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ORIGINAL ARTICLE

The impact of primary tumor localization on survival and treatment outcomes in patients with metastatic colorectal cancer-a multicenter study

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Summary

Purpose: *To investigate the effects of sidedness on survival and treatment outcomes in patients with metastatic colorectal cancer (mCRC), since the accumulated data have increasingly reported that patient with right-sided mCRC are found to be associated with worse overall survival (OS) and poor response to anti-epidermal growth factor receptor (anti-EGFR) agents.*

Methods: *This was a multi-center retrospective analysis of 177 patients with mCRC, who were treated and followed between 2014 and 2018 in different parts of Turkey. Patients were divided into 2 groups according to the primary tumor localization as right or left colon cancer. Clinical and demographic characteristics, treatment outcomes, and survival were analyzed to determine whether there was any association with tumor localization.*

Results: *There were 53 (30%) patients with mCRC in the right group and 124 (70%) in the left group, with no difference between the groups in terms of clinical and demographic characteristics. There was no difference in OS between the left and right side localization in any RAS-mutant mCRC patients (22.1 vs. 27.9 months, respectively, p=0.19), whereas patients with all RAS-wild type tumor in the right colon were associated with a worse OS than left-sided counterparts (19.4 vs 29.9 months, respectively, p=0.01). Multivariate analysis revealed that the right-sided tumor (HR, 1.74; 95% CI: 1.165-2.608; p=0.007), the presence of comorbid disease (HR, 1.58; 95% CI: 1.079-2.321, p=0.019), body mass index (BMI) <25 (HR, 1.61; 95% CI: 1.108-2.352, p=0.013), grade III tumor (HR, 1.65; 95% CI: 1.109-2.457, p=0.014), and being unable to metastasectomy (HR, 2.10; 95% CI: 1.235-3582, p=0.006) were found to be independent predictors of worse survival.*

Conclusion: *While right side localization was an independent negative predictor of survival in patients with mCRC, tumor sidedness was not found to be associated with response to treatment. The worse OS in right localization may be due to the aggressive nature of right-sided colon tumors which show faster progression, since their response to treatment does not appear to be different.*

Key words: *anti-EGFR therapy, anti-VEGF therapy, metastatic colorectal cancer, prognosis, survival, sidedness*

Introduction

Metastatic colorectal cancer (mCRC) is one of the most aggressive malignancies with high morbidity and mortality rates worldwide [1,2]. Although the risk of developing colon cancer may occur at all ages, the risk increases especially in patients over 50 years of age. However, the mortality of colon cancer has started to decline worldwide over the past two or three decades due to widespread use of endoscopic and/or other annual screening methods. Moreover, early diagnosis of colon cancer by screening methods has significantly reduced the morbidity and mortality rates of these patients [3]. However, in the historical process of colon cancer, especially until 10 years ago, no further detailed information about this disease was available, except the simple histopathological findings and

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the clinical course of advanced disease. In addition, cure of this disease had only been possible in operable patients with very early disease stage and 5-year OS rates had almost always been close to zero in locally advanced and metastatic groups due to poor effectiveness of adjuvant or palliative chemotherapy, with 2-year OS rates being poor [4]. Nevertheless, some patients had responded well to fluoropyrimidine + oxaliplatine- or irinotecan-containing regimens, while others had not [5,6]. In recent years, because this is a highly vascular tumor, the addition of anti-vascular endothelial growth factor (anti-VEGF) agents (bevacizumab or ziv-aflibercept) together with FOLFIRI or FOLFOX combination has resulted in an average of 6 months of progression-free survival (PFS) and OS, allowing patients to live longer than a year; however, most patients still continue to develop progression and die at the end of the first year [7-9]. For this reason, identifying the molecular and genetic basis of the disease, and determining the disease-causing driver mutations along with the factors that can predict the clinical course and response to therapy have been an issue of intense investigation.

As a result of previous studies, some genetic properties were discovered in tumor tissues of mCRC patients, such as KRAS, NRAS, and BRAF mutations and the presence of microsatellite instability (MSI-H). By discovering the driver mutations along with the monoclonal antibodies against these mutations, a high clinical success rate was achieved. To illustrate, a significant improvement in clinical response, PFS and OS rates was shown with the addition of anti-epidermal growth factor receptor (anti-EGFR) antibodies (panitumumab or cetuximab) to either FOLFOX or FOLFIRI combination in mCRC patients without RAS mutation (RAS-wild type) [10-14]. However, treatment with anti-EGFR monoclonal antibodies in mCRC still lacks clinical and molecular biomarkers that correlate with treatment response. In many large phase III trials comparing anti-VEGF versus anti-EGFR therapy, it was found that the addition of anti-EGFR monoclonal antibodies to first-line chemotherapy was only effective in patients with RAS- and BRAF-wild mCRC, but not in patients with mutant tumors; however, the addition of anti-VEGF agents to chemotherapy was found to be beneficial, regardless of the mutation status. Therefore, treatments in patients with mCRC in the first-line setting have, nowadays, been established as chemotherapy + anti-EGFR or anti-VEGF agent, depending on the RAS mutation status [14,15]. It is postulated that primary tumor localization may have importance on clinical results and survival in many cancer types [16]. More recently, retrospective evaluation of the data of phase III studies examining the efficacy of anti-VEGF and anti-EGFR therapies has revealed that the prognosis according to primary tumor location is worse in the right-sided mCRC patients compared to the left-sided counterparts, showing that anti-EGFR therapy in right-sided mCRC even with all-RAS- and BRAF-wild type is not found to be effective but detrimental in some series, whereas response to anti-VEGF therapy compared to anti-EGFR antibodies is found to be better in right-sided but similar in left-sided tumors, irrespective of the mutation status. Therefore, given the knowledge mentioned above, oncological clinical guidelines have made recommendations regarding which targeted agent should be used in combination according to the tumor laterality [17-19].

However, it has been previously seen in many types of cancer that gastrointestinal cancers, especially stomach and colorectal, may have different clinical course and response to therapies due to different ethnic origins [20]. Most of the previous retrospective data on this issue are related to the European and American population, hence it is important to perform this analysis in Turkey, which is a bridge country between Asia and Europe. For this reason, we intended to analyze the response of right and left colon tumors to anti-EGFR versus anti-VEGF agents and their effects on survival in patients with *de novo* mCRC, with the goal of enlightening the status of mCRC patients in Turkish population.

Methods

Patients and enrollment

This study was a multicenter retrospective analysis of 177 patients with *de novo* mCRC from a cohort including 314 CRC, who were treated and followed between January 2014 and December 2018 in different centers of Turkey. Patients with mCRC were grouped as right or left mCRC based on the primary tumor localization, according to the literature suggestion as follows: left colon: splenic flexure, descending colon, sigmoid colon, and rectum; right colon: cecum, ascending colon, and hepatic flexure [21]. Patients with mCRC, in whom tumors were located in the transverse colon, were excluded from the study (n=10). Clinical and demographic characteristics, treatment outcomes, and survival were analyzed to determine if there was any association with tumor localization.

Statistics

SPSS version 22.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. P values less than 0.05 were considered as statistically significant. Descriptive statistics were presented as percentages and medians. Categorical variables were assessed using the chi-square test or Fisher's exact test. Survival

Table 1. Comparison of demographic and clinical features according to tumor localization

Variables	*Right (n=53)* *n (%)*	*Left (n=124)* *n (%)*	*Total N=177* *n (%)*	*p value*
Median age, years, n (range)	61.0 (36-78)	61.5 (27-84)	61 (27-84)	0.70
Gender				0.23
Male	27 (50.9)	75 (60.5)	102 (57.6)	
Female	26 (49.1)	49 (39.5)	75 (42.4)	
ECOG performance status				0.48
0	26 (49.1)	68 (54.8)	94 (53.1)	
I-II	27 (50.9)	56 (45.2)	83 (46.9)	
Comorbidity				0.90
Yes	18 (34.0)	41 (33.1)	59 (33.3)	
No	35 (66.0)	83 (66.9)	118 (66.7)	
Alcohol consumption				0.15
Yes	7 (13.2)	8 (6.5)	15 (8.2)	
No	46 (86.8)	116 (93.5)	162 (91.5)	
Smoking				0.60
Yes	23 (43.4)	59 (47.6)	82 (46.3)	
No	30 (56.6)	65 (52.4)	95 (53.7)	
Familial history				0.67
Yes	9 (17.0)	18 (14.5)	27 (15.3)	
No	44 (83.0)	106 (85.5)	150 (84.7)	
BMI				0.72
<25	22 (41.5)	50 (40.3)	72 (40.7)	
≥25	28 (52.8)	70 (56.5)	98 (55.4)	
Unknown	3 (5.7)	4 (3.2)	7 (4.0)	
LVI				0.38
No	14 (26.4)	41 (33.1)	55 (31.1)	
Yes	39 (73.6)	83 (66.9)	122 (68.9)	
PNI				0.90
No	20 (37.7)	48 (38.7)	68 (38.4)	
Yes	33 (62.3)	76 (61.3)	109 (61.6)	
Histopathological grade				0.19
I-II	31 (58.5)	85 (68.5)	116 (65.5)	
III	22 (41.5)	39 (31.5)	61 (34.5)	
Palliative surgery				0.86
No	37 (69.8)	85 (68.5)	122 (68.9)	
Yes	16 (30.2)	39 (31.5)	55 (31.1)	
Metastasectomy				0.76
No	45 (84.9)	103 (83.1)	148 (83.6)	
Yes	8 (15.1)	21 (16.9)	29 (16.4)	
RAS status				0.60
Mutant	21 (39.6)	44 (35.5)	65 (36.7)	
Wild	32 (60.4)	80 (64.5)	112 (63.3)	
*First-line CT				0.49
FOLFOX/FOLFIRI +Bevacizumab	34 (64.2)	86 (69.4)	120 (67.8)	
FOLFOX/FOLFIRI +Cetuximab/Panitumumab	19 (35.8)	38 (30.6)	57 (32.2)	
*FOLFOX/FOLFIRI +Bevacizumab				0.85
Partial response	21 (61.8)	56 (65.1)	77 (64.2)	
Stable disease	6 (17.6)	16 (18.6)	22 (18.3)	
Progressive disease	7 (20.6)	14 (16.3)	21 (17.5)	

Continued on the next page

Variables	*Right (n=53) n (%)*	*Left (n=124) n (%)*	*Total N=177 n (%)*	*p value*
*FOLFOX/FOLFIRI +Cetuximab/Panitumumab				0.23
Partial response	7 (36.8)	23 (60.5)	30 (52.6)	
Stable disease	7 (36.8)	8 (21.1)	15 (26.3)	
Progressive disease	5 (26.3)	7 (18.4)	12 (21.1)	
Second-line CT				0.87
Yes	31 (58.5)	71 (57.3)	102 (57.6)	
No	22 (41.5)	53 (42.7)	75 (42.4)	
Survival				0.50
Alive	14 (26.4)	39 (31.5)	53 (29.9)	
Dead	39 (73.6)	85 (68.5)	124 (70.1)	

OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, CT: Chemotherapy, LVI: Lymphovascular invasion, PNI: Perineural invasion. *Based on the investigator choice of therapy.

Table 2. Overall survival according to sidedness and treatments in RAS-wild vs. RAS-mutant group

Variables	*Wild (n=112) n (%)*	*Median OS (months)*	*Mutant (n=65) n (%)*	*OS*
Localization				
Right	32 (28.6)	19.4	21 (32.3)	22.1
Left	80 (71.4)	29.9	44 (67.7)	27.9
		p=0.01		p=0.19
*First-line CT				24.6
FOLFIRI/FOLFOX + Bevacizumab	55 (49.1)	25.7	65 (100)	
FOLFIRI/FOLFOX + Ctx/pan	57 (50.9)	25.7	0 (0.0)	
		p=0.66		

CT: Chemotherapy, Ctx: Cetuximab, Pan: Panitumumab, OS: Overall survival, *based on the investigator choice of chemotherapy.

analysis was carried out using the Kaplan–Meier method and differences in survival were compared with log-rank test. Variables with p values <0.15 in univariate analysis were evaluated by multivariate Cox regression analysis, with backward selection to identify the independent predictors of OS. OS was described as the time from the date of diagnosis of mCRC to the date of death due to any reason or the date of last follow-up.

Ethical approval

All of the stages performed in this analysis were compatible with the 1964 declaration of Helsinki and its subsequent amendments or comparable ethical standards.

Results

The study included 177 *de novo* mCRC patients from 3 centers in Turkey, with 124 of them being in the left and 53 in the right group, showing no difference between the groups in terms of clinical and demographic characteristics (Table 1). When com-

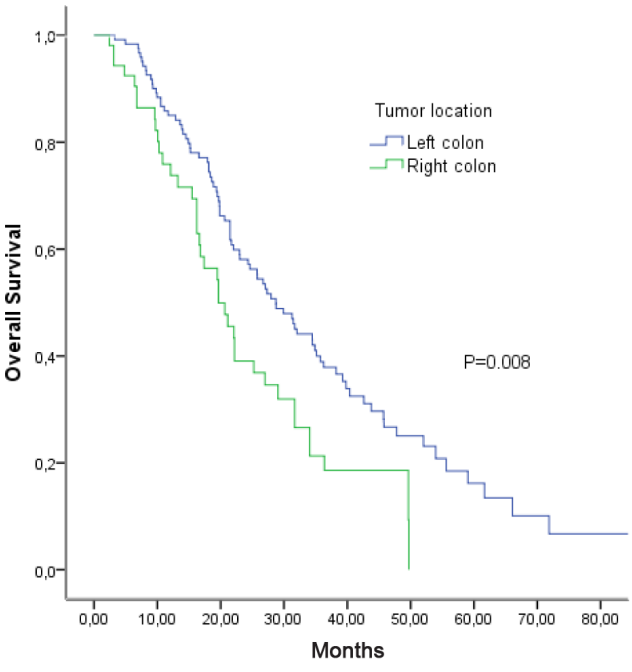

Figure 1. Overall survival according to sidedness.

Table 3. Univariate and multivariate analysis for median overall survival (months)

Variables	*Total, (N=177)* *n (%)*	*Univariate analysis for median OS (months)*	*p value*	*Multivariate analysis for OS*
Age, years			0.31	
<65	112 (63.3)	28.7		
≥65	65 (36.7)	22.9		
Gender			0.67	
Male	102 (57.6)	25.7		
Female	75 (42.4)	25.7		
ECOG performance score			0.89	
0	94 (53.1)	22.9		
I-II	83 (46.9)	27.9		
Comorbidity			0.03	1
No	118 (66.7)	29.9		p=0.019, HR=1.58,
Yes	59 (33.3)	18.5		CI 1.079-2.321
Alcohol consumption			0.37	
Yes	15 (8.5)	31.4		
No	162 (91.5)	24.3		
Smoking			0.58	
Yes	82 (46.3)	25.7		
No	95 (53.7)	25.7		
BMI			0.11	1
≥25	98 (55.4)	28.7		p=0.013, HR=1.61,
<25	72 (40.7)	19.8		CI 1.108-2.352
LVI			0.71	
No	55 (31.1)	27.0		
Yes	122 (68.9)	24.6		
PNI			0.63	
No	68 (38.4)	25.7		
Yes	109 (61.6)	25.7		
Histopathological grade			0.01	1
I-II	116 (65.5)	28.7		p=0.014 HR=1.65,
III	61 (34.5)	20.6		CI 1.109-2.457
Palliative surgery			0.85	
No	122 (68.9)	24.3		
Yes	55 (31.1)	29.0		
Metastasectomy			0.006	1
Yes	29 (16.4)	45.7		p=0.006, HR=2.10,
No	148 (83.6)	22.1		CI 1.235-3582
Tumor localization			0.008	1
Left	124 (70.1)	28.7		p=0.007, HR=1.74,
Right	53 (29.9)	19.6		CI 1.165-2.608
RAS status			0.42	
Mutant	65 (36.7)	24.6		
Wild-type	112 (63.3)	25.7		
*First-line therapy			0.58	
Bevacizumab-based	120 (67.8)	25.7		
Cetuximab/ Panitumumab - based	57 (32.2)	25.7		
Second-line therapy			0.39	
Yes	102 (57.6)	27.0		
No	75 (42.4)	21.4		

OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, LVI: Lymphovascular invasion, PNI: Perineural invasion. *Based on the investigator choice of therapy.

Table 4. Comparison of median overall survival according to demographic features for left versus right colon cancer

Variables	*Right* *Median OS (months)*	*p value*	*Left* *Median OS (months)*	*p value*
Age, years		0.28		0.37
<65	22.1		31.7	
>65	16.2		27.0	
Gender		0.03		0.04
Male	22.1		27.3	
Female	19.6		34.8	
ECOG performance status		0.46		0.78
0	20.6		27.3	
I-II	19.6		28.7	
Comorbidity		0.008		0.33
Yes	16.2		22.9	
No	22.1		31.7	
Alcohol consumption		0.13		0.58
Yes	25.2		31.4	
No	19.6		27.0	
Smoking		0.11		0.13
Yes	22.1		27.3	
No	19.6		31.2	
BMI		0.70		0.16
<25	16.7		25.7	
≥25	25.2		34.4	
LVI		0.60		0.87
No	19.6		31.7	
Yes	20.6		27.9	
PNI		1.0		0.46
No	19.6		27.9	
Yes	21.1		31.2	
Histopathological grade		0.02		0.19
I-II	22.1		31.2	
III	16.7		25.7	
Palliative surgery		0.08		0.49
No	16.7		28.7	
Yes	27.0		31.4	
Metastasectomy		0.01		0.05
No	17.3		25.7	
Yes	49.7		45.7	
RAS status		0.37		0.50
Mutant	22.1		27.9	
Wild	19.4		29.9	
*First -Line therapy		0.26		0.87
FOLFOX/FOLFIRI +Bevacizumab	19.6		27.9	
FOLFOX/FOLFIRI +Cetuximab/Panitumumab	20.6		29.9	
Second line therapy		0.89		0.55
Yes	19.6		29.9	
No	20.6		25.7	

OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, LVI: Lymphovascular invasion, PNI: Perineural invasion. *Based on the investigator choice of chemotherapy.

paring the RAS mutant- versus all RAS wild-type tumors in both sides, there was no difference in OS according to the treatment patients received. There was no difference in OS between the left-sided and right-sided tumors in RAS-mutant mCRC patients (22.1 vs. 27.9 months, respectively, p=0.19), whereas those with all-RAS-wild type tumor in the right colon were associated with a shorter OS than left-sided counterparts (19.4 vs 29.9 months, p=0.01) (Table 2). In univariate analysis, right-sided tumors (19.6 vs. 28.7 months, p=0.008) (Figure 1), having comorbid disease (18.5 vs. 29.9 months, p=0.03), grade III tumor (20.6 vs. 28.7 months, p=0.014), and being unable to metastasectomy (22.1 vs. 45.7 months, p=0.006) were associated with OS. Multivariate analysis revealed that right-sided tumors (HR, 1.74; 95% CI: 1.165-2.608; p=0.007), presence of comorbid disease (HR, 1.58; 95% CI:1.079-2.321, p=0.019), BMI <25 (HR, 1.61; 95% CI:1.108-2.352, p=0.013), grade III tumor (HR, 1.65; 95% CI:1.109-2.457, p=0.014), and being unable to metastasectomy (HR, 2.10; 95% CI:1.235 -3582, p=0.006) were found to be independent predictors of worse survival (Tables 3 and 4).

Discussion

Currently, chemotherapies in combination with anti-VEGF or anti-EGFR agents are still standard of care in the first- and second-line setting in unresectable or advanced mCRC, providing an OS of approximately 40 months with the optimal first-line chemotherapy combinations according to RAS and BRAF status. Previous phase III randomized trials showed that the addition of anti-EGFR or anti-VEGF agents to either FOLFOX or FOLFIRI combination in the first-line setting was associated with favorable OS, PFS, and overall response rate (ORR) [9,22]. In our study, there was no difference in ORR in mCRC patients receiving anti-EGFR versus anti-VEGF treatment in right-and left-sided RAS-wild tumors and there is no clear point regarding this issue in previous studies reported in the literature. In a study by Moretto et al. including a total of 75 (14 right-sided vs. 61 left-sided) previously treated patients with RAS- and BRAF-wild mCRC, no clinical response was observed with anti-EGFR therapy (as single agent or in combination with irinotecan) in any of the patients with right-sided tumors compared to ORR of 41% in those with left-sided tumors. This finding was one of the first studies that raised questions regarding the impact of laterality in colon cancer [23]. The CRYSTAL trial showed that ORR was significantly worse in the right-sided tumors in a cohort of 175 RAS-wild mCRC patients treated with FOLFIRI + Cetuximab (42.4 vs. 72.5, p=0.001) [12,17,24]. These findings raised suspicions about whether or not anti-EGFR therapy is of benefit in right-sided mCRC. In the CALGB/SWOG80405 study, all RAS-wild mCRC patients receiving chemotherapy with either bevacizumab or cetuximab in the first-line setting were compared. This analysis showed that ORR was significantly better in the left-sided tumors treated with either bevacizumab- or cetuximab-containing regimen, compared with the right-sided tumors (bevacizumab 39.7% vs. 57.9%, p=0.003 and cetuximab 42.3% vs. 69.4%, p<0.001, respectively). However, in the same study, when comparing the efficacy of bevacizumab versus cetuximab in each side, ORR was found to be equal in right-sided tumors, whereas ORR favored cetuximab in the left-sided tumors (57.9% vs. 69.4%, p=0.005) [25]. In the FIRE III randomized study, 199 mCRC patients treated with either FOLFIRI+bevacizumab or FOLFIRI+cetuximab in the first-line setting were compared. This trial reported that Bevacizumab and cetuximab were found to be associated with better ORR in right-sided and left-sided tumors, respectively [14]; however, the difference was not statistically significant, similar to our findings. In the pooled analysis of phase III and phase II studies comparing bevacizumab versus anti-EGFR therapy in RAS-wild mCRC patients treated in the first-line setting, anti-EGFR therapy was found to be superior to bevacizumab in the left-sided, but not in the right-sided tumors, in terms of OS, PFS, and ORR. In the same analysis, it was observed that the right-sided RAS-wild mCRC patients had significantly poorer survival than the left-sided counterparts, with similar results found in our analysis (19.4 vs. 29.9 months, p=0.01) [24].

According to the findings of our study, right-sided tumors, being unable to metastasectomy, low BMI, high histological grade, and the presence of comorbid disease were independent predictors of poor survival. The unfavorable survival for right colon cancer appears to be associated with RAS-wild mCRC patients in our analysis and this finding is consistent with the literature [24,26]. Being able to perform metastasectomy may be sufficient to provide cure in these patients and result to a spectacularly favorable OS [27]. As shown in our study, patients undergoing metastasectomy were found to have significantly better OS than those ineligible for metastasectomy, with an independent predictor of prolonged OS in multivariate analysis. The negative effect of comorbid diseases (i.e., arterial hypertension, diabetes mellitus, and coronary arterial disease) on survival in cancer is already a well-known issue [28] and this has been shown in our study. Likewise, as shown in many

metastatic diseases including mCRC [29], a high histopathological tumor grade in our analysis was found to be an independent predictor of worse survival. Aside from its retrospective nature, the major limitations in our study were as follows: 1) It included a relatively smaller sample size compared to similar studies; 2) Because it has been reported that response to anti-EGFR agents in patients with RAS-wild but BRAF-mutant tumor is highly unlikely in CRC, BRAF mutation analysis was needed but it was not possible to perform in all RAS-wild patients, hence the treatment establishment could not be based on BRAF status in our population; 3) Our analysis did not include data of PFS, because of some missing information.

In conclusion, the right-side origin of the primary tumor in patients with RAS-wild mCRC was found to be an independent negative predictor of poor survival. As given above, the primary tumor localization did not influence the efficacy of anti-EGFR or anti-VEGF therapy combined with chemotherapy in the first-line setting in all RAS-wild mCRC patients. Our findings and previous literature data should be evaluated by randomized and prospective clinical studies.

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Conflict of interests

The authors declare no conflict of interests.

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