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Original Article

Factors Affecting Recurrence in Transverse Colon Tumors: A Single-Center Study

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Keywords: ECOG; histopathological subtype; lymphovascular invasion; MSI status; pathological T stage; perineural invasion; prognosis; recurrence factors; transverse colon cancer.

ABSTRACT

Objective: The localization of colon tumors has prognostic significance. Based on the origin of the primary mass, tumors are classified as right or left colon tumors. During embryological development, right colon tumors (RCC) originate from the mid-gut, while left colon tumors (LCC) originate from the hind-gut. Transverse colon tumors (TCC) account for 10% of all colon tumors. Due to their heterogeneous embryological development, these tumors can behave similarly to either right or left colon tumors. Our knowledge of prognosis is limited due to their inclusion in studies as right colon tumors or exclusion from studies. Our study aims to investigate whether TCC differs from right or left colon tumors by utilizing clinical, pathological, and molecular prognostic factors known to be important in colon cancer, as well as their anatomical localization.

Methods: Non-metastatic patients who underwent surgery for transverse colon cancer at our hospital were retrospectively included. Demographic data, pathological features, and treatment status were analyzed.

Results: Seventy-six patients with transverse colon tumors who underwent surgery were included in our study. No significant difference was found between recurrence and gender, comorbidity, type of surgery, stage at diagnosis, grade, pathological nodal stage, MSI status, and adjuvant treatment status ($p>0.05$). However, a significant difference was observed in the relationship between recurrence and histopathological subtype, ECOG, perineural invasion, lymphovascular invasion, and pathological T stage. Multivariable analysis of parameters associated with recurrence revealed that the presence of perineural invasion alone increased recurrence by 25 times and was found to be an independent poor prognostic factor.

Conclusion: Perineural invasion was found to be an independent prognostic indicator that predicts recurrence by 25 times in non-metastatic patients with transverse colon tumors. This result can be effectively used in predicting prognosis and making treatment decisions in patients.

INTRODUCTION

The primary tumor localization in colorectal cancers holds prognostic significance in both the local and metastatic stages.[1] Tumors are classified as right or left colon cancers based on the origin of the primary mass. Masses located proximal to the splenic flexure are considered right colon tumors, while those distal to it are classified as left colon tumors. During embryonic development, right colon tumors (RCC) originate from the mid-gut, and left colon tumors (LCC) from the hindgut, resulting in distinct anatomical, developmental, and carcinogenic differences.[2] Due to these fundamental differences, right and left colon tumors not only exhibit variations in prognosis but also demonstrate distinct surgical approaches in the local stage and predictive differences in response to therapeutic agents in the metastatic stage. In metastatic disease, anti-EGFR agents are preferred in left-sided, RAS/BRAF wild-type tumors in addition to chemotherapy, whereas Bevacizumab is used alongside chemotherapy in right-sided tumors.[3-6] However, the adjuvant treatment of surgically resected localized transverse colon tumors is similar to that of tumors originating from other parts of the colon.

The proximal two-thirds of the transverse colon, including the hepatic flexure, is considered to be of midgut origin, while the distal one-third, including the splenic flexure, is derived from the hindgut. Transverse colon cancers (TCC) account for only 10% of all colon cancers.[7] Due to their heterogeneous embryologic development, these tumors may exhibit behavior akin to either right or left colon cancers. Like right-sided tumors, TCCs are often diagnosed with bulky masses at an advanced stage (T4), as they do not present with specific symptoms until late

in their course.[8] Additionally, microsatellite instability is frequently observed in these tumors.[9]

Conversely, like LCCs, RAS/BRAF wild-type tumors in TCCs have shown good responses to anti-EGFR therapy.[10] Due to their inclusion in studies alongside right-sided tumors or their exclusion from studies altogether, there needs to be more information on the treatment responses and prognosis of these tumors.[11,12] A retrospective analysis demonstrated that tumors originating from the transverse colon have a distinct mutational profile and consensus molecular subtype (CMS) frequencies compared to left- and right-sided colorectal cancers.[9] This study highlighted that transverse colon tumors exhibit unique mutational characteristics that differentiate them from both right and left colon tumors, suggesting that they should be regarded as separate entities.

Given these considerations, our study aims to investigate whether TCC differs from right or left colon cancers by examining clinical, pathological, and molecular prognostic factors and assessing the impact of anatomical localization, which is known to be significant in colon cancer.

MATERIALS AND METHODS

Study Design and Patients

We evaluated patients diagnosed with transverse colon cancer who underwent surgery and received follow-up care at our center, between 2005 and 2024. Our study was designed as a retrospective, cross-sectional, and descriptive analysis. Transverse colon tumors were defined to include those located at the hepatic flexure and those distal to the splenic flexure. All patients included in our study were non-metastatic and aged 18 years or older. The localization of all tumors was verified through both colonoscopy and radiological imaging methods. A total of 76 patients with surgically resected transverse colon cancer who met the study's inclusion criteria were analyzed.

This study complied with the Declaration of Helsinki, and local ethics committee approval was obtained from our hospital (Approval number: 2024/010.99/6/10, approval date: 26.07.2024).

Clinical Data Collection

We collected demographic data from the study population, including sex, age, and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis. Additionally, we assessed the type of surgery performed, whether the operation was conducted as an emergency, whether patients received adjuvant therapy, and, if so, the specific drugs included in the adjuvant treatment. Histopathological data were also collected, including pT, pN, tumor grade, presence of a mucinous component, lymphovascular invasion (LVI)/perineural invasion (PNI), and tumor localization (hepatic flexure, mid-transverse colon, splenic flexure). Furthermore, metastasectomies and systemic treatments administered to patients who experienced recurrence were evaluated.

Statistical Analysis

The primary outcome variables were disease-free survival (DFS), defined as the time from diagnosis to disease recurrence or the development of distant metastasis, and overall survival (OS), defined as the time from diagnosis to death from any cause. Chi-square and Fisher's exact tests were employed to compare categorical variables such as age, gender, and ECOG performance score. The relationships between clinicopathologic parameters were initially analyzed using univariate logistic regression. The Cox regression model was applied to identify the most significant predictor variables through univariate and multivariate analyses. A p-value of <0.05 was considered statistically significant for all analyses. Statistical analyses were conducted using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA).

RESULTS

A total of 76 patients diagnosed with localized or locally advanced transverse colon cancer who underwent surgery were included in our study. The median age of the patients was 60.76 years (range: 29-86 years). Forty-seven patients (61.8%) were male, and 29 (38.2%) were female. The clinicopathologic characteristics of the patients are summarized in Table 1. Ninety percent of the patients had an ECOG score of 0 or 1. Emergency surgery due to obstruction or perforation was performed in 7 patients (9.6%). The most common pathological stages observed were pT3 (72.4%) and N0 (64.5%). The most frequently diagnosed stage at presentation was stage 2 (59.2%), followed by stage 3 (35.5%). Adenocarcinoma was the most common histological type (78.9%), with mucinous adenocarcinoma observed in 15 patients (19.7%).

Among stage 2 patients, key factors influencing the decision to administer adjuvant therapy included high microsatellite instability (MSI) rate of 26.8%, grade 3 disease in 15.5% of patients, inadequate lymph node dissection (<12 lymph nodes) in 14.7%, presence of lymphovascular invasion in 70.6%, perineural invasion in 68.2%, and pT4 tumor stage in 19.7%. Adjuvant therapy was administered to 46 patients (60.5%), with XELOX being the most commonly used regimen (65.9%). The most frequent duration of treatment was six months (68.2%).

During the follow-up period, 11 patients experienced recurrence or metastasis. Systemic treatment was administered to six of these patients. No statistically significant differences were found between recurrence and factors such as gender, comorbidity, type of surgery, stage at diagnosis, tumor grade, pathological nodal stage, MSI status, and receipt of adjuvant therapy ($p>0.05$). However, significant associations were observed between recurrence and histopathological subtype, ECOG performance score, perineural invasion, lymphovascular invasion, and pathological T stage (Table 2). In the multivariable analysis of recurrence-related parameters, the presence of perineural invasion emerged as an independent poor prognostic factor,

Table 1. Demographic and Clinical Characteristics of Patients

Varaible	n=76 (%)
Age (mean±SD)	60.76±13.3
Gender	
Female	29 (38.2)
Male	47 (61.8)
Comorbidity (n=73)	
Present	32 (43.8)
Absent	41 (56.2)
Type of surgery (n=73)	
Emergency	7 (9.6)
Elective	66 (90.4)
Histopathology	
Adenocarcinoma	60 (78.9)
Mucinous adenocarcinoma	15 (19.7)
Medullary carcinoma	1 (1.3)
Grade (n=71)	
Grade 1	11 (15.5)
Grade 2	49 (69.0)
Grade 3	11 (15.5)
Lymphovascular Invasion (n=68)	
Present	48 (70.6)
Absent	20 29.4)
Perineural Invasion (n=66)	
Present	45 (68.2)
Absent	21 (31.8)
Pathological T Stage	
T1	1 (1.3)
T2	5 (6.6)
T3	55 (72.4)
T4	15 (19.7)
Pathological N Stage	
N0	49 (64.5)
N1	20 (26.3)
N2	7 (9.2)
Lymph Node Dissection (n=75)	
<12 lymph nodes	11 (14.7)
≥12 lymph nodes	64 (85.3)
Microsatellite Instability (n=56)	
MSI-Low	13 (23.2)
MSI-Stabil	28 (50.0)
MSI-High	15 (26.8)
Stage at Diagnosis	
I	4 (5.3)
II	45 (59.2)
III	27(35.5)
Age	
>60 years	38 (50.0)
≤60 years	38 (50.0)
ECOG (n= 65)	
0	33 (50.8)
1	26 (40.0)
2	5 (7.7)
3	1 (1.5)
Adjuvant Therapy	
Received	46 (60.5)
Not received	30 (39.5)
Adjuvant Chemotherapy Regimen (n=44)	
XELOX	29 (65.9)
FOLFOX	3 (6.8)
Capecitabine	12 (27.3)
Duration of Adjuvant Therapy (n= 44)	
3 months	12 (27.3)
4 months	2 (4.5)
6 months	30 (68.2)
Recurrence	
Present	11 (14.5)
Absent	65 (85.5)

ECOG: Eastern Cooperative Oncology Group; n: number of patients; T stage: tumor stage; N stage: node stage; MSI: Microsatellite Instability; MSI-Low: Microsatellite Instability-Low MSI-Stabil: Microsatellite Stable; MSI-High: Microsatellite Instability-High; XELOX: Capecitabine + Oxaliplatin; FOLFOX: 5-Fluorouracil + Leucovorin + Oxaliplatin; SD: Standard Deviation.

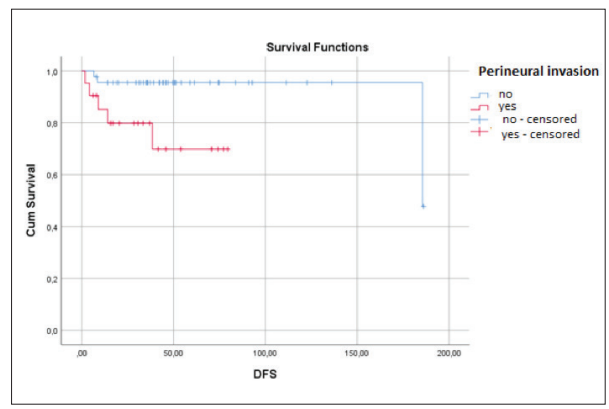

Figure 1. Kaplan_Meier curve of disease-free survival analysis according to perineural invasion.

increasing the risk of recurrence by 25-fold (HR 25.7, 95% CI: 1.23-534.8, p=0.03) (Fig. 1). The mean DFS for patients without perineural invasion was 177.7 months, compared to 60.8 months for those with perineural invasion.

DISCUSSION

The localization of the primary tumor has become increasingly important in the management of metastatic colorectal cancer. Whether the tumor is localized in the right or left colon significantly influences the approach to the disease and treatment options. However, considering the embryonic development, vascularization, and lymphatic drainage of the colon, more than a simple right-left classification may be required to capture the complexity of the disease entirely, necessitating more detailed subtyping of the colon. Research in this area is ongoing.[7,9,13]

Table 2. Analysis of Factors Influencing Disease-Free Survival (DFS) in Patients

All Patients (n=76)	Recurrence n=11	p	Multivariate analysis HR (95%CI)	p
Gender				
Female	5	0.34		
Male	6			
Comorbidity (n=73)				
Present	6	0.35		
Absent	4			
Type of Surgery (n=73)				
Emergency	1	0.72		
Elective	9			
Histopathology				
Adenocarcinoma	7			
Mucinous adenokarsinom	3	0.00*	9.57 (0.88-103.3)	0.06
Medullary Carcinoma	1			
Grade n=71				
Grade 1	2			
Grade 2	6	0.84		
Grade 3	2			
Lymphovascular Invasion n=68				
Present	6	0.03*	0.9 (0.13-6.70)	0.95
Absent	4			
Perineural Invasion n=66				
Present	5	0.01*	25.7 (1.23-534.8)	0.03*
Absent	3			
Pathological T Stage				
T1	0			
T2	1	0.02*	3.77 (0.44-32.03)	0.22
T3	5			
T4	5			
Pathological N Stage				
N0	4			
N1	5	0.08		
N2	2			
Lymph Node Dissection n=75				
<12 lymph nodes	2	0.58		
≥12 lymph nodes	8			
Microsatellite Instability n=56				
MSI-Low	2			
MSI-Stabil	4	0.89		
MSI-High	3			
Stage at Diagnosis				
I	0			
II	4	0.07		
III	7			
Age				
>60 yaş	6	0.48		
≤60 yaş	5			
ECOG n=65				
0	3			
1	5	0.00*	3.92 (0.60-25.50)	0.15
2	0			
3	1			
Adjuvant Therapy				
Received	6	0.81		
Not Received	5			
Adjuvant Chemotherapy Regimen n=44				
XELOX	3			
FOLFOX	1	0.36		
Capecitabine	1			
Duration of Adjuvant Therapy n=44				
3 months	1			
4 months	0	0.73		
6 months	4			

ECOG: Eastern Cooperative Oncology Group; n: number of patients; T stage: tumor stage; N stage: node stage; MSI: Microsatellite Instability; MSI-Low: Microsatellite Instability-Low MSI-Stabil: Microsatellite Stable; MSI-High: Microsatellite Instability-High; XELOX: Capecitabine + Oxaliplatin; FOLFOX: 5-Fluorouracil + Leucovorin + Oxaliplatin; SD: Standard Deviation.

In our study, we evaluated the impact of clinicopathological and molecular data on recurrence and survival in patients with surgically treated transverse colon cancer. Despite the retrospective nature of our study, the relatively small sample size, and the challenges in accessing detailed patient data, our patient sample was consistent with literature data.[8,9,11,14] Previous analyses have often categorized transverse colon tumors with right-sided colon tumors, yet these tumors can exhibit behaviors similar to both right- and left-sided colon cancers.[15-17] As a result, making definitive statements regarding the treatment approach and prognosis of these tumors is challenging.

Given these considerations, we included 76 patients in our study, focusing on transverse colon cancer as a separate group. Most of our patients were male (61.8%), and the mean age was 60.76 years. The most common stage at diagnosis was stage 2 (59.2%). While literature suggests that left-sided colon tumors are more prevalent in males compared to right-sided tumors, there is limited detailed data on transverse colon tumors by gender.[18,19] In our study, 15 patients (19.7%) had mucinous histology. Large studies have shown that mucinous histology is observed in 19% of right-sided colon tumors, compared to 4% of all colon tumors.[20] This finding aligns the mucinous histology rate in our study more closely with right-sided colon tumors.

There is conflicting literature on the prognosis of tumors with mucinous histology. Some studies report a negative impact on survival, while others do not find a significant effect.[21,22] In our study, the overall survival of patients with mucinous histology was similar to that of the general patient population. The small sample size in our study may explain the lack of a significant difference in survival. It is known that the MSI-H status can reach up to 30% in tumors originating from the right colon, whereas it is observed in only 2% of left-sided colon tumors.[23] The MSI-H rate in our study was 26.8%, similar to right-sided colon tumors. During the follow-up, 11 patients experienced recurrence, with factors such as ECOG performance score, pathological T stage, lymphovascular invasion, and, most notably, perineural invasion being highlighted as significant.

Two studies in the literature are particularly noteworthy in comparison to our study. A study by Küçükarda et al.[24] investigated prognostic factors in patients with surgically treated transverse colon cancer. The study excluded stage 4 patients, similar to our patient population. It was reported that transverse colon tumors showed a molecular and prognostic course more similar to right-sided colon tumors, and BRAF mutation was identified as a poor prognostic factor even in early-stage disease. However, we did not analyze BRAF mutation in early-stage patients in our study, so we cannot comment on this finding.

Another study by Roberto et al.[12] presented data on 97 patients with stage 1-4 transverse colon tumors. Unlike our study, stage 4 patients were included. Similar to our findings, most patients were male (61%), and 68% had an ECOG score of 0. The study reported an MSI-H rate of 26%, a KRAS mutation rate of 37%, and a BRAF mutation rate of 24%. High tumor grade and BRAF mutation positivity were identified as factors negatively affecting overall survival.

Our study has some limitations. First, it was a retrospective study conducted at a single oncology center. Second, we could not analyze all patients' molecular data due to the lack of comprehensive data in patient files. A large-scale, multi-center prospective study is needed to validate the prognostic factors for TCC.

Conclusion

This study provides more comprehensive insights into the clinicopathological characteristics of TCC patients. It emphasizes the role of PNI as a potential predictive factor of response to targeted treatment in patients with a worse prognosis, even from the early stages of the disease. We encourage further clinical trials, including TCC patients, to establish new treatment algorithms specific to this subgroup of colon cancer.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26.07.2024, Decision No: 2024/010.99/6/10).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: D.I.; Design: D.I.; Supervision: D.I., H.S.; Fundings: D.I., H.S.; Materials: D.I., O.K.; Data collection &/or processing: D.I., O.K.; Analysis and/or interpretation: D.I., H.S.; Literature search: D.I.; Writing: D.I., O.K.; Critical review: D.I., H.S.

Conflict of Interest

None declared.

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Transvers Kolon Tümörlerinde Nükse Etki Eden Faktörler: Tek Merkez Deneyimi

Amaç: Kolon tümörlerinde primer kitlenin lokalizasyonu prognostik önem göstermektedir. Primer kitlenin orijin aldığı bölgeye göre sağ veya sol kolon tümörü tanımı kullanılmaktadır. Embriyolojik gelişim esnasında sağ kolon tümörleri (RCC) mid-gut; sol kolon tümörleri (LCC) ise hind-gut'tan köken alırlar ve lokal evrede cerrahi yaklaşımlar, metastatik evrede ise kullanılan tedavi ajanlarına karşı prediktif farklar izlenmektedir. Transvers kolon tümörleri (TCC) tüm kolon tümörlerinin yüzde 10'luk kısmını oluşturmaktadır. Bu tümörler, heterojen embriyolojik gelişimleri nedeniyle sağ veya sol kolon gibi davranış gösterebilirler. Klinik çalışmalarda çoğunlukla sağ kolon tümörlerine dahil edilmeleri ya da çalışmadan dışlanmaları nedeniyle prognoz hakkında net bilgimiz bulunmamaktadır. Çalışmamızda kolon kanserinde önemini bildiğimiz klinik, patolojik ve moleküler prognostik faktörleri ve anatomik lokalizasyonunun fark gösterip göstermediğini kullanarak TCC'nin sağ veya sol kolon tümörlerinden farklı olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Hastanemizde transvers kolon kanseri nedeniyle ameliyat olmuş nonmetastatik hastalar retrospektif olarak dahil edildi. Demografik veriler ve patolojik özellikleri ile tedavi durumları incelendi.

Bulgular: Çalışmamıza transvers kolon yerleşimli ameliyat edilmiş 76 hasta alındı. Nüks ile cinsiyet, komorbidite, operasyon şekli, tanı anı evresi, grade, patolojik nod evresi, MSI durumu ve adjuvan tedavi durumunun ilişkisi incelendiğinde anlamlı fark bulunmadı ($p>0.05$). Histopatolojik alt tip, ECOG, perinöral invazyon, lenfovasküler invazyon ve patolojik T evresi ile nüks ilişkisi incelediğinde anlamlı fark olduğu görüldü. Nüks ile ilişkisi olan parametrelerin multivariable analizinde ise perinöral invazyon varlığının tek başına nüksü 25 kat artırıp bağımsız kötü prognostik faktör olduğu bulundu.

Sonuç: Çalışmamızda nonmetastatik opere transvers kolon yerleşimli kolon kanserli hastalarda perinöral invazyonun nüksü 25 kat öngören bağımsız prognostik bir belirteç olduğu bulundu. Bu sonuç, hastalarda prognozu öngörmek ve tedavi kararı verme sürecinde etkili kullanılabilir.

Anahtar Sözcükler: ECOG; histopatolojik alt tip; lenfovasküler invazyon; MSI durumu; nüks faktörleri; patolojik T evresi; perinöral invazyon; prognoz; transvers kolon kanseri.