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ORIGINAL RESEARCH

Prognostic Factors for Survival in Transverse Colon Cancers

Ahmet Küçükarda[1] · Ali Gökyer[1] · Sezin Sayın[2] · İvo Gökmen[1] · Erkan Özcan[1] · Osman Köstek[3] · Muhammet Bekir Hacıoğlu[1] · Sernaz Uzunoğlu[1] · İrfan Çiçin[1] · Bülent Erdoğan[1]

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Abstract

Background Transverse colon cancer (TCC) is a rare condition that accounts for 10% of all colon cancers. TCC was accepted more likely right-sided colon cancers. We aimed to investigate whether TCC differs from other colon tumors by using clinical, pathological, and molecular prognostic factors known to be important in colon cancer and if it differs in its own anatomical structure.

Patients and Methods We evaluated local and locally advanced TCC patients between 2007 and 2020 years for demographics data, symptoms, treatment status, and histopathological and molecular features.

Results Overall, 107 TCC patients were included in this study. According to the molecular data analysis of 44, 35, and 23 patients for MSI, RAS, and BRAF status, respectively, 7 (15.9%) were MSI-H, 13 (37.1%) were RAS mutant, and 11 (47.8%) had BRAF V600E mutation. The median follow-up time was 31.5 months. Median disease-free survival (DFS) was 5.19 months, and median OS was 88.3 months for the whole study population. The tumor stage was the most significant prognostic factor for DFS and OS. Although BRAF mutation was not a significant marker for DFS, it was an independent prognostic marker for OS (HR 3.90 95% CI 1.42–10.7). There were no statistically significant differences between proximal two-thirds and distal one-third tumor location.

Conclusion TCC has molecular features and prognostic factors more likely RCC and no differences between proximal and distal sub-parts. BRAF V600E mutation status is an independent predictor of survival even in the early stages of TCC.

Keywords Transverse colon cancer · Prognosis · Survival · BRAF V600E · Pathological stage

Introduction

Although the colon is a single organ, it consists of many parts that are quite different from each other in terms of anatomical, histological, and molecular features. During embryological development, the right-sided colon develops from the mid-gut, and the left side arises from the hind-gut [1]. The transverse colon is between hepatic flexure to splenic flexure of the colon. The proximal two-thirds considered as right while the latter third was left colon [2].

While colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths [3], transverse colon cancer (TCC) is a rare condition that accounts for 10% of all [4]. In recent years, researchers have focused on primary tumor location firstly on metastatic disease stages, and then other studies showed that it is essential also in localized stages [5, 6]. Like right-colon cancers (RCC), TCC shows a poor prognosis; symptoms are insidious and non-specific. Diagnosis is often delayed, and cancers present as bulky T4 lesions in 20–40% and present a microsatellite instability (dMMR/MSI-H) status in many cases [7, 8]. On the other side, 30–50% of transverse cancers involve infiltrating, constricting lesions that may cause obstruction or perforation, and RAS/RAF wild metastatic TCC cases more responsive anti-EGFR treatments like left colon cancers (LCC) rather than RCC [9, 10]. If it is accepted as a unique disease, only one study shows poor tumor differentiation and BRAF mutation status are independent prognostic factors [11].

✉ Ahmet Küçükarda
ahmetkucukarda22@gmail.com

[1] Division of Medical Oncology, Department of Internal Medicine, Trakya University School of Medicine, Edirne, Turkey

[2] Trakya University School of Medicine, Edirne, Turkey

[3] Edirne Sultan, 1 Murat State Hospital, Edirne, Turkey

As shown in previous studies, sidedness is a surrogate prognostic and predictive marker for localized or metastatic CRC patients [5, 6]. Most studies have been used to assess TCC as part of the RCC or excluded them due to their heterogeneous presentation [5, 11]. However, according to its embryological origins, tumors arising from the transverse colon may share characteristics with RCC and LCC [12]. Thus, it is still not fully explained if TCC behavior is more right-sided rather than left-sided or has its clinicopathological features and a different clinical outcome.

The primary treatment of localized colon cancer is surgical resection [13]. There were only randomized controlled trials about surgical resection of TCC, and these trials are inadequate for oncological outcomes of patients because they do not consist of adjuvant and recurrence treatments [14, 15]. Based on current evidence from these trials, survival outcomes are equivalent between segmental resection and extended hemicolectomy except for the surgical complications of patients [15, 16].

For all these reasons, in this study, we aimed to investigate whether TCC differs from other colon tumors by using clinical, pathological, and molecular prognostic factors known to be important in colon cancer and if it differs in its own anatomical structure.

Materials and Methods

Study Design and Patient's Features

Our study design was retrospective, descriptive, and cross-sectional. We evaluated TCC patients between 2007 and 2020 years for this trial at the Trakya University Hospital, Department of Medical Oncology. TCC was defined as a colon tumor originating distally to the hepatic flexure and proximally to the splenic flexure. All patients were above 18 years old and had surgery for local and locally advanced diseases. They had pre-operative radiological imaging and colonoscopy and verified tumor in transverse colon localization during surgery and pathological examination. Transverse colon was divided at three parts. Proximal part was defined as two-thirds of total transverse colon, and distal part was defined as the last one-third of total length. Patients diagnosed with de novo metastatic and inoperable locally advanced TCC, patients who had hepatic and splenic flexure-originated tumors, and missing data required for the study were excluded. Totally 107 of 149 patients were included according to inclusion and exclusion criteria.

This study was conducted in compliance with the postulates of the Declaration of Helsinki, and the local ethical committee of Trakya University Hospital approved the trial.

Clinical Data Collection

We evaluated the study population for demographics data (sex, age, Eastern Cooperative Oncology Group (ECOG) performance status at the time of primary diagnosis), symptoms at the clinical onset, surgical treatment method (extended hemicolectomy or transverse colectomy), and adjuvant therapy status. Both histopathological (pT, pN, the grade of differentiation, mucinous component, lymphovascular invasion (LVI)/perineural invasion (PNI), and tumor localization—proximal or distal transverse colon) and molecular (KRAS, BRAF V600E, and MSI) features were retrieved from the patient's medical files.

Statistical Analysis

Outcome variables were disease-free survival (DFS), defined as the time from the diagnosis to disease recurrence or development of distant metastasis, and overall survival (OS), defined as the time between diagnosis and death for any cause. Chi-square and Fisher exact tests were used to compare categorical variables such as age, gender, and ECOG performance score. The relation between clinicopathologic parameters was first analyzed using univariate logistic regression. The Cox regression model was applied to identify the best predictor variables using univariate and multivariate analyses. The significant p-value was < 0.05 for all. IBM SPSS Statistics 23.0 (IBM Corp., Armonk, New York, USA) was used for statistical analyses.

Results

Patient's Characteristics

Overall, 107 local and locally advanced TCC patients were included in this study. Their clinicopathological features were summarized in Table 1. The median age was 63 years (range 55–72 years). Fifty-nine patients (55.1%) were male, and 74 (64.4%) had an ECOG performance score of 0 or 1. Only 19.6% presented with obstruction or perforation, and 84 (78.5%) of them have had an extended hemicolectomy. Thirty-seven (34.6%) cases have diagnosed at stage III, and 60 (56.1%) patients received adjuvant chemotherapy after curative resection.

The tumors were more frequently pT3 (55.1%) than pT4 (28.1%), with lymphovascular (54.2%) and perineural invasion (18.7%). According to WHO classification, most of the cases were classified as well (21.5%), moderate (57.9%), and poorly/undifferentiated (20.6%), respectively, regardless of mucinous histology (26.2%). According to the molecular

Table 1 Clinicopathologic features of study population and comparison of groups according to tumor localization

Parameters	All patients ($n=107$)	Proximal 2/3 localization ($n=62$)	Distal 1/3 localization ($n=45$)	*P* value
Age, years, *n* (%)				
Median (IQR)	63 (55–72)	63 (55–74)	63 (57.5–68.5)	0.84
≤ 63	56 (52.3)	33 (53.2)	23 (51.1)	
> 63	51 (47.7)	29 (46.8)	22 (48.9)	
Gender, *n* (%)				
Female	48 (44.9)	32 (51.6)	16 (35.6)	0.12
Male	59 (55.1)	30 (48.4)	29 (64.4)	
ECOG performance score, *n* (%)				
ECOG 0–1	74 (69.2)	42 (67.7)	32 (71.1)	0.83
ECOG ≥ 1	33 (30.8)	20 (32.3)	13 (28.9)	
Tumor onset, *n* (%)				
Anemi/pain/weight loss	86 (80.4)	49 (79.0)	37 (82.2)	0.81
Obstruction/perforation	21 (19.6)	13 (21.0)	8 (17.8)	
Primary surgery type, *n* (%)				
Extended hemicolectomy	84 (78.5)	48 (77.4)	36 (80.0)	0.82
Transverse colectomy	23 (21.5)	14 (22.6)	9 (20.0)	
Pathological TNM stage, *n* (%)				
Stage I	17 (15.9)	10 (16.1)	7 (15.6)	0.59
Stage II	53 (49.5)	33 (53.2)	20 (44.4)	
Stage III	37 (34.6)	19 (30.6)	18 (40.0)	
Pathological tumor size, *n* (%)				
T1	4 (3.7)	3 (4.8)	1 (2.2)	0.33
T2	14 (13.1)	7 (11.3)	7 (15.6)	
T3	59 (55.1)	38 (61.3)	21 (46.7)	
T4	30 (28.1)	14 (22.6)	16 (35.6)	
Pathological node status, *n* (%)				
N0	69 (64.5)	43 (69.4)	26 (57.8)	0.43
N1	31 (29.0)	15 (24.2)	16 (35.6)	
N2	7 (6.5)	4 (6.5)	3 (6.7)	
Mucinous histology, *n* (%)				
No	79 (73.8)	45 (72.6)	34 (75.6)	0.83
Yes	28 (26.2)	17 (27.4)	11 (24.4)	
Tumor differentiation, *n* (%)				
Grade 1	23 (21.5)	14 (22.6)	9 (20.0)	0.22
Grade 2	62 (57.9)	32 (51.6)	30 (66.7)	
Grade 3	22 (20.6)	16 (25.8)	6 (13.3)	
Lymphovascular invasion, *n* (%)				
No	49 (45.8)	28 (45.2)	21 (46.7)	0.99
Yes	58 (54.2)	34 (54.8)	24 (53.3)	
Perineural invasion, n(%)				
No	87 (81.3)	52 (83.9)	35 (77.8)	0.46
Yes	20 (18.7)	10 (16.1)	10 (22.2)	
Dissected lymph node, *n* (%)				
< 12	58 (54.2)	31 (50.0)	27 (60.0)	0.33
≥ 12	49 (45.8)	31 (50.0)	18 (40.0)	
Adjuvant chemotherapy, *n* (%)				
No	60 (56.1)	38 (61.3)	22 (48.9)	0.24
Yes	47 (43.9)	24 (38.7)	23 (51.1)	
Microsatellite instability, *n* (%)				
MSS	37 (34.6)	22 (35.5)	15 (33.3)	0.44
MSI-H	7 (6.5)	3 (4.8)	4 (8.9)	
Missing value	63 (58.9)	37 (59.8)	26 (57.8)	
RAS status, *n* (%)				
Wild	22 (20.6)	13 (21.0)	9 (20.0)	0.99
Mutant	13 (12.1)	7 (11.3)	6 (13.3)	
Missing value	72 (67.3)	42 (67.7)	30 (66.7)	

data analysis of 44, 35, and 23 patients for dMMR (mismatch repair deficiency), RAS, and BRAF status, respectively, 7 (15.9%) were MSI-H, 13 (37.1%) were RAS mutant, and 11 (47.8%) had BRAF V600E mutation.

When we compared patients according to proximal two-thirds or distal one-third tumor location, there were no statistically significant differences between the two groups, as seen in Table 1.

Survival Analysis

The median follow-up time was 31.5 months (range 9.8–71.8 months). At the date of the last follow-up day, 55 (51.1%) patients had disease progression, and 49 (45.8%) of them died. Median DFS was 5.19 months (95% CI 2.8–7.6), and median OS was 88.3 months (95% CI 73.6–103.0) for the whole study population.

The pathological tumor stage was the most significant prognostic factor for DFS with an HR 2.41 (95% CI 1.34–4.34) (Fig. 1B). Patients with stage I tumors had an excellent DFS with a median of 25 months (95% CI 20.8–29.3), while stage III patients had a median of 3.2 months (95% CI 2.9–3.5) ($p < 0.01$). BRAF mutant cases showed the worst DFS with a median of 2.6 months (95% CI 1.0–4.2) against the BRAF wild group (12.7 months (95% CI 0.1–32.2)), despite not statistically significant ($p = 0.10$) (Fig. 1C).

In the univariate analysis for DFS, ECOG performance score 0–1, disease stage I–II, non-mucinous histology, and no perineural invasion were those variables that significantly predict DFS. However, in multivariate analysis, only ECOG performance score (HR 2.07, 95% CI 1.12–3.85) and stage of disease (HR 1.97, 95% CI 1.07–3.64) were independent prognostic factors for DFS (Table 2).

Although BRAF mutation was not a significant marker for DFS, it was a statistically significant marker for OS. BRAF V600E mutant patients compared to those with BRAF V600E wild, median OS was 2.0 months (95% CI 0.1–7.3) versus 16.6 months (95% CI 7.7–73.0) ($p < 0.01$) (Fig. 1F). Also, MSS cases had a worse median OS (25.0 months versus 105.5 months) than MSI-H cases, but not statistically significant ($p = 0.11$) (Fig. 1D).

In the univariate analysis for OS, age < 63 years, ECOG performance score 0–1, presentation without obstruction or perforation, disease stage I–II, non-T4 tumor size, well or moderate tumor grade (G1–2), no PNI, treated with adjuvant chemotherapy, and BRAF wild status were significantly predicting OS. Nevertheless, in multivariate analysis, having stage I or II diseases (HR 15.22 95% CI 1.96–118.1) and being BRAF V600E wild (HR 3.90 95% CI 1.42–10.7) were only independent predictors of OS (Table 2) (Fig. 2).

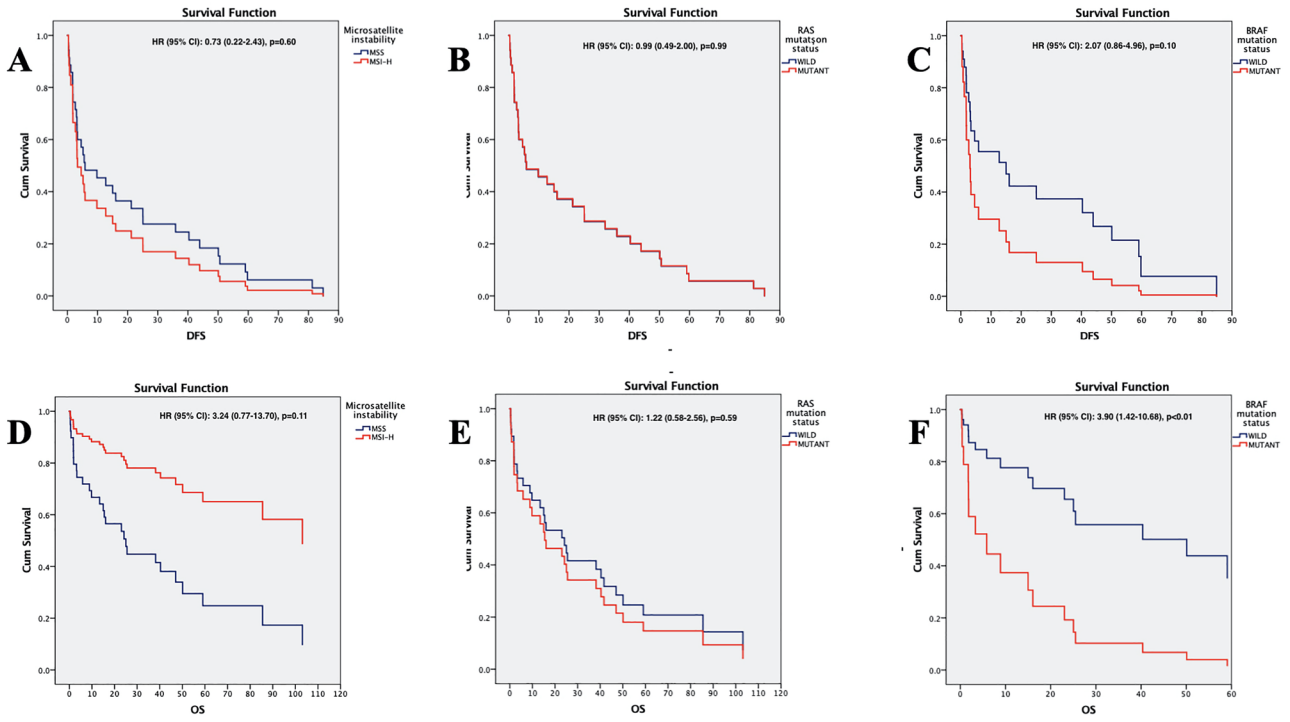

Fig. 1 Kaplan Meier survival analyses for disease-free survival and overall survival according to molecular features. **A** Microsatellite instability status (DFS). **B** RAS mutation status (DFS). **C** BRAF V600E mutation status (DFS). **D** Microsatellite instability status (OS). **E** RAS mutation status (OS). **F** BRAF V600E mutation status (OS)

Table 2 Univariate and multivariate analysis of disease free survival and overall survival in study population

	Disease free survival analyses				Overall survival analyses			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI, lower–upper)	*P* value	HR (95% CI lower–upper)	*P* value	HR (95% CI lower–upper)	*P* value	HR (95% CI lower–upper)	*P* value
Age								
≤ 63	Ref	0.17			Ref	< 0.01	Ref	0.87
> 63	1.51 (0.84–2.73)				5.02 (2.62–9.59)		1.16 (0.20–6.84)	
Gender								
Female	Ref	0.47			Ref	0.16		
Male	1.22 (0.71–2.11)				1.52 (0.85–2.72)			
ECOG								
0–1	Ref	< 0.01	Ref	0.02	Ref	< 0.01	Ref	0.06
> 1	2.26 (1.31–3.92)		2.07 (1.12–3.85)		7.46 (4.17–13.3)		6.29 (0.93–42.5)	
Symptoms								
Other symptoms	Ref	0.62			Ref	< 0.01	Ref	0.87
Obstruc./Perforation	1.15 (0.65–2.04)				3.70 (2.08–6.59)		1.16 (0.20–6.84)	
Surgery								
Extended hemicol	Ref	0.99			Ref	0.34		
Transverse colectomy	1.01 (0.53–1.92)				1.37 (0.71–2.64)			
Stage								
Stages I–II	Ref	< 0.01	Ref	0.03	Ref	< 0.01	Ref	0.01
Stage III	2.41 (1.34–4.34)		1.97 (1.07–3.64)		2.46 (1.40–4.33)		15.22 (1.96–118.1)	
T stage								
T1–3	Ref	0.22			Ref	< 0.01	Ref	0.04
T4	1.41 (0.81–2.44)				2.15 (1.21–3.81)		0.21 (0.05–0.92)	
Mucinous histology								
No	Ref	0.04	Ref	0.11	Ref	0.09		
Yes	1.89 (1.04–3.44)		1.69 (0.89–3.20)		1.70 (0.92–3.13)			
Tumor grade								
Grades 1–2	Ref	0.92			Ref	0.04	Ref	0.52
Grade 3	0.97 (0.53–1.76)				1.91 (1.03–3.56)		0.55 (0.09–3.37)	
LVI								
No	Ref	0.08			Ref	0.16		
Yes	1.67 (0.95–2.95)				1.51 (0.85–2.68)			
PNI								
No	Ref	0.03	Ref	0.85	Ref	0.03	Ref	0.05
Yes	1.97 (1.05–3.67)		1.07 (0.52–2.21)		2.02 (1.07–3.83)		7.31 (0.98–54.33)	
Dissected LAP								
≥ 12	Ref	0.60			Ref	0.16		
< 12	1.16 (0.67–2.00)				1.51 (0.85–2.69)			
Adjuvant Chemo								
Yes	Ref	0.12			Ref	0.02	Ref	0.09
No	1.55 (0.89–2.70)				2.06 (1.13–3.74)		4.70 (0.76–28.98)	
MMR Status								
MSS	Ref	0.60			Ref	0.11		
MSI–H	1.38 (0.41–4.62)				3.24 (0.77–13.70)			
RAS Status								
Wild	Ref	0.98			Ref	0.60		
Mutant	0.99 (0.49–2.00)				1.22 (0.58–2.57)			
BRAF Status								
Wild	Ref	0.10			Ref	< 0.01	Ref	0.02
Mutant	2.07 (0.86–4.96)				3.90 (1.42–10.7)		7.30 (1.08–49.40)	

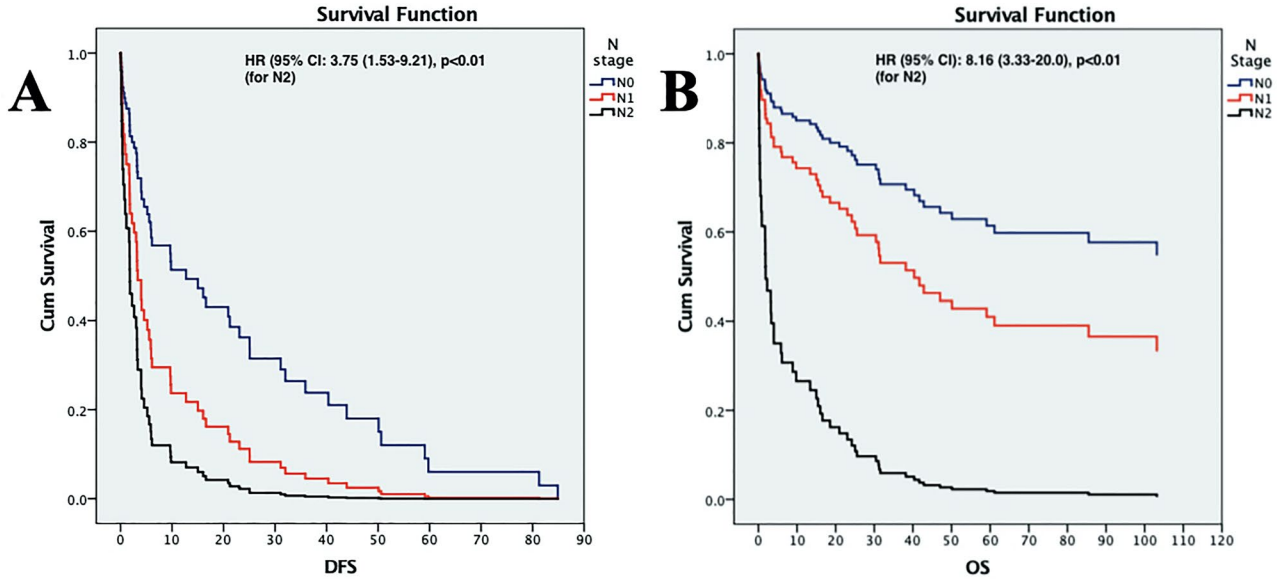

Fig. 2 Kaplan Meier survival analyses for disease-free survival and overall survival according to nodal status (N stage). **A** DFS. **B** OS

According to the disease stage, when we looked at the effect of adjuvant treatment on DFS and OS, it differs. In the stage II cases, not statistically significant, but 5.5 months DFS (9.6 vs. 4.1 months) and 24.4 months OS (112.4 vs. 88.0 months) were gained. On the other hand, in stage III patients, DFS was better with adjuvant therapy (median 6.0 vs. 1.7 months, $p < 0.01$). The most common benefit was for OS with 99.3 months vs. 3.5 months, and this was statistically significant (HR 95% CI 20.74, 6.35–67.74, $p < 0.01$) (Fig. 3) (Table 2).

Pathological nodal involvement (N stage) was significantly associated with DFS (HR 3.75, 95% CI 1.53–9.21, $p < 0.01$) and OS (HR 8.16, 95% CI 3.33–20.0, $p < 0.01$) in the univariate analysis. However, it was not included in the multivariate models and table because pN covariates linearly with TNM stage III (Fig. 2).

When we compared patients according to proximal two-thirds or distal one-third tumor location, there were no statistically significant differences between the two groups, as seen in Table 1 and Fig. 4.

Correlation Between BRAF Status with Clinicopathologic Parameters

BRAF V600E mutation status was one of the most important prognostic and predictive factors for survival, as seen above. So we compared BRAF V600E wild and mutant groups according to their clinicopathologic features and

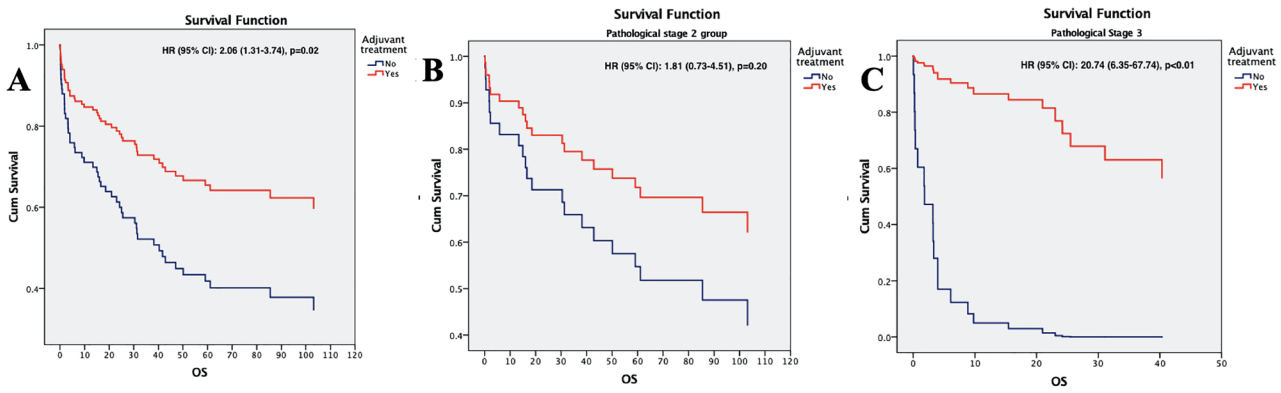

Fig. 3 Kaplan Meier survival analyses of adjuvant treatment effect on overall survival according to disease pathological stage. **A** All study population. **B** Pathological stage II group. **C** Pathological stage III group

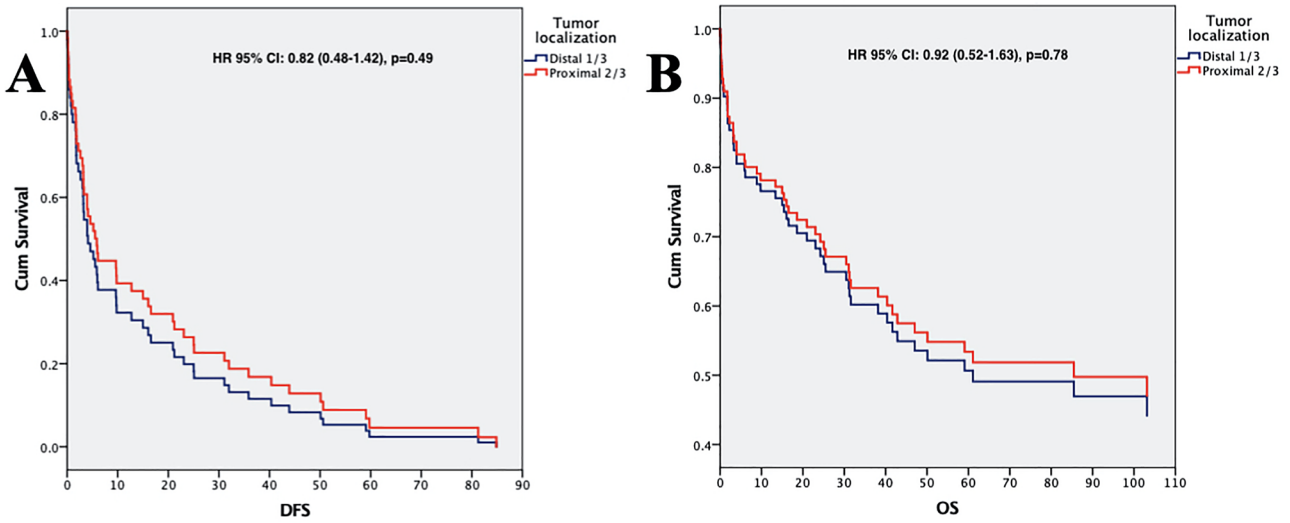

Fig. 4 Kaplan Meier survival analyses for disease-free survival and overall survival according to tumor location. **A** DFS. **B** OS

reported in Table 3. There were no statistically significant differences between the two groups. However, as seen in the table, BRAF V600E mutant cases were older (81.8%), ECOG performance status was worse (72.7% of them were ECOG ≥ 1), and primarily low or moderate grade (90.9%) and non-mucinous (90.9%) tumors had BRAF mutation. According to molecular analysis, BRAF V600E mutant cases were frequently MSS (90.9%) and RAS wild (81.8%) (Table 3).

Discussion

To the best of our knowledge, this was the first study to investigate the prognostic factors and survival outcomes after curative resection for localized TCC patients from the oncological point of view. This research consists of 107 patients, and we found no statistically significant differences between proximal and distal sides of the transverse colon in its own anatomical structure. ECOG performance score, nodal involvement (N stage), and pathological tumor stage are the independent prognostic factor for DFS. Although the stage of the disease is an essential predictor of OS, too, BRAF V600E mutation that was positive for 47.8% of TCC cases in this study is the most significant molecular predictor of survival regardless of the TNM stage.

We used clinical, pathological, and molecular prognostic determinants for CRC patients either in diagnosis or in the metastatic stages in daily clinical practice. Many series reports an adverse prognostic impact of clinical obstruction and gross perforation at the time of diagnosis [17, 18]. Mainly LCC presents with these symptoms, and these cases generally have more advanced stage and unfavorable histologic features [18]. In our study, 21 (19.6%) cases present with obstruction or perforation, and 13 (61.9%) of them from proximal transverse localization contrary to expectations. Our patients whose tumor occurred with obstruction or perforation showed a worse OS than the other tumor manifestations (HR 3.70, 95% CI 2.08–6.59, $p > 0.01$).

Pathological factors like local tumor extension (T stage), nodal involvement (N stage), presence of LVI or PNI, and poor differentiation of tumor are significant predictors of oncological outcomes, especially in stage II patients [19–22]. Also, nodal status is important for TNM staging of disease. The presence of nodal involvement changes the stage from II to III [23]. Our patients diagnosed with mostly T3 (55.1%)–T4 (28.1%) tumors, 69 (64.5%) of them had no nodal metastasis, 22 (20.6%) poor differentiated, 58 (54.2%) LVI, and 87 (81.3%) PNI positive. From these factors, only nodal status is an independent predictor of both DFS and OS in our research.

The different epidemiological and clinicopathological features of CRCs based on their anatomical location are also supported by a different pattern of the molecular profile from right-side to left-side colon [24]. We know that approximately 30% of all RCC are dMMR/MSI-H as recognized by the presence of MSI-H phenotype, whereas only 2% of LCC show the MSI-H phenotype [25]. In the present study, 7 (15.9%) of 44 patients were MSI-H. These data suggest that the transverse colon is more like RCC in terms of immune-phenotype. It is essential to consider the use of immune checkpoint inhibitors in the first-line setting and avoid useless 5-fluorouracil-based chemotherapy in MSI-H TCC [26].

From a molecular perspective, 22 (62.8%) of 35 patients were KRAS wild and 11 (47.8%) of 23 tumors BRAF

Table 3 Correlation between BRAF statuses with clinicopathologic parameters

Parameters	BRAF wild ($n=12$)	BRAF mutant ($n=11$)	P value
Age, years, *n* (%)			
≤63	6 (50.0)	2 (18.2)	0.19
>63	6 (50.0)	9 (81.8)	
Gender, *n* (%)			
Female	4 (33.3)	6 (54.5)	0.41
Male	8 (66.7)	5 (45.5)	
ECOG performance score, *n* (%)			
ECOG 0–1	9 (75.0)	3 (27.3)	0.03
ECOG ≥ 1	3 (25.0)	8 (72.7)	
Tumor onset, *n* (%)			
Anemi/pain/weight loss	8 (66.7)	8 (72.7)	0.99
Obstruction/perforation	4 (33.3)	3 (27.3)	
Tumor localization, *n* (%)			
Proximal two-thirds location	6 (50.0)	6 (54.5)	0.99
Distal one-thirds location	6 (50.0)	5 (45.5)	
Pathological TNM stage, *n* (%)			
Stage I–II	5 (41.7)	7 (63.6)	0.41
Stage III	7 (58.3)	4 (36.4)	
Pathological tumor size, *n* (%)			
T1–3	6 (50.0)	7 (63.6)	0.68
T4	6 (50.0)	4 (36.4)	
Pathological node status, *n* (%)			
N−	5 (41.7)	7 (63.6)	0.41
N+	7 (58.3)	4 (36.4)	
Mucinous histology, *n* (%)			
No	9 (75.0)	10 (90.9)	0.59
Yes	3 (25.0)	1 (9.1)	
Tumor differentiation, *n* (%)			
Grade 1–2	8 (66.7)	10 (90.9)	0.32
Grade 3	4 (33.3)	1 (9.1)	
Lymphovascular invasion, *n* (%)			
No	4 (33.3)	7 (63.6)	0.22
Yes	8 (66.7)	4 (36.4)	
Perineural invasion, n(%)			
No	10 (83.3)	6 (54.5)	0.19
Yes	2 (16.7)	5 (45.5)	
Microsatellite instability, *n* (%)			
MSS	12 (100)	10 (90.9)	0.48
MSI-H	0 (0)	1 (9.1)	
RAS status, *n* (%)			
Wild	7 (58.3)	9 (81.8)	0.37
Mutant	5 (41.7)	2 (18.2)	

V600E mutant, respectively. A high rate of KRAS wild-type tumors was more like LCC, while the high prevalence of BRAF V600E mutations was more similar with RCC [8, 24]. KRAS mutations can be identified in 12 to 75% of CRC; they have been independently associated with a worse prognosis either locally or in metastatic settings [27]. In our study, being KRAS wild or mutant did not affect the survival (HR 1.22, 95% CI 0.58–2.57, $p=0.60$). According to the literature, BRAF mutation is a strong negative prognostic marker for early-stage and advanced/recurrent tumors, especially in non-MSI-H tumors regardless of sidedness and other molecular factors. However, this negative effect on prognosis seems more evident in RCC than LCC [28, 29]. Our study reported that the situation is actual for TCC. Our BRAF V600E mutant cases had a worse prognosis when compared with wild-type tumors regardless of MSS/MSI-H status compatible with literature (HR 7.30, 95% CI 1.08–49.40, $p=0.02$).

There is no consensus on the appropriate extent of surgical resection for tumors of TCC. A conservative treatment, which is transverse colectomy, is safe and has similar oncological results and postoperative complication rates compared to extended colectomy [15, 16]. Most of the patients were treated with extended right or left hemicolectomy in our population, and there were no statistically significant differences between the two surgical methods compatible with literature (HR 1.37, 95% CI 0.71–2.64, $p = 0.34$).

In literature, there was only one recently published study evaluating TCC patient's oncological outcomes. In the retrospective analysis of Roberto M et al., 97 stages I–IV TCC patients were reviewed and most of TCC cases were male (61%), with 70 years old (62%), and good performance status (ECOG PS 0, 68%). Forty (48%) tumors were poorly/undifferentiated regardless of mucinous component (30%). Molecular data, 8 (26%), 45 (63%), and 14 (24%) were MSI-H, KRAS wild-type, and BRAF V600E mutant, respectively. Colon obstruction/perforation (HR = 2.65, 95% CI 1.01–7.01) and BRAF mutant (HR = 3.03, 95% CI 0.97–9.50) cases showed a worst, despite not statistically significant, DFS. Only tumor grade differentiation (HR = 5.26, 95% CI 1.98–14.01) and BRAF mutation status (3.71, 95% CI 1.07–12.89) were independent prognostic factors for OS [11]. When we compared our research, the study population has similar clinicopathological characteristics except for stage IV tumors and tumor differentiation. MSI-H rates were low (15.9%), and BRAF V600E mutation rates were high (47.8%) in our study. Both studies show that the presence of BRAF V600E mutation significantly worsens oncological outcomes.

There were some limitations in our present study. First, this was a retrospective study performed in a single oncology center. Second, we could not analyze all patient's molecular data because of largely missing data in patients' files. Third, we did not evaluate the recurrent or metastatic state treatments of patients, and that might limit the accuracy of our results. A further large-scale multi-center prospective study is required to validate the prognostic factors for TCC.

Conclusion

The present study demonstrated that TCC has molecular features and prognostic factors more likely RCC and no differences between proximal and distal sub-parts. Although pathological tumor stage is the most common prognostic factor for oncological outcomes, BRAF V600E mutation status is an independent predictor of survival even in the early stages of TCC. This situation may change treatment algorithms of TCC patients with the validation of randomized controlled clinical trials.

Author Contribution AK: data analysis/manuscript writing/editing, AG, SS: Manuscript writing/editing, İG: Data collection, EÖ, OK: Data collection/management, MBH: Manuscript writing/editing, BE: Manuscript writing/editing, SU: Manuscript writing/editing, İÇ, BE: Supervision/Project development.

Declarations

Ethical Approval Institutional Review Board approval was obtained. All procedures performed in studies involving participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and is later amendments or comparable ethical standards.

Conflict of Interest The authors declare no competing interests.

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