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Assessment of tumor location in adjuvant treatment decision for stage II colon cancer

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ABSTRACT

Aims: In stage II colon cancer, the aim is to evaluate the impact of tumor location and other clinicopathological factors on prognosis and survival.

Methods: The study included a total of 93 patients diagnosed with stage II colon cancer between January 2018 and December 2022, comprising 41 females and 52 males. Clinicopathological factors related to the patients were retrospectively investigated. Factors found to be significant in univariate analysis were further evaluated through multivariate analysis to identify independent factors.

Results: As a result of univariate analysis, variables such as tumor location (right-left colon), perineural invasion, surgical margin, intestinal obstruction, and lymph node dissection were found to be statistically significant for the risk of death ($p<0.05$). These variables, identified as significant in univariate analyses, were included in the multivariate cox regression model. According to the result of the multivariate cox regression model, individuals with intestinal obstruction were determined to have a 7.07 times higher risk of death (HR: 7.07; 95% CI: 2.42-20.62; $p<0.001$).

Conclusion: We observed an association between left colon tumors in stage II patients and poorer survival, and we noted that intestinal obstruction has an independent prognostic effect on survival.

Keywords: Adjuvant chemotherapy, colon cancer, prognosis, tumor localization

INTRODUCTION

Colorectal cancers (CRC) rank as the third most common cancer worldwide and represent the second leading cause of cancer-related deaths. Tumors located proximal to the splenic flexure are classified as right-sided, whereas those situated at or distal to the splenic flexure are termed left colon tumors.[1]

Right and left colon tumors originate from different embryological origins. The proximal two-thirds of the transverse colon derive from the midgut and are perfused by the superior mesenteric artery, while the distal one-third arises from the hindgut and is perfused by the inferior mesenteric artery.[2] These distinct embryological origins contribute to differences in the biology of these tumors.

The colon harbors a rich microbiota composed of intestinal bacteria. Notably, substantial differences exist in mucosal microbiota between patients with right-sided and left-sided colon cancer.[3] Additionally, the epithelia of the right and left colon exhibit distinct gene methylation and expression profiles.[4,5] Key oncogenes and tumor suppressors carry different mutations in right and left colon cancers. BRAFV600E and KRAS mutations are more prevalent in right colon tumors, whereas APC and TP53 mutations are frequently observed in left colon tumors.[6-8] The presence of mutations in APC, TP53, and KRAS may lead to diverse prognostic outcomes in CRC.[8] In addition to point mutations, amplifications of tyrosine kinases such as ERBB2 and epidermal growth factor receptor (EGFR), which are susceptible to targeted interventions, demonstrate higher prevalence in left-sided CRC.[9]

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Microsatellite instability (MSI) is observed up to 10 times more frequently in right colon tumors compared to left colon tumors.[10,11] MSI is a hypermutable condition resulting from the loss of DNA mismatch repair activity and is found in approximately 15% of all colorectal cancers. While 3% of these cases are associated with Lynch syndrome, the remaining 12% of sporadic MSI-high tumors are characterized by hypermethylation of the MLH1 gene, typically occurring in tumors with a CpG island methylator phenotype.[12] MSI has prognostic significance and contributes to clinical differences between right and left colon cancers, with MSI-high tumors exhibiting a better prognosis.[13]

There are distinct prognostic differences between right and left colon tumors based on the tumor stage. Metastatic colorectal cancer arising from the right colon typically exhibits a poorer prognosis when contrasted with metastatic colorectal cancer originating from the left colon.[14] In stage III disease, disease-free survival is shown to be lower in patients with right colorectal cancer.[15] For stage I and II diseases, conflicting prognosis results exist.

In early-stage colorectal cancers (stage I-III), surgical resection is the primary treatment method. For stage III disease, standard adjuvant therapy is advised for all patients, whereas for stage II disease, adjuvant chemotherapy is recommended specifically for those deemed at high risk.[1] Factors influencing the decision for adjuvant therapy in stage II disease include clinical and pathological risk factors such as lymphovascular invasion (LVI), perineural invasion (PNI), tumor perforation (TP), ileus, tumor budding (TB), and the number of removed lymph nodes being <12, as well as poorly differentiated histology.[2-4]

Notably, tumor localization is not among the factors influencing the adjuvant chemotherapy decision in stage II colon cancer. This study aims to evaluate right and left colon tumors, which differ embryologically, clinically, and prognostically, in stage II colon cancers concerning the decision for adjuvant treatment. The research also seeks to explore the relationship between clinicopathological factors and patients prognosis.

METHODS

The study initiated with approval of the Kayseri City Hospital Clinical Researches Ethics Committee (Date: 22.08.2023, Decision No: 895). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted with patients aged 18 and above who underwent surgery and were diagnosed with stage II colon cancer between January 2018 and December 2022. A total of 93 patients under follow-up at Karadeniz Technical University and Kayseri City Hospital were included in the study. Epidemiological, pathological, and clinical characteristics of the patients were retrospectively recorded. Eight patients with insufficient data recorded in the hospital information system were excluded from the study. Patients with rectal cancer, as their treatments differ from colon cancer, were not included in the study. Tumors located in the cecum, ascending colon, and transverse colon were categorized as right colon cancer, while those situated in the splenic flexure, descending colon, sigmoid colon, and rectosigmoid were classified as left colon cancer. Data usage permission was obtained from relevant institutions, and ethics committee approval was obtained.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)." Descriptive statistics were presented as n and % for categorical variables, and mean±SD for continuous variables. The Kaplan-Meier method was employed to compare survival and Progression-Free Survival (PFS) times among various clinical parameter groups. Overall survival (OS) was calculated from the time of diagnosis to the last evaluation or death. PFS was evaluated as the time to recurrence or metastasis. Finally, multivariate cox Regression results for the risk of death associated with various clinical factors were provided, considering $p<0.05$ as statistically significant.

RESULTS

A total of 93 patients, including 41 females and 52 males, were included in the study. The mean age of the patients was determined to be 67.68±9.69. Right colon cancer was present in 32.3% of the patients, while left colon cancer was present in 67.7%. Demographic, pathological, and clinical characteristics of the patients are presented in Table 1.

As seen in Table 2, the overall median OS (months) could not be reached.

There was a statistically significant difference in median OS (months) among the right-left colon (p=0.048), grade (p=0.001), intestinal obstruction (p<0.001), and TB (p=0.049) groups (Figure 1,2,3,4).

As observed in Table 3, the overall median PFS (months) could not be reached.

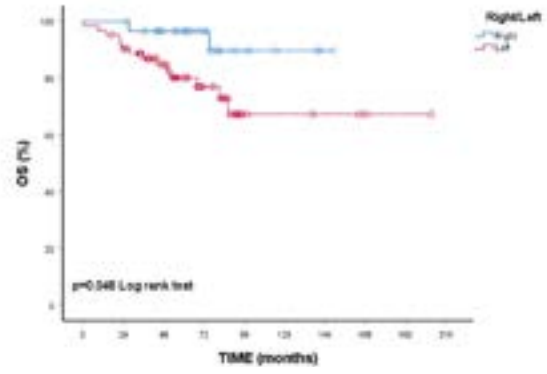

Figure 1. The relationship between right and left colon OS

OS: Overall survival

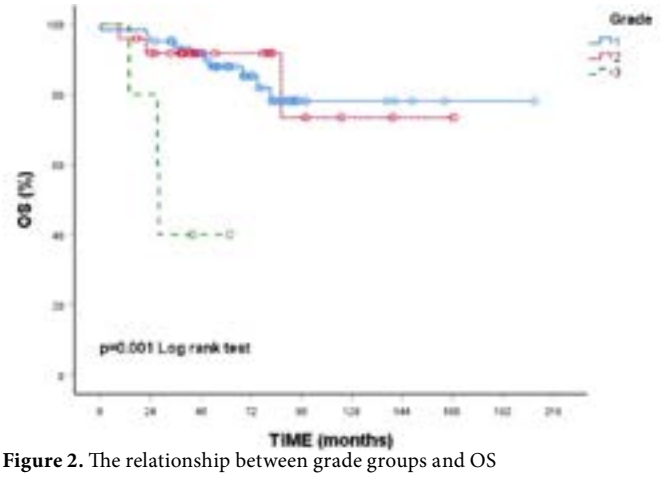

Figure 2. The relationship between grade groups and OS

OS: Overall survival

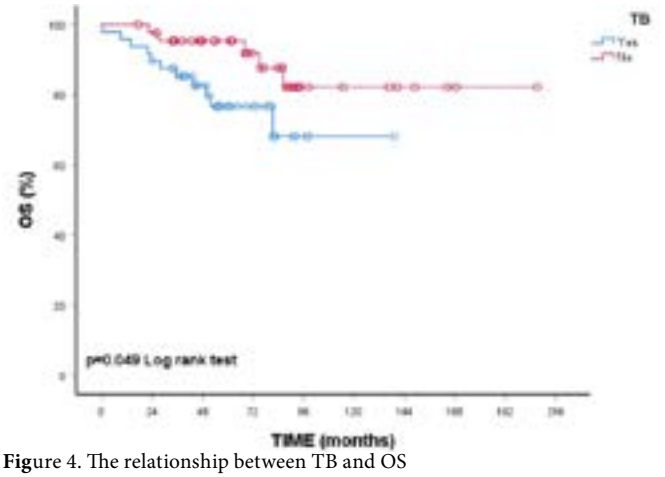

Figure 4. The relationship between TB and OS

TB: Tumor budding OS: Overall survival

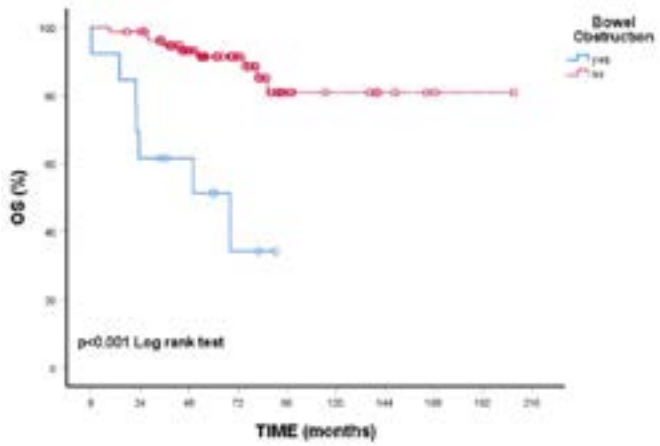

Figure 3. The relationship between bowel obstruction and OS

OS: Overall survival

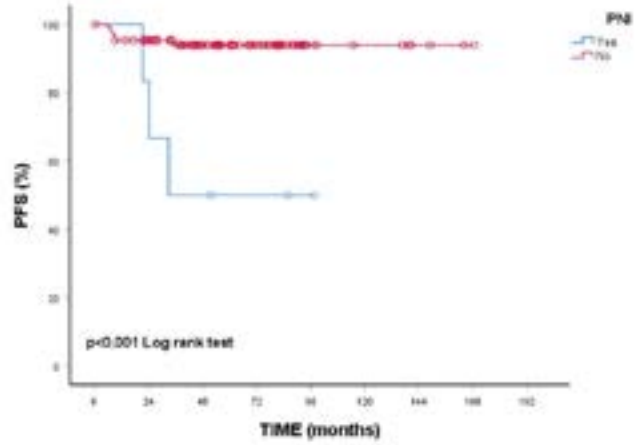

Figure 5. The relationship between PNI and PFS

PNI: Perineural invasion, PFS: Progression-Free Survival

There was a statistically significant difference in median PFS (months) among the PNI groups (p<0.001) (Figure 5).

As shown in Table 4, the variables right-left colon, PNI, CS, intestinal obstruction and removed lymph node were found to be statistically significant in terms of the risk of death (p<0.05) according to univariate (single-variable) analysis. These significant variables identified in univariate analysis were included in the multivariate cox regression model. According to the results of the multivariate cox regression model, individuals with intestinal obstruction were determined to have a 7.07 times higher risk of death (HR:7.07; 95% CI: 2.42-20.62; p<0.001) (p<0.001, -2 loglikelihood= 114.06).

DISCUSSION

According to the location of the tumor in the proximal and distal segments of the colon, the existence of two different categories of colorectal cancer has been suggested in many studies.[1,16,17] Despite having different biological and clinical characteristics, the role of tumor location in adjuvant therapy and the clinicopathological factors affecting adjuvant treatment decisions are often overlooked in studies related to colorectal cancer treatment. In our study, we investigated the role of tumor location in adjuvant therapy and the clinicopathological factors influencing adjuvant treatment decisions in stage II colon cancer. We observed that left colon tumors are associated with poorer survival and that intestinal obstruction has an independent prognostic effect on survival.

There are conflicting findings regarding the association between cancer location and mortality. It is known that right colon cancer has a worse prognosis than left colon cancer.[16] However, conflicting results have been reported in terms of prognosis according to stages. In one study, the mortality of right colon cancer was found to be higher in stage III colon cancer, whereas in our study, similar to our study, lower mortality was observed in patients with stage II colon cancer.[17,19] In another study, localized right colon cancer was found to have a better prognosis than left colon cancer in stage I-III.[18] Another study evaluated the effect of tumor location on prognosis in patients with stage II colon cancer and found that there was no statistically significant difference between tumor location and PFS and OS.[19]

There are studies reporting that right colon cancer has a higher risk of death than left colon cancer. [16,18,20,21] However, when classified by stage, studies have shown no difference in mortality between right and left colon in stage I colon cancer (HR, 1.003; P=93), and lower mortality similar to our study

Table 1. Examination of some demographic and clinical characteristics according to colon region

	Colon side		Statistic	p
	Right (n=30)	Left (n=63)		
Age	76 (45 - 86)	74 (40 - 96)	-0.530	0.596[m]
Gender				
Female	11 (36.7)	30 (47.6)	0.989	0.320[x]
Male	19 (63.3)	33 (52.4)		
Tumor Localization				
Rectosipmoid	---	6 (9.5)		
Sigmoid	---	41 (65.1)		
Descending colon	---	14 (22.2)		
Splenic flexure	---	1 (1.6)	---	
Transverse colon	3 (10)	1 (1.6)		
Ascending colon	19 (63.3)	---		
Cecum	8 (26.7)	---		
LVI				
Present	5 (16.7)	4 (6.3)	---	0.142[f]
Absent	25 (83.3)	59 (93.7)		
PNI				
Present	1 (3.3)	5 (7.9)	---	0.660[f]
Absent	29 (96.7)	58 (92.1)		
Grade				
1	18 (60)	45 (71.4)		
2	9 (30)	16 (25.4)	2.383	0.327[f]
3	3 (10)	2 (3.2)		
MSI IHK				
Not examined	4 (13.3)[a]	20 (31.7)[a]		
Stable	19 (63.3)[a]	42 (66.7)[a]	12.675	**0.002**[f]
High	7 (23.3)[a]	1 (1.6)[b]		
Localized perforation				
Present	0 (0)	2 (3.2)	---	1.000[f]
Absent	30 (100)	60 (96.8)		
Surgical margin				
Negative	28 (93.3)	57 (90.5)	---	1.000[f]
Positive	2 (6.7)	6 (9.5)		
Intestinal obstruction				
Present	2 (6.7)	11 (17.5)	---	0.211[f]
Absent	28 (93.3)	52 (82.5)		
Tumor budding				
Present	16 (55.2)	32 (50.8)	0.153	0.696[x]
Absent	13 (44.8)	31 (49.2)		
Removed lymph node				
≥12	28 (93.3)	47 (74.6)	---	0.050[f]
<12	2 (6.7)	16 (25.4)		
Mortality				
Alive	28 (93.3)	49 (77.8)	---	0.081[f]
Ex	2 (6.7)	14 (22.2)		
Adjuvant chemotherapy				
Present	13 (43.3)	17 (27)	2.486	0.115[x]
Absent	17 (56.7)	46 (73)		
Follow-up duration, Mean±SD	66.03±36.11			

m: Mann Whitney U testi, x: Pearson chi-square testi, f: Fisher's exact testi, a-b: No difference between groups with the same letter (Bonferroni corrected Z testi), median (min.-max.), n (%)

Table 2. Overall survival (OS) comparisons according to pathological features

OS (months)	2 years %	5 years %	Median (95% CI)	p
General	93.5	85.8	– (–)	
Right-left				
Right	100.0	96.6	– (–)	0.048
Left	90.4	80.1	– (–)	
LVI (Lymphovascular invasion)				
Present	88.9	88.9	– (–)	0.743
Absent	94.0	85.4	– (–)	
PNI (Perineural invasion)				
Present	–	66.7	– (–)	0.510
Absent	93.1	87.9	– (–)	
Grade				
1	95.2	88.0	– (–)	
2	91.8	91.8	– (–)	0.001
3	80.0	40.0	27.93 (26.28–29.57)	
MSI (Microsatellite instability)				
Not examined	83.3	79.2	– (–)	
Stable	96.7	88.0	– (–)	0.593
High	–	87.5	– (–)	
Surgical margin				
Negative	94.1	87.1	– (–)	0.246
Positive	87.5	70.0	– (–)	
Intestinal obstruction				
Present	61.5	51.3	68.00 (13.49–122.50)	<0.001
Absent	98.8	91.4	– (–)	
TB (Tumor budding)				
Present	89.6	76.6	– (–)	0.049
Absent	97.7	95.3	– (–)	
Removed lymph node				
≥12	96.0	89.5	– (–)	0.101
<12	83.3	71.4	– (–)	

The Kaplan–Meier curve and Log–rank test revealed statistically significant results with p<0.05.

Table 3. Progression-free survival (PFS) comparisons among patients

PFS (months)	2 years %	5 years %	Median (95% CI)	p
General	94.5	90.8	– (–)	
Right–left				
Right	–	96.7	– (–)	0.183
Left	91.8	87.9	– (–)	
PNI (Perineural invasion)				
Present	83.3	50.0	32.90 (–)	<0.001
Absent	95.3	93.9	– (–)	
SM (Surgical margin)				
Negative	95.2	92.6	– (–)	0.053
Positive	85.7	68.6	– (–)	
Intestinal obstrution				
Present	82.5	82.5	– (–)	0.186
Absent	96.3	92.2	– (–)	
TB (Tumor buding)			– (–)	
Present	95.6	90.7	– (–)	0.937
Absent	93.3	90.8	– (–)	
Removed lymph node				
≥12	96.0	93.0	– (–)	0.154
<12	87.8	81.1	– (–)	

The Kaplan-Meier curve and Log-rank test revealed statistically significant results with p < 0.05.

Table 4. Multivariate cox regression results for various clinical variables

OS (Overall survival)	Multivariate	
Variables	HR (95% CI)	p
Right-left (Ref: right)	2.87 (0.60-13.70)	0.185
PNI (Ref: absent)	1.39 (0.29-6.55)	0.672
CS (Ref: negative)	4.66 (0.90-23.95)	0.065
Intestinal obstruction (Ref: absent)	7.07 (2.42-20.62)	<0.001
Number of removed lymph nodes <12 (Ref: adequate)	1.27 (0.42-3.80)	0.669
p<0.001; -2 Log Likelihood=114.06		

has been reported in stage II right colon cancer (HR, 0.91; p<0.001).[18,20]

The inconsistent correlation between mortality and tumor location across different stages remains inadequately elucidated. However, this could be related to tumor biology. It is known that MSI tumors have a better overall prognosis.[21,22] MSI is more commonly observed in right colon tumors than in left colon tumors.[1] In a study, it was shown that MSI positivity is more common in stage II right colon cancers compared to stage III and IV[23] This may explain the better observed mortality in stage II disease in the right colon.

Intestinal obstruction stands as one of the high-risk factors impacting the consideration for adjuvant treatment in patients diagnosed with stage II colon cancer. However, data on the impact of obstruction on the prognosis of colorectal cancer are conflicting. Some studies have shown that intestinal obstruction has no prognostic effect on survival.[24,25] However, similar to our study, a multicenter analysis conducted by the gastrointestinal tumor study group showed that obstruction is an important prognostic indicator independent of stage.[26]

The distribution between right and left colon cancers of the patients in our study reflects the epidemiological trends observed in clinical practice. This strengthens the applicability of our findings to the clinical setting. However, the most important limitation of our study is that it was retrospective and the number of patients was limited. We believe that our findings can be improved and the prognostic significance of the distinction between right and left colon can be better examined in studies involving more patients and centers.

Limitations

Most important limitation of our study is that it was retrospective and the number of patients was limited. We believe that our findings can be improved and the prognostic significance of the distinction between right and left colon can be better examined in studies involving more patients and centers

CONCLUSION

Considering the significant differences in clinical, histological, microbiota, mutation, and genomic profiles between right and left colon tumors, it is plausible that they may exhibit different outcomes based on stages. While right colon tumors are generally considered to have a worse prognosis, we believe they may have a better prognosis in stage II patients. We think there is a need for more comprehensive studies that include a larger number of patients, where tumor location and clinicopathological factors are evaluated in the decision-making process for adjuvant treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kayseri City Hospital Clinical Researches Ethics Committee (Date: 22.08.2023, Decision No: 895).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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