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Prognostic impact of primary tumor location on survival in metastatic colorectal cancer patients: A single center experience

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Abstract
Primary tumor location (PTL) is associated with very different outcomes in patients with metastatic colorectal cancer (mCRC). Clinical trials suggest that right side tumor location is an indicator of poor prognosis for patients with mCRC. The relationship between the primary tumor location and clinicopathological features such as; gender, family history, carcinoembryonic antigen (CEA) level, metastasectomy status, the presence of a mucinous component, RAS mutation status, and overall survival (OS) were evaluated. A total of 253 patients (203 left-sided, 50 right-sided) were included in the study. Median OS time for patients with metastatic right sided colon tumors were 19 (15.2-22.7) months, and OS for left sided colon tumors were 35 (29.5-40.4) months. The left-sided colon group's OS time was significantly higher than the right-sided colon group ($p < 0.001$). The survival rate of patients with eastern cooperative oncology group performance status (ECOG-PS) 0-1, panRAS wild type (WT), metastasectomy, CEA level <5 ng/ml, were better than those of patiens with ECOG-PS>,1 panRAS mutant, CEA level ≥5 ng/mL and non-metastasectomy. The difference between these two groups were significantly associated with an improved OS ($p < 0.001$). Our study suggests that tumor location is an essential prognostic factor in patients with mCRC to be independent of other prognostic factors. OS was significantly longer in the patients with left-sided mCRC than right-sided.

Keywords: Metastatic colorectal cancer, primary tumor location, prognostic factor

Introduction

Various clinical and pathological features such as age, performance score, RAS and BRAF mutation status, tumor differentiation, metastasectomy, number of chemotherapy, and biologic agents available can affect survival rates in patients with metastatic colorectal cancer (mCRC) [1-3]. Furthermore, the new data obtained from the retrospective evaluation of recent studies indicate that if primary tumor located in right-side of the colon, it is an independent risk factor related with shorter overall survival (OS) than the left-sided tumor in mCRC patients.

Left and right-sided colon cancer have different unique molecular and pathologic features. Right-sided colon cancers are seen more frequently in women, at a more advanced stage in the diagnosis and have more mucinous histology and immunogenicity, more frequent microsatellite instability (MSI), RAS, BRAF, and PIK3CA mutation frequency. Also, the epidermal growth factor receptor (EGFR) pathway activation is more common in left-sided colon tumors, unlike right-sided colon tumors. [1,4-5]. These differences may be explained with embryologically by the differentiation of the left colon from the hindgut and the right colon from midgut [6].

All of these causes can result in marked poor prognosis of right-sided tumors, but the primary tumor location (PTL) has not been adequately assessed as an independent risk factor. In this study, we aimed to analyze that is PTL a reliable independent risk factor for survival in mCRC.

Material and Methods

Participants

Our cross-sectional study was conducted as retrospectively through searching the patient data recorded in a single center of Turkey between 01.06.2014 and 01.06.2017. The right and left sides of the colon tumor were defined according to the splenic flexure. If the tumors located in the region from the cecum to the splenic flexure were defined as the right side tumor. The section from the splenic flexure to the anal canal was accepted as the left side. Patients with anal canal were not included in the study. Tumor location was determined by examining the operation, pathology and colonoscopy reports. Only patients who could receive chemotherapy for the treatment of mCRC were included in the study. Patients who had a secondary malignancy or lost to follow-up or poor performance status (ECOG>2) were excluded. OS was

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defined as the time from diagnosis of metastatic colorectal cancer to death. Totally 282 patients diagnosed with mCRC enrolled in the study.

The relationship between the PTL and OS were evaluated for gender, family history, the presence of a mucinous component, KRAS, and NRAS mutation status, in univariate analysis. Multivariate analyses were performed to determine the prognostic significance of PTL in the study groups. The parameters for prognostic significance were: stage, presence of mucinous component, carcinoembryonic antigen (CEA) levels (≥5 and <5ng/dL) at diagnosis, eastern cooperative oncology group (ECOG) performance status (PS), gender, metastasis after progression or initially metastatic right and left side tumor localization, presence of cancer in the patient's family, and a history of surgical operation.

Statistical analysis

Statistical package program of IBM Statistics 15.0 (SPSS) was used. Descriptive statistics were presented as mean ± standard deviation and median (min-max). Chi-square test was used to compare categorical data between groups. The Kolmogorov Smirnov test was used to examine the distribution of variables between groups. The independent samples t-test was used to compare the homogenous non-distribution data. The Kaplan-Meier method was used to calculate the survival rate and the log-rank test was performed to compare the survival rate distributions between groups. Cox regression model was used to examine the relationship between independent variables and survival. Hazard Ratio (HR) and 95% confidence interval (Cl) were calculated. A P value lower than 0.05 considered statistically significant.

Ethics

This study was approved on the institutional review board of the hospital and was performed compatibility by all principles of the Helsinki Declaration.

Results

Totally 253 patients with mCRC who are of 203 (80%) left-sided and of 50 (20%) right-sided included in the study after exclusion of 53 patients. Only those who could receive chemotherapy were included. The patients who have poor performance status were not included in the study. Gender of left and right-sided colon cancer patients were 80 (40%), 21 (42%) female and 123 (60%), 29 (58%) male, respectively.(p=0.7). The age of patients with left-sided colon cancer was 60.1 ± 12.5 years and 61 ± 11.9 of right-sided colon cancer patients (p=0.56). One hundred fourteen patients (56.2%) died in the left-side colon cancer group, and 36 patients (72%) died in the right-side colon cancer group (p=0.04). The number of patients with a mucinous component in the left colon was 54 (26.6%) and was 21 (42%) of patients with right colon cancer (p=0.03). When compared the ECOG performance status (score ≤1 and> 1), stage at diagnosis (stage 3 and 4), family history of cancer, CEA level (<5 and ≥5), surgical of metastasis status there was no statistically significant difference (p >0.05 for all) between left-sided and right-sided mCRC. Patients and tumor characteristics are summarized in Table 1.

OS value of the patients with the right-sided patients were 19 months (95% CI, 15.2-22.7 months), while left-sided primary tumor was 35 months (95% CI, 29.5-40.4 months) (p<0.001) (Figure 1). Cox-regression analysis was used to determine independent factors associated with OS. RAS mutation status of patients was compared with overall survival. The OS of panRAS WT patients were 25 (4-60) months while the OS of RAS-mutant patients were 18 (1-60) months; this difference was statistically significant (p<0.001).There was no statistically significant difference (p = 0.53) between the RAS mutation frequencies on the left side and right side tumor. The OS of the patients undergoing metastasectomy was 35.67 months, and without metastasectomy was 24.31 months (p<0.001). OS of patients with CEA level <5 ng/ml at diagnosis was significantly higher than patients with ≥five ng/ml (32 months versus 18 months), respectively (p< 0.001).PTL (HR: 0.521, 95% CI: 0.348-0.781, p=0.002), surgical status (HR: 3.02, 95% CI:2.04-4.47, p<0.001) and ECOG performance status (HR:0.524, 95% CI:0.330-0.831, p=0.006) were independent prognostic factor related to other factors (Table 2).

Table 1. Characteristics of the study population

Metastatic Colorectal Cancer(mCRC)			
	Left side (n=203)	**Right side (n=50)**	**P**
Age (Mean±St.D.)	60±12.5	61.2±11.9	0.5
Gender (n)			0.7
Female	80	21	
Male	123	23	
Overall Survival [Median(min-max)] (month)	35 (29-40)	19(15-22)	0.003
ECOG PS score (n)			0.4
0-1	179	42	
>1	24	8	
The last condition (n)			
Exitus	114	36	
Live	89	14	
Stage (n)			0.31
Stage 3	59	11	
Stage 4	144	39	
Family History(n)			0.87
No	148	37	
Yes	55	13	
Mucinous Component status			0.033
positive	54	21	
negative	149	29	
Carcinoembryonic antigen (n)			0.1
<5	115	22	
≥5	88	28	
Surgery (n)			0.19
no	73	23	
yes	130	27	
Metastasis (n)			0.15
after progression	56	9	
at diagnosis	147	41	
panRAS mutation			0.53
mutant type	88	24	
wild type	86	19	
Metastasectomy			0.5
yes	43	9	
no	142	39	

Table 2. Multivariate analysis in metastatic colorectal cancer patients

	HazardRatio	95.0% CI	p
Gender	0.882	0.625-1.208	0.5
Primertumorside	0.521	0.348-0.781	0.002
Stage	0.863	0.435-1.714	0.67
ECOG score	0.554	0.345-0.89	0.01
Familyhistory	1.213	0.827-1.788	0.32
Mucinouscomponentstatus	0.882	0.608-1.28	0.5
Surgery of metastase	3.016	2.04-4.46	<0.001
Carcinoembryonicantigen	0.807	0.561-1.161	0.24

ECOG= Eastern Cooperative Oncology Group

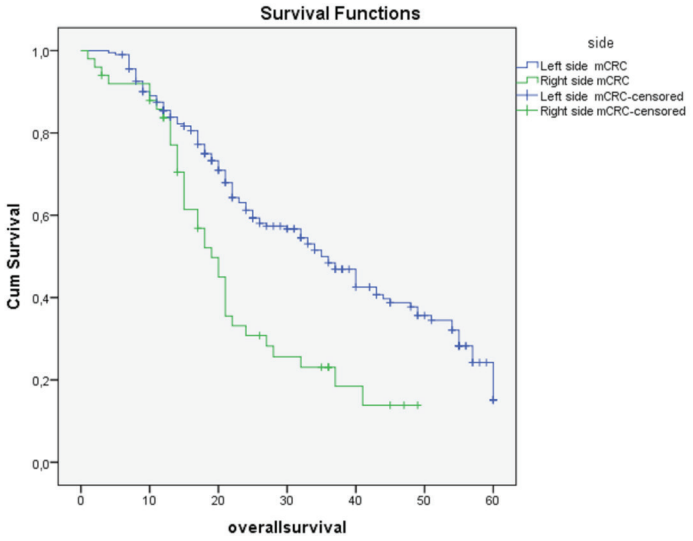

Figure 1. Comparing overall survival between the left and right-sided colon tumor

Discussion

In our study, we demonstrated that the overall survival was significantly higher in favor of the left-sided colon tumor compared to those of the right-side colon tumor. Also, the panRAS-WT, metastasectomy, group of patients with ECOG PS 0-1, normal CEA level at diagnosis, had a better survival rate and this was statistically significant (p<0.001). Regardless of CEA level, ECOG-PS, metastasectomy status, panRAS status, and left-sided tumors have been shown to have better survival outcomes.

Several clinical studies have shown that metastatic colorectal cancer patients comes associated with various clinical outcomes of the primary tumor site. Studies that retrospectively examine the association of PTL with survival time are generally phase-3 randomized studies in which the survival contribution of biological agents is reduced. These studies are investigated the survival contribution of anti-EGFR biological agents such as panitumumab and cetuximab in panRAS wild-type colorectal cancer patients [7-12].

In the meta-analysis of 13 randomized studies, the results revealed that the right-sided tumors resulted in worse survival time when compared to left-sided tumors. The results of this meta-analysis also showed that the addition of anti-EGFR agents to the chemotherapy treatment of left-sided panRAS wild-type patients provides more survival benefit when compared to anti-vascular endothelial growth factor (VEGF). However, the same benefit has not been observed for right-sided tumors. Although the idea that anti-VEGF therapy may be a contributory factor in right-sided tumors, it is unclear what the optimal treatment for these tumor types is [13,14]. In the Provetta cohort [15], it was also determined that the tumor location produced statistically significant differences in OS outcomes. In this study, the median OS for left and right-sided tumor patients was 42 and 24.8 months, respectively.

Kim et al. [16] examined the relationship between PTL and OS in the BRAF V600E mutant, panRAS WT patients. Although this study yielded worse OS outcomes (right: 4.1 months, left: 13 months; p <0.001), left-side tumors had better survival outcomes compared with right-sided tumors. Shahid et al. [17] conducted a study with a heterogeneous (panRAS WT / mutant, BRAF WT / mutant) patient group, similar to our study. The study examined the association of PTL with survival, and they found that the OS of the right-sided patients was 14 months and OS of the left-sided patients was 20.5 months. This result was statistically significant (p <0.001). Timothy et al. [18] conducted a study similar to Shahid et al.'s, and it showed that similar results (right side: 18.2 months, left side: 20.4 months; p <0.001).

Our study from single-center involving 253 patients confirms that the primary tumor location is an independent prognostic factor in real-world patients with metastatic colorectal cancer. Patients with right-sided tumor have an inferior survival rate compared with patients whose tumors originate in the left-side colon.

The limitations of this study include the absence of BRAF V600E mutation analysis in the entire patient group, no survival analysis based on chemotherapy options, fewer patient groups compared to other reviews and retrospective study.

Conclusion

Our study confirms the findings from the previous studies and supports the idea that tumor location is a prognostic factor independent of the other prognostic factors in patients with mCRC. Thus, the OS of left-sided metastatic colon cancer patients is significantly higher than that of right-sided patients. These studies, which support the notion that the location is an independent prognostic variable, suggest that further studies are needed to understand the pathophysiology

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Competing interests
The authors declare that they have no competing interest.

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Ethical approval
This study was approved on the institutional review board of Bezmialem Vakıf University Hospital.

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