010-2022). Patients were stratified by histology (MAC vs. non-MAC) and tumor site (colon vs. rectum). Multivariable Cox proportional hazards regression was performed to evaluate overall survival (OS), adjusting for demographic and clinical covariates. A formal interaction term (histology×location) was included to assess effect modification.

Results: Among the total cohort, 17.096 (6.0%) patients exhibited MAC. Compared with non-mucinous tumors, mucinous tumors were significantly associated with advanced stage, higher grade, and female sex ($p<0.001$). Multivariable analysis identified MAC [hazard ratio (HR): 1.373; 95% confidence interval (CI): 1.326-1.422] and rectal location (HR: 1.066; 95% CI: 1.027-1.106) as independent predictors of mortality. Importantly, a significant interaction was detected between mucinous histology and rectal location (HR: 1.289; 95% CI: 1.203-1.381; $p<0.001$), indicating that the negative prognostic effect of MAC is amplified in rectal tumors. Consequently, 5-year OS was lowest for rectal MAC (55.1%) compared with colonic MAC (61.1%) and non-mucinous subtypes (colon: 68.5%; rectum: 68.7%) ($p<0.001$).

Conclusion: Primary tumor location significantly modified the prognostic impact of mucinous histology. The survival disadvantage of MAC is disproportionately severe in rectal cancer compared with colon cancer, suggesting that rectal MAC represents a distinct, aggressive entity requiring site-specific risk stratification and tailored management strategies.

Keywords: Colorectal cancer, mucinous adenocarcinoma, prognosis, SEER program

Introduction

Mucinous adenocarcinoma (MAC) represents a distinct histopathological subtype of colorectal cancer (CRC), accounting for approximately 10% to 20% of all cases (1). Histologically, MAC is defined by the presence of abundant extracellular mucin comprising more than 50% of the tumor volume (2). Beyond its morphological features, this subtype exhibits a unique molecular profile compared to non-MAC, characterized by the overexpression of MUC2, a higher frequency of microsatellite instability (MSI), and increased rates of *BRAF* mutations (3).

Despite these well-defined characteristics, the prognostic significance of mucinous histology remains a subject of ongoing debate (4). While several studies identify MAC as an independent adverse prognostic factor, others suggest that the

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survival disparity disappears when adjusting for disease stage (2). Clinical management is further complicated by evidence suggesting that mucinous tumors display reduced sensitivity to standard treatments. Pharmacogenomic studies indicate that MAC often harbors mutations in genes such as *TYMP* and *ATP7B1*, which may confer resistance to 5-fluorouracil and oxaliplatin (2).

A critical factor that may elucidate these conflicting prognostic data is the primary tumor location. The colon and rectum are biologically distinct entities arising from different embryological origins, often described as a continuum of molecular alterations rather than a single disease (5). Consequently, the impact of mucinous histology may not be uniform throughout the colorectum. Previous literature suggests that while rectal MAC is consistently associated with poor outcomes, the prognostic value of colonic MAC remains controversial (2,4).

We hypothesized that the prognostic effect of mucinous histology is not static but is modified by the primary tumor site. Therefore, this study aimed to determine whether tumor location (colon vs. rectum) significantly modifies the prognostic impact of mucinous histology in patients with non-metastatic CRC.

Material and Methods

Data Source and Study Population

This retrospective cohort study used data from the surveillance, epidemiology, and end results (SEER) 17 registries research database (November 2024 submission), which covers approximately 26.5% of the United States population. Data were extracted using SEER*Stat software (version 9.0.42.0). Adult patients (≥18 years) diagnosed with CRC between 2010 and 2022 were identified. The year 2010 was selected to ensure the availability of contemporary staging and treatment variables. Patients were excluded if they had (1) primary tumors located outside the colorectum (e.g., anus or small intestine); (2) non-adenocarcinoma histology; (3) *in situ* disease, unknown stage, or diagnosis only by death certificate or autopsy; (4) appendiceal tumors, overlapping lesions, or colon not otherwise specified; (5) metastatic disease at diagnosis; (6) a non-first primary malignancy; or (7) missing survival time or follow-up data (Figure 1).

Variables and Definitions

The histologic subtype was defined using the histologic type variable of the International Classification of Diseases for Oncology, third edition. MAC was identified using codes 8480/3 and 8481/3, whereas all remaining adenocarcinoma histologies were classified as non-mucinous. Tumor location was derived from the primary site variable and categorized as colon (C18.0-C18.9) or rectum (C19.9-C20.9). Tumor extent

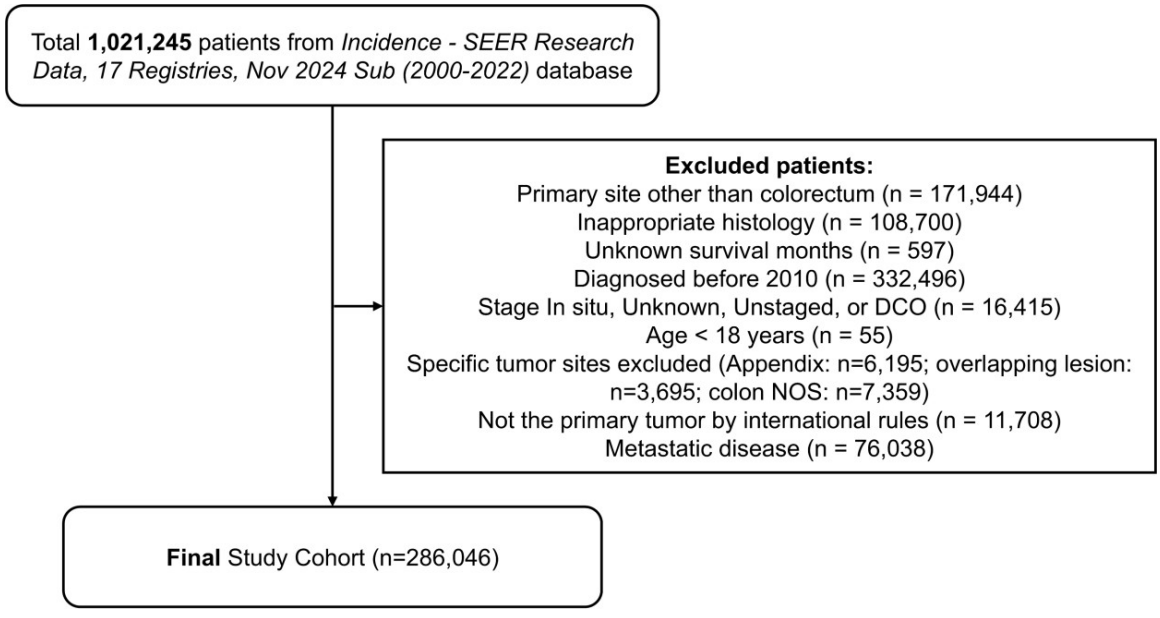


Figure 1. Study flow diagram

SEER: Surveillance, epidemiology, and end results, NOS: Not otherwise specified, DCO: Death certificate only

was determined using the SEER combined summary stage (2004+) with expanded regional codes and was dichotomized as node-negative (localized only or regional by direct extension only) versus node-positive (regional lymph node involvement with or without direct extension). Histological grade was grouped as well- or moderately differentiated versus poorly differentiated or undifferentiated. Treatment variables, including cancer-directed surgery, radiotherapy, and chemotherapy, were obtained from the SEER recode variables and dichotomized for analysis as "yes" versus "no/unknown". The primary endpoint was overall survival (OS), defined as the interval from diagnosis to death from any cause or to the last follow-up, based on the SEER survival months and vital status variables.

Statistical Analysis

Baseline characteristics were compared between histological groups using the chi-square test for categorical variables and the Student's t-test for continuous variables. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. To evaluate the independent association between histology and OS, a multivariable Cox proportional hazards regression model was constructed, adjusting for age, sex, race, stage, grade, surgery, radiotherapy, and chemotherapy. To test the hypothesis that the prognostic impact of mucinous histology differs by tumor site, a formal interaction term (histology×location) was included in the model. The proportional hazards assumption was verified using Schoenfeld residuals. All statistical analyses were performed using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Survival analyses were conducted using the survival and survminer packages. All tests were two-sided, with statistical significance set at $p<0.05$.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki. SEER data are publicly available and de-identified; therefore, institutional review board approval and informed consent were not required. Access to the database was granted after signing the SEER data use agreement.

Results

Baseline Characteristics

A total of 286.046 patients with non-metastatic CRC were included, of whom 17.096 (6.0%) had MAC and 268.950 (94.0%) had non-mucinous tumors. Significant demographic differences were observed between the two groups; patients with MAC were older (mean age 68.7±14.1 vs. 66.4±13.4 years; $p<0.001$) and were more likely to be female (50.0% vs. 46.6%; $p<0.001$) and white (81.9% vs. 78.1%; $p<0.001$) compared to those with non-MAC tumors. Regarding tumor characteristics, MAC demonstrated a marked right-sided predominance: 63.8% of MAC cases were located in the right colon, compared with 40.8% of non-MAC tumors ($p<0.001$).

Conversely, primary rectal tumors were significantly less common in the MAC group (11.5%) than in the non-MAC group (23.8%). Histologically, mucinous tumors displayed more aggressive features at presentation, including a higher prevalence of stage III disease (41.2% vs. 34.6%; $p<0.001$) and a higher prevalence of poor differentiation (grade III-IV: 18.7% vs. 12.5%; $p<0.001$). Treatment patterns also varied: MAC patients underwent surgery more frequently (97.8% vs. 92.7%) but were less likely to receive radiotherapy than the non-MAC group (Table 1).

Multivariable Analysis and Interaction Assessment

To account for potential confounders, a multivariable Cox proportional hazards model was constructed (Table 2). After a median follow-up of 76 months, advanced age, male sex, stage III disease, high histological grade, and lack of surgery or of chemotherapy were identified as significant independent predictors of mortality ($p<0.001$ for all). The model revealed that both mucinous histology [hazard ratio (HR): 1.373, 95% confidence interval (CI): 1.326-1.422, $p<0.001$] and rectal location (vs. colon) (HR: 1.066, 95% CI: 1.027-1.106, $p=0.001$) were independent predictors of poorer OS. A significant interaction was observed between mucinous histology and rectal cancer (HR: 1.289, 95% CI: 1.203-1.381, $p<0.001$), indicating that the negative prognostic effect of MAC was significantly amplified in rectal tumors compared with colonic tumors.

Kaplan-Meier Survival Analysis

Kaplan-Meier curves, stratified by combined histology and tumor location, demonstrated significant differences in OS among the four subgroups (log-rank $p<0.001$) (Figure 2). Patients with non-mucinous tumors exhibited the most favorable survival outcomes, regardless of tumor location. In contrast, patients with mucinous histology demonstrated poorer survival, which was most pronounced in those with rectal primaries. The 5-year OS rates were 68.5% (95% CI: 68.2-68.7) for colon non-MAC; 68.7% (95% CI: 68.3-69.2) for rectum non-MAC; 61.1% (95% CI: 60.2-61.9) for colon MAC; and markedly lower for rectum MAC at 55.1% (95% CI: 52.7-57.5).

Table 1. Baseline characteristics of the study population stratified by histology

Characteristic	Total, n=286.046	MAC, n=17.096	Non-MAC, n=268.950	p-value*
Age, mean ± SD, years	66.5±13.5	68.7±14.1	66.4±13.4	**<0.001**
Age category, n (%) <65 years ≥65 years	 122.653 (42.9) 163.393 (57.1)	 6.025 (35.2) 11.071 (64.8)	 116.628 (43.4) 152.322 (56.6)	**<0.001**
Sex, n (%) Female Male	 133.810 (46.8) 152.236 (53.2)	 8.544 (50.0) 8.552 (50.0)	 125.266 (46.6) 143.684 (53.4)	**<0.001**
Race, n (%) White Other	 223.972 (78.3) 62.074 (21.7)	 13.998 (81.9) 3.098 (18.1)	 209.974 (78.1) 58.976 (21.9)	**<0.001**
Tumor location, n (%) Right colon Left colon Rectum	 120.557 (42.1) 99.510 (34.8) 65.979 (23.1)	 10.908 (63.8) 4.217 (24.7) 1.971 (11.5)	 109.649 (40.8) 95.293 (35.4) 64.008 (23.8)	**<0.001**
Stage, n (%) I-II III	 186.068 (65.0) 99.978 (35.0)	 10.058 (58.8) 7.038 (41.2)	 176.010 (65.4) 92.940 (34.6)	**<0.001**
Histological grade, n (%) I-II III-IV	 249.365 (87.2) 36.681 (12.8)	 13.902 (81.3) 3.194 (18.7)	 235.463 (87.5) 33.487 (12.5)	**<0.001**
Surgery, n (%) Performed Not performed/unknown	 266.078 (93.0) 19.968 (7.0)	 16.724 (97.8) 372 (2.2)	 249.354 (92.7) 19.596 (7.3)	**<0.001**
Radiotherapy, n (%) Yes No/unknown	 44.611 (15.6) 241.435 (84.4)	 1.638 (9.6) 15.458 (90.4)	 42.973 (16.0) 225.977 (84.0)	**<0.001**
Chemotherapy, n (%) Yes No/unknown	 103.020 (36.0) 183.026 (64.0)	 6.301 (36.9) 10.795 (63.1)	 96.719 (36.0) 172.231 (64.0)	**<0.001**

*: Student's t-test and chi-square test, as appropriate, MAC: Mucinous adenocarcinoma, SD: Standard deviation

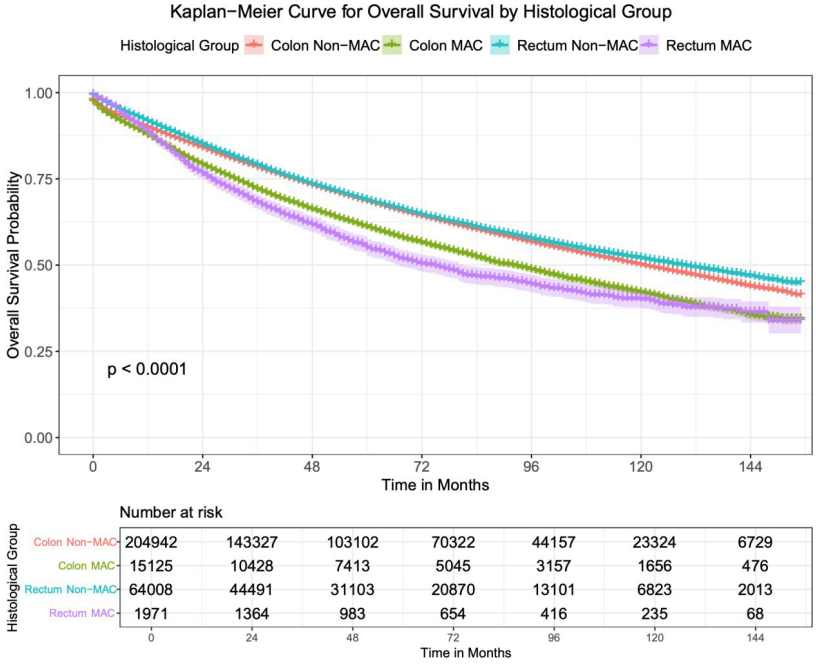


Figure 2. Kaplan-Meier estimates of overall survival stratified by combined tumor location and histology

MAC: Mucinous adenocarcinoma

Table 2. Multivariable Cox regression analysis for overall survival in non-metastatic colorectal cancer

Factor	HR	95% CI	p-value*
Age ≥65 years	2.750	2.710-2.791	**<0.001**
Male sex	1.145	1.130-1.159	**<0.001**
White race	1.044	1.028-1.060	**<0.001**
Stage III (vs. I-II)	1.935	1.905-1.965	**<0.001**
Grade III-IV (vs. I-II)	1.367	1.344-1.391	**<0.001**
Surgery not performed/unknown	3.771	3.691-3.853	**<0.001**
Radiotherapy no/unknown	0.921	0.898-0.945	**<0.001**
Chemotherapy no/unknown	1.754	1.722-1.787	**<0.001**
Rectal cancer (vs. colon)	1.066	1.027-1.106	**0.001**
Mucinous histology (vs. non-mucinous)	1.373	1.326-1.422	**<0.001**
Mucinous histology *x* rectal cancer¥	1.289	1.203-1.381	**<0.001**

*: Cox proportional hazards model, ¥: The significant interaction term (p<0.001) confirms a quantitative effect modification by rectal location on the prognostic impact of mucinous histology, CI: Confidence interval, HR: Hazard ratio

Discussion

The present study, utilizing a large population-based cohort from the SEER database, demonstrates that the prognostic impact of mucinous histology in non-metastatic CRC is significantly modified by the primary tumor location. While MAC was identified as an independent predictor of poor survival overall, our interaction analysis revealed that this adverse effect is disproportionately amplified in rectal tumors than in colonic tumors. These findings challenge the traditional view of MAC as a uniform clinical entity and underscore the necessity of site-specific risk stratification.

Our baseline analysis confirms that MAC exhibits a distinct clinicopathological profile characterized by a predilection for the right colon, female sex, advanced age, and higher tumor grade. These findings align with previous population-based studies (6,7). Consistent with the established literature, we observed that MAC presents with more advanced disease stages at diagnosis (8). Despite adjustment for confounders such as stage, grade, and receipt of treatment, MAC remained an independent adverse prognostic factor. This supports the meta-analysis by Zhang et al. (8), which identified MAC as a risk factor for poor survival even in patients treated with standard adjuvant chemotherapy, and contradicts earlier suggestions that stage correction negates the prognostic significance of mucinous histology (2).

The most critical finding of this study is the statistically significant interaction between histology and tumor site. The survival disadvantage associated with MAC was markedly more pronounced in the rectum (5-year OS: 55.1%) than in the colon (5-year OS: 61.1%); the HR for the interaction term confirmed that mucinous histology had a stronger adverse prognostic effect in rectal than in colonic tumors. This biological heterogeneity is likely driven by differences in treatment response and molecular background. Rectal cancer management relies heavily on neoadjuvant chemoradiotherapy (nCRT) to achieve local control and tumor downstaging. However, a meta-analysis by McCawley et al. (9) demonstrated that rectal MAC is associated with a significantly reduced rate of pathological complete response and tumor downstaging following nCRT, as well as higher rates of positive resection margins. The resistance of mucinous tumors to radiation and fluorouracil-based therapies may partly explain the poorer survival outcomes observed in our rectal MAC cohort (10).

Pharmacogenomic data provide a molecular basis for this chemoresistance. Reynolds et al. (11) identified that MAC harbors distinct somatic mutation profiles, including alterations in *TYMP* and *ATP7B*, which are associated with resistance to 5-fluorouracil and oxaliplatin. Furthermore, clinical studies have consistently shown that MAC patients exhibit poorer response rates to oxaliplatin and irinotecan-based regimens compared to non-mucinous subtypes (12). In the context of colon cancer, where surgery is the primary curative modality and systemic therapy is adjuvant, the impact of chemoresistance might be partially mitigated by adequate surgical resection. Conversely, in the rectum, where multimodality therapy is crucial for R0 resection, this intrinsic resistance likely contributes to the wider survival gap observed in our study.

Another contributing factor to the site-specific prognosis may be differences in the prevalence of MSI. Colonic MAC is frequently associated with MSI-high status, which, despite resistance to 5-fluorouracil, generally confers a more

favorable prognosis and responsiveness to immunotherapy (13,14). Conversely, rectal MAC generally lacks a favorable MSI-high status. Evidence suggests these tumors fall into a distinct molecular class known as consensus molecular subtype 4 (CMS4), the mesenchymal subtype, a biologically aggressive group prone to stromal invasion and poor prognosis (14). Although our dataset lacked specific molecular variables, the observed survival patterns are consistent with this molecular divergence.

The clinical implications of our findings suggest that rectal MAC requires a more aggressive or alternative therapeutic approach. Standard neoadjuvant regimens may be insufficient for this subgroup. Recent evidence suggests that optimizing surgical quality is paramount; Yin et al. (15) proposed that the standard 12-lymph-node harvest might be inadequate for MAC and recommended a threshold of at least 17 nodes to improve prognostic stratification and survival. Additionally, the development of MAC-specific nomograms that incorporate age and stage has shown promise in better predicting cancer-specific survival, allowing for more personalized follow-up and adjuvant strategies (16). For early-onset or stage III cases, despite presumed chemoresistance, systemic therapy remains associated with survival benefits and should not be withheld (17,18).

Study Limitations

This study has several strengths, including the use of a large, nationally representative database and the formal testing of a statistical interaction term. However, limitations exist. First, the SEER database lacks granular data on specific chemotherapy regimens and crucial molecular variables. The absence of data regarding mismatch repair status or MSI status, specific genetic mutations (e.g., KRAS, BRAF), and CMS classification prevents a definitive mechanistic explanation of the observed biological interaction between tumor site and histology.

Second, data regarding patient comorbidities and performance status are unavailable; given the older age of MAC patients, these unmeasured confounders may have influenced OS. Third, because the database does not record tumor recurrence patterns, we could not evaluate disease-free survival or local recurrence rates, which are particularly relevant endpoints in rectal cancer. Furthermore, the SEER classification of radiotherapy and chemotherapy into binary categories ("yes" or "no/unknown") may introduce misclassification bias. Pooling patients with unknown treatment status with genuinely untreated individuals may confound accurate estimation of the effect of these therapies on survival outcomes. Finally, histologic subtyping relied on local pathology reports without central review, potentially introducing inter-observer variability in the the quantitative definition of mucinous histology (>50% mucin content).

Conclusion

Primary tumor location significantly modifies the prognostic impact of mucinous histology in non-metastatic CRC. While mucinous histology is an adverse prognostic factor overall, its negative impact is disproportionately severe in rectal cancer compared to colon cancer. These findings suggest that rectal MAC represents a distinct and particularly aggressive clinical entity, likely driven by intrinsic resistance to standard neoadjuvant therapies and characteristic molecular features. Clinicians should consider mucinous histology and tumor location jointly when determining prognosis. Future research should focus on elucidating the molecular drivers of rectal mucinous tumors to develop targeted therapeutic strategies that overcome their inherent treatment resistance.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. SEER data are publicly available and de-identified; therefore, institutional review board approval was not required.

Informed Consent: Informed consent was not required. Access to the database was granted after signing the SEER data use agreement.

Acknowledgments

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Footnotes

Authorship Contributions

Surgical and Medical Practises: R.I., Z.A., Concept: R.I., A.O., Z.A., Ö.A., Design: R.I., A.O., Z.A., Ö.A., Data Collection or Processing: R.I., Z.A., Analysis or Interpretation: R.I., A.O., Ö.A., Literature Search: R.I., A.O., Writing: R.I., A.O.

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

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Reader Questions

Based on the manuscript: "Prognostic Impact of Mucinous Adenocarcinoma According to Primary Tumor Location in Non-metastatic Colorectal Cancer"

1. What was the primary objective of this study?

A. To compare chemotherapy regimens in colorectal cancer

B. To determine whether primary tumor location modifies the prognostic effect of mucinous histology

C. To evaluate immunotherapy outcomes in mucinous colorectal cancer

D. To compare right- and left-sided colon cancer only

Correct Answer: B. To determine whether primary tumor location modifies the prognostic effect of mucinous histology

2. What percentage of the study population had mucinous adenocarcinoma (MAC)?

A. 2%

B. 6%

C. 12%

D. 18%

Correct Answer: B. 6%

3. Which subgroup demonstrated the poorest 5-year overall survival?

A. Colon non-mucinous adenocarcinoma

B. Rectal non-mucinous adenocarcinoma

C. Colon mucinous adenocarcinoma

D. Rectal mucinous adenocarcinoma

Correct Answer: D. Rectal mucinous adenocarcinoma

4. Which statistical approach was used to evaluate whether tumor location modified the prognostic effect of mucinous histology?

A. Propensity score matching

B. Logistic regression

C. Interaction term (histology×location) in a multivariable Cox model

D. Competing-risk analysis

Correct Answer: C. Interaction term (histology×location) in a multivariable Cox model

5. According to the study findings, what was the principal clinical implication?

A. Mucinous histology has no prognostic significance.

B. Colon and rectal mucinous cancers have identical outcomes.

C. Primary tumor location significantly modifies the adverse prognostic impact of mucinous histology.

D. All mucinous colorectal cancers should receive immunotherapy.

Correct Answer: C. Primary tumor location significantly modifies the adverse prognostic impact of mucinous histology.