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ORIGINAL ARTICLE

Prognostic significance of primary tumor localization in patients with metastatic colorectal cancer: Is it beneficial to select targeted treatment? Real-life experience from Turkey

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Summary

Purpose: *The purpose of this study was to investigate the prognostic value,and the effect of primary tumor location on targeted therapy selection in patients with metastatic colorectal cancer (mCRC).*

Methods: *A total of 201 patients with de novo mCRC who received first line treatment were retrospectively analyzed. Clinicopathological features, treatment outcomes, the primary tumor surgery, metastasectomies/local therapies and survivals were evaluated in terms of both RAS mutation status and primary tumor sidedness.*

Results: *Tumor localization showed 140 (69.7%) patients with left-sided and 61 (30.3%) with right-sided tumors. Median progression-free survival (PFS) and overall survival (OS) were significantly shorter in patients with right-sided tumor than those with left-sided tumors (10.1 vs 12.9 months, p=0.005; 25 vs 44.4 months, p=0.008, respectively). In addition,the median OS interval of patients receiving anti-VEGF containing regimen was better than those treated with anti-EGFR containing regimen (50.7 vs. 26.9 months, p=0.001). Multivariate analysis indicated that age (HR:0.41,p=0.045), primary tumor resection (HR:0.41,p=0.037) and primary tumor localization (HR:0.38,p=0.021) for PFS and age (HR:0.39, p=0.09), the presence of BRAF mutation (HR:0.59,p=0.019) and the type of targeted therapy (HR:3.16,p=0.025) for OS were independent prognostic factors.*

Conclusions: *Our results showed that primary tumor location is a prognostic factor in mCRC patients regardless of RAS status. Primary tumor location before treatment decision may be a simple indicator predicting survival and in choosing targeted agent.*

Key words: *tumor sidedness, RAS mutation, anti-EGFR therapy, anti-VEGF therapy, colorectal cancer*

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourthmost frequent cause of cancer-related deaths worldwide. Association with high mortality and frequency rates led to maintain its importance for decades [1,2]. Important developments have been emerged in the past two decades to improve the clinical outcomes of CRC, including several therapeutic agents for chemotherapy and targeted therapy. However, 24-41% of patients die within 5 years following a surgical resection with curative intent, and 56-78% of patients die within 2-3 years after palliative treatments. Therefore, it is necessary to identify novel and readily available prognostic factors for risk stratification and to predict treatment efficiency in both early and advanced staged CRC [3,4].

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Recently, there are growing data about tumor location, particularly its predictive and prognostic significance on survival [1-3]. The majority of publications revealed that right-sided CRCs has association with shorter progression-free survival (PFS) and overall survival (OS) and they are more frequently characterized with BRAF mutation positivity and the existence of microsatellite instability; moreover, left-sided tumors more frequently have gene expression profiles characteristic of epidermal growth factor receptor (EGFR) and HER2-neu amplifications [4-6]. On the other hand, RAS and B-RAF mutations are predictive markers for efficacy of anti-EGFR therapies. Previous randomized studies showed that adding anti-EGFR monoclonal antibodies to irinotecan or oxaliplatin-based therapies significantly improved PFS in the first-line treatment of patients with K-RAS wild type mCRC [7]. In addition, further studies with extended analyses (K and N-RAS analyses) also revealed a significant survival improvement with chemotherapy plus anti-EGFR monoclonal antibodies [5,8].

In terms of primary tumor location in patients with mCRC, recent randomized studies have demonstrated that treatment outcomes with biologic agents might be changed [7-10]. Moreover, a meta-analysis of three important studies showed that anti-EGFR therapies compared with anti-VEGF therapies when added to standard chemotherapy provided a significant survival benefit in patients with RAS wild type left-sided mCRC [11]. In addition to survival benefit, these studies and their meta-analyses retrospectively showed a predictive role of tumor localization in selecting of anti-EGFR or anti-VEGF therapies [7,9-14]. Therefore, so far no prospective study to stratify targeted-treatment according to primary tumor localization has been reported. In the present study, we aimed to evaluate the prognostic significance of tumor localization in patients with mCRC. Moreover, the predictive importance and its effect on determining treatment were also investigated in RAS wild-type subgroup from Turkish real-life expreience.

Methods

Between 2013 and 2018, a total of 201 mCRC patients who had not received systemic treatment were included in the study. The primary tumor was staged according to the AJCC 7th TNM staging classification for CRC. Patient data were retrospectively obtained from patients' charts with respect to age, gender, histopathological type, tumor localization, RAS (K-RAS and N-RAS) and BRAF mutations status, the site of metastasis, systemic treatments in metastatic line,the presence of metastatectomy and other local treatments and responses to treatment and survival after written informed consent had been obtained from patients or their relatives.

The eligibility criteria consisted of patients aged ≥18 years with histologically diagnosed CRC and *de novo* metastatic CRC and survival expectancy longer than 3 months. Patients who had insufficient disease information, unknown K-RAS and N-RAS mutation status and had early stage disease at diagnosis were excluded from data analysis. The Local Ethics Committee of Istanbul Medipol University approved the study.

Of 201 patients having K-RAS and N-RAS mutation tests (RAS mutations), 96 (47.8%) had RAS wild-type mCRC, while 105 (52.2%) had RAS status was found to be RAS mutant. Patients with RAS wild-type mCRC were treated with first-line anti-EGFR (cetuximab or panitumumab) or anti-VEGF (bevacizumab) containing combination therapies of fluorouracil with leucovorin and either irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen). In addition, patients with RAS mutation (K-RAS or N-RAS) also received first-line anti-VEGF containing combination therapies. FOLFIRI was administered as 180 mg/m^2 irinotecan and 400 mg/m^2 leucovorin followed by a 400 mg/m^2 bolus fluorouracil and a 48-h infusion of 2400 mg/m^2 fluorouracil, repeated every 2 weeks. FOLFOX6 was administered as 85 mg/m^2 oxaliplatin and 400 mg/m^2 leucovorin, followed by a 400 mg/m^2 bolus fluorouracil, followed by 48-h infusion of 2400 mg/m^2 of fluorouracil, repeated every 2 weeks. Cetuximab was administered as 400 mg/m^2 i.v. on day 1, then 500 mg/m^2 every 2 weeks. Bevacizumab was administered as 5 mg/kg every 2 weeks. Treatment was continued until disease progression or unacceptable toxic effects.

Left-sided tumors were determined those arising from the splenic flexure, descending colon, sigmoid colon or rectum. Right-sided tumors were classified as those arising from the appendix, cecum, ascending colon, hepatic flexure, or transverse colon. The response to treatment was assessed by chest CT scan and abdominopelvic CT scan or MRI findings using. Responses to treatment were evaluated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A complete response (CR) was defined as the disappearance of all measurable disease, a partial response (PR) represented a decrease of at least 30% of the tumor volume and stable disease (SD) defined small changes that did not meet the above criteria without actual progression of disease. Progressive disease (PD) was defined as more than 20% increase in tumor volume or any new sites of disease.

Statistics

All data were analyzed with SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The clinicopathological factors of the tumor localization and RAS mutation status groups were compared by means of the chi-square test and Fisher's exact test. The survival analyses and curves were established with the Kaplan-Meier method and compared with the log-rank test. PFS was defined from the initiation of treatment until disease first progression or to the date of death or loss of follow-up. OS was defined as the time from diagnosis to the date

of the patient's death or loss of follow-up. Univariate and multivariate analyses were performed with the Cox proportional hazards model to evaluate the importance of the tumor localization and other clinicopathological features. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided and p values less than 0.05 were considered statistically significant.

Results

Eighty-one patients (40.3%) were female and 120 (59.7%) male, with a median age of 59 years (range 28-84). Based on the tumor localization, in 140 (69.7%) patients tumors were classified as left-sided and 61 (30.3%) as right-sided. One hundred and one patients (52.2%) had RAS mutated tumor, while 96 patients (47.8%) had RAS wild type tumor. In the majority of patients (86.6%) BRAF mutation status was found to be wild type. The most common metastatic site was the liver (46.2%).

Significant difference was only detected between tumor localization groups with respect to the presence of BRAF mutation (p=0.013). The presence of BRAF mutation was significantly higher in right-sided tumors compared with left-sided tumors. One hundred and thirty one (65.2%) patients out of 201 were administered anti-VEGF containing regimen, and 70 (34.8%) anti-EGFR in the first-line setting. The median number of cycles was 12 in the anti-EGFR group versus 11 in the anti-VEGF group. The relationship between tumor localization and clinicopathological factors is summarized in Table 1.

At a median follow-up of 20.4 months (range 4.5-70.9), the median PFS was 12.5 months and the median OS was also 24.3 months for all patients. Univariate analysis was performed for PFS and OS in all mCRC cohort and showed that age, the presence of primary surgery, tumor localization, the presence of metastasectomy and/or local treatment were important factors for PFS. However, age and tumor localization were significant prognostic indicators for OS. In other words, median PFS and OS intervals for patients with left-sided tumors was significantly better compared to patients with right-sided tumors (PFS: 12.9 vs 10.1 months, p=0.003, and OS: 33.1 vs. 25 months, p=0.005, respectively; Figures 1 and 2).

Table 1. The correlation between tumor localization and clinicopathological factors

Factors	*Right-sided n (%)*	*Left-sided n (%)*	*p*
Gender			0.16
Female	20 (32.8)	61 (43.6)	
Male	41 (67.2)	79 (56.4)	
Age (years)			0.28
<60	37(60.7)	72 (51.4)	
>60	24 (39.3)	68 (48.6)	
Surgery for primary tumor			0.21
Absent	42 (68.9)	83 (59.3)	
Present	19 (31.1)	57 (40.7)	
RAS status (K&N-RAS)			0.54
Wild-type	29 (47.5)	67 (47.9)	
Mutated	32 (52.5)	73 (52.1)	
B-RAF status			0.013
Wild-type	50 (81.9)	130 (92.8)	
Mutated	6 (9.8)	0 (0)	
Unknown	5 (8.3)	10 (7.2)	
Combination treatment			<0.001
Oxaliplatin-based	38 (37.3)	11 (10.5)	
Irinotecan-based	64 (62.7)	94 (89.5)	
Targeted-treatment			0.40
Anti-VEGF	41 (67.2)	90 (64.3)	
Anti-EGFR	20 (32.8)	50 (35.7)	
Progression			0.49
Absent	31 (50.8)	73(52.1)	
Present	30 (49.2)	67 (47.9)	

Multivariate analysis with the Cox proportional hazards model was performed in order to further evaluate all of the significant prognostic factors that were detected in the univariate analysis for all mCRC patients. This showed that age (HR: 0.52, p=0.025), tumor localization (HR: 0.53, p=0.032), the presence of surgery for primary tumor (HR: 0.41, p=0.003) and the presence of metastasectomy and/or local treatment (HR: 0.35, p=0.029) were indipendent prognostic factors for PFS. Multivariate analysis was carried out for OS, and it demonstrated that age (HR: 0.59, p=0.023), tumor localization (HR: 0.66, p=0.043), RAS mutation status (HR: 2.67, p= 0.009) and the type of targeted agent (HR: 2.81, p=0.008) were independent prognostic indicators. The results of multivariate analysis for both PFS and OS in all patients with in CRC are shown in Table 2.

When the RAS wild type patient group was analyzed separately, the median age of the patients were 58.5 (range 28-80), while 59 (61.5%) patients were male and 37 (38.5%) female. According to tumor localization, 29 patients (30.2%) had disease in the right colon and 67 (69.8%) in the left colon. Most patients had BRAF wild-type (72.9%). Twenty nine (39.2%) of the patients received bevacizumab containing regimens and the remaining 67 (69.8%) were treated with anti-EGFR containing regimens. After first-line treatment 18.8% of the patients underwent metastasectomy and/or local treatment. In the univariate analysis for PFS, age, surgery for colon, tumor localization, metastasectomy and/or local treatment were found to be important prognostic factors in RAS wild type group (Table 3). On the other hand, median PFS duration was significantly shorter in patients with right-sided tumors than those with left-sided tumors (10.1 vs 12.9 months, p=0.005, Figure 3). When univariate analysis for OS was performed in RAS wild type,

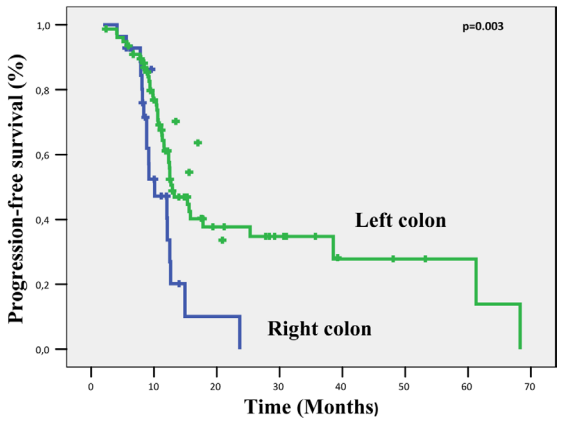

Figure 1. Progression-free survival according to tumor location for all RAS group.

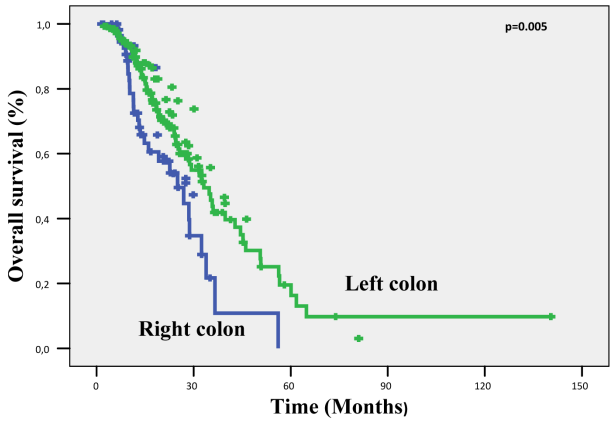

Figure 2. Overall survival according to sidedness in patients with mCRC regardless of RAS status.

Table 2. Multivariate analysis results for OS and PFS in patients with metastatic colorectal cancer

Factor	x^2	*p*	*HR**	*95% CI*
PFS				
Age (<60 vs >60 years)	5.0	0.025	0.52	0.29-0.92
Tumor localization (left and right)	4.6	0.032	0.53	0.29-0.84
Primary surgery	8.5	0.003	0.41	0.23-0.74
RAS mutation status	0.88	0.34	0.70	0.33-1.47
Targeted treatment type	1.22	0.26	0.63	0.28-1.41
Metastasectomy and/or local treatment	4.79	0.029	0.35	0.14-0.89
OS				
Age (<60 vs >60 years)	4.9	0.023	0.59	0.37-0.99
Tumor localization (left and right)	3.0	0.043	0.66	0.41-1.05
Primary surgery	1.5	0.21	0.73	0.45-1.19
RAS mutation status	6.8	0.009	2.67	1.28-5.56
Targeted treatment type	6.9	0.008	2.81	1.30-6.06
Metastasectomy and/or local treatment	0.9	0.75	0.92	0.55-1.54

* HR: to determine the relative risk of death and recurrence, CI: confidence interval, OS: overall survival, PFS: progression-free survival

age, tumor localization, BRAF mutation status, the type of target agent were significantly prognostic indicators (Table 3). In other words, the median OS interval of patients receiving anti-VEGF containing regimens was 50.7 months while for patients treated with anti-EGFR containing regimens it was 26.9 months (p=0.001). Similar to PFS, median OS was significantly better in patients with RAS wild type and left-sided tumors compared to patients with right-sided tumors (44.4 vs 25 months, respectively; p=0.008, Figure 4).

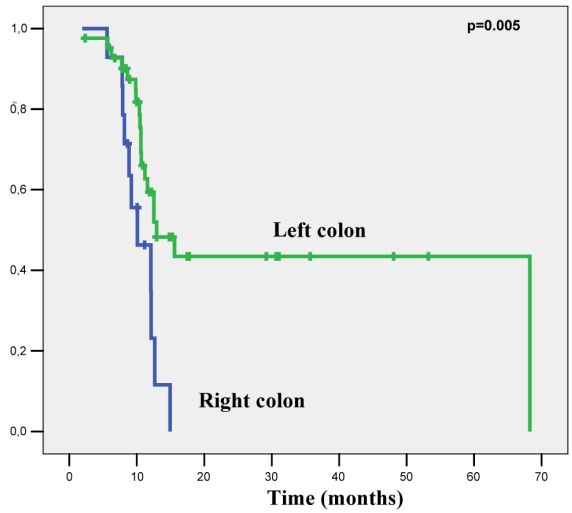

Figure 3. Median PFS duration was significantly shorter in patients with right-sided tumor than those with left-sided tumors (10.1 vs 12.9 months, p=0.005) for RAS wild type group.

In addition, multivariate analysis indicated that age (HR: 0.41, p=0.045), primary surgery (HR: 0.41, p=0.037) and tumor localization (HR:0.38, p=0.021) for PFS and age (HR:0.39, p=0.09), the presence of BRAF mutation (HR:0.59, p=0.019) and the type of targeted therapy (HR:3.16, p=0.025) for OS were independent prognostic factors. The results of multivariate analysis for both PFS and OS in all patients with mCRC are summarized in Table 4.

Discussion

In the present study, we investigated the prognostic importance of primary tumor localization in patients with mCRC, and its predictive impact on the treatment in patients with

RAS wild type subgroup treated with first-line anti-EGFR or anti-VEGF therapies in combination with irinotecan or oxaliplatin-based chemotherapy

Table 3. Univariate analysis results for PFS in patients with RAS wild type mutation

Variant	*Median PFS (months)*	*12-month PFS ratio (%)*	*95% CI*	*p*
Age, years				0.034
<60	11.2	76.3	9.5-12.8	
>60	12.6	67.6	NA	
Gender				0.46
Male	12.5	50.3	10.6-14.4	
Female	12.6	65.5	11.6-13.7	
Primary surgery				0.008
Yes	41.5	76.1	9.5-11.7	
No	10.6	41.0	NA	
Surgical type				0.87
Curative	NR	NA	NA	
Palliative	15.6	67.5	12.0-19.1	
Tumor localization				0.005
Right	10.1	46.3	6.2-13.9	
Left	12.9	87.4	8.4-17.3	
BRAF mutation status				0.99
Wild type	12.5	57.1	10.0-15.0	
Mutant	NR	NA	NA	
Unknown	11.6	39.1	9.1-14.1	
Targeted agent type				0.32
Bevacizumab	10.6	41.4	8.4-12.7	
Anti-EGFR	12.6	78.7	11.4-13.9	
Metastasectomy and/or local treatment				0.037
Yes	55.0	NA	NA	
No	12.0	50.7	10.1-14.0	

PFS: progression-free survival, CI: confidence interval, NA: not available, NR: could not be reached, EGFR: epidermal growth factor receptor.

Table 4. Multivariate analysis results for PFS and OS in patients with RAS wild type

Factor	x^2	*p*	*HR**	*95% CI*
PFS				
Age (<60 vs. >60 years)	3.8	0.045	0.41	0.16-1.0
Tumor localization (left and right)	5.3	0.021	0.38	0.16-0.86
Primary surgery	4.3	0.037	0.41	0.17-0.94
Targeted agent type	3.6	0.35	0.41	0.16-1.02
Metastasectomy and/or local treatment	1.1	0.30	0.45	0.10-2.04
OS				
Age (<60 and >60 years)	4.3	0.038	0.39	0.16-0.95
Tumor localization (left and right)	1.4	0.23	0.60	0.26-1.39
BRAF mutation status	5.4	0.019	0.59	0.38-0.92
Targeted agent type	5.0	0.025	3.16	1.15-8.65
Metastasectomy and/or local treatment	0.8	0.99	0.99	0.43-2.27

* HR: to determine the relative risk of death and recurrence, CI: confidence interval, OS: overall survival, PFS: progression-free survival

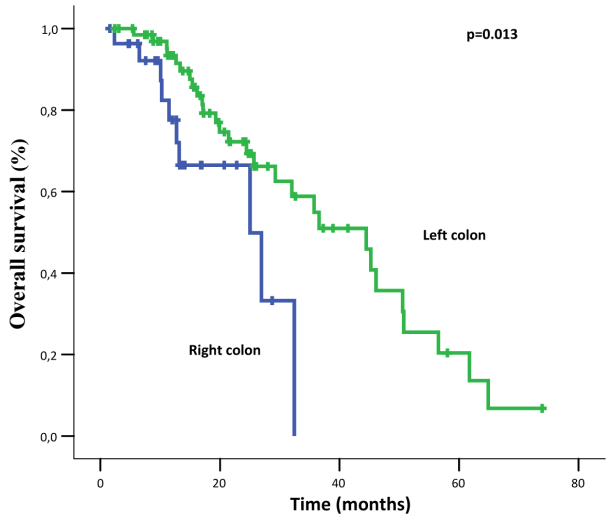

Figure 4. Overall survival curves in terms of sidedness in patients with RAS wild type mCRC.

regimens. The prevalence of B-RAF mutation was significantly higher in patients with left-sided tumors than for those with left-sided tumors. In all cohort and RAS wild type patients, primary tumor localization was found to be independent prognostic factor for both PFS and OS. No significant difference in PFS was detected with treatments using anti-EGFR compared with anti-VEGF added to chemotherapy backbone as first-line treatments for patients with RAS wild type mCRC. On the other hand, OS for patients treated with anti-VEGF containing regimens was significantly better than those receiving anti-EGFR containing regimens, regardless of tumor sidedness in RAS wild type subgroup.

In recent studies, it has been demontrated that tumors located in the right and left colon have different molecular and genetic characteristics and this may have a role in treatment planning [12-14]. In addition, it was shown that the presence of RAS wild type and BRAF wild type were the most common tumors in the left colon, whereas RAS and BRAF mutations were commonly seen in the right colon [15-17]. In our study, when the molecular genetic differences were evaluated in the whole population; 52.2% of the patients were RAS mutant, whereas 6 patients (3%) were BRAF mutant patients. The presence of RAS mutation was similar to the literature regarding primary tumor location. On the other hand, 6 of 6 BRAF mutant patients had right-sided tumor. This situation was statistically higher than the ones that were compatible with the literature and left colon [18,19]. BRAF is another component of the RAS-RAF-MAPK pathway, with an incidence of 4-8% in CRC [20,21]. While 95% of the cancers with BRAF mutation are located in the right, only 48% of BRAF wild type cancers are right-sided. However, the incidence of BRAF mutation was 18.4-22.4% in right-sided cancers and 1.3-7.8% in left-sided and rectal cancers [17]. Many studies have shown that BRAF mutation is associated with right-sided cancer. In a study by Yamauchi et al a significant linear decrease was observed in the incidence of BRAF mutation when the tumor location moved from the right colon to the rectum (40-2.3%) [22].

Many studies have investigated the relationship between survival and tumor sideness. In general, left-sided cancers were found to be associated with better prognosis and longer survival and this relationship may vary according to the stages. However, different results have been reported in different studies and it is thought that this may be due to the analysis parameters and patient het-

erogeneity in the studies [14,23-25]. In our study, regardeless of the RAS mutation, the median PFS duration in patients with right colon tumors was significantly worse compared to those with the left colon tumors. Similarly, when OS was evaluated, the median OS was significantly shorter in right-sided tumors than that in left colon tumors. Considering these data, in our study the right colon tumors were found to be associated with shorter PFS and OS in patients with mCRC and thus, our findings appear to be compatible with the literature [3,9,26-28].

In a recent meta-analysis of 66 studies, it was shown that left-located tumors were associated with significantly less mortality independent of stage [5]. In another meta-analysis including the final phase II and III studies, tumor localization has proven to be an independent prognostic factor for PFS and OS in mCRC [12]. In yet another study, it was reported that tumor location was not a prognostic factor for PFS, but had a predictive value [29]. In our study, only *de novo* mCRC patients were included and this supports the fact that our study is more homogeneous and our findings are consistent in terms of the relationship between treatment outcomes and primary tumor localization. Moreover, in our study, primary tumor localization was shown to be an independent prognostic factor for both PFS and OS regardless of RAS mutation status compatible with the literature [5,11,12].

A retrospective analysis of the phase-III CALGB / SWOG 80405 study regarding primary tumor localization, which analyzed the efficacy of bevacizumab or cetuximab addition to chemotherapy in patients with RAS wild type with mCRC, also revealed that median OS in patients with mCRC with primary right colon localization was shorter than those in the left colon localization [30,31]. Similarly, in a study investigating mCRC with 198 KRAS wild type mutation, it was shown that the right-located tumors were associated with high CIMP and BRAF mutations, which resulted in poor survival and anti-EGFR response [31]. Similar results were obtained in a metanalysis performed by Eklöf et al who reported that BRAF mutation was generally observed in right-located tumors and was associated with poor prognosis [32].

In our study, there was no significant difference between RAS mutant and RAS wild type patients in terms of survival. However, when the right-sided and left-sided cancers were separately analyzed, the median PFS and OS durations of RAS-wild type right-sided cancers were significantly worse than those with tumors on the left colon. Our findings were thus consistent with the literature [7,11,12]. In subsequent multivariate analyses, primary tumor localization for PFS was found to be an independent prognostic factor, both in the whole population and in the RAS-wild type subgroup. But, for OS, primary tumor localization was an independent prognostic indicator in RAS wild type subgroup while it was in the whole population. This difference may be due to the relatively low sample size of RAS-wild type and right-sided patients.

Most of the data on anti-EGFR treatment in mCRC patients were performed with cetuximab. Studies have shown that combination therapy with cetuximab improves survival in RAS wild type tumors. In a study investigating the efficacy of chemotherapy and cetuximab combination in mCRC, comparison of tumor localization showed the median PFS was 7.7 months and median OS 23.6 compared with 7.7 months. When KRAS mutation status was not detected, there was no significant difference in KRAS mutant tumors in terms of PFS and OS, but it was determined that tumor localization was effected in KRAS wild type tumors on PFS and OS [10]. Brule et al found that patients with KRAS-wild type left-sided mCRC had a longer duration of PFS in patients with cetuximab chemotherapy combination [29]. Similarly, anti-EGFR treatment has been shown to be more useful in patients with left-sided RAS and BRAF wild types [11,12].

There are two phase III and one phase II study comparing the head-to-head chemotherapy combination with anti-VEGF and anti-EGFR agents in patients with metastatic CRC [9,34-36]. The retrospective analysis of CRYSTAL [37] and FIRE-3 phase III studies in the RAS wild type patient population with mCRC who were treated with a combination of cetuximab chemotherapy it has been shown to have a longer survival in patients with left-sided tumors compared to those with right-sided disease [7]. On the other hand, when anti-VEGF treatment is added to chemotherapy, it also prolongs the survival in mCRC patients. In a study carried out by Boisen et al, 1947 patients were analyzed in order to investigate the relationship between primary tumor location and survival in patients with mCRC. Thirty-nine percent of the patients had right colon and 61% left colon. The median OS was 20.5 months in the left-sided tumors and 14 months ($p<0.001$) in the right-sided tumors. Survival in patients with CapeOX plus bevacizumab treated for primary sigmoid and rectal region was found to be better than in patients with tumor in other regions of the colon [38].

In the CALGB/SWOG80405 study, all RAS-wild type patients with mCRC who were treated with chemotherapy with either bevacizumab or cetuxi-

mab in the fist-line setting were retrospectively analyzed. The findings revealed that ORR was significantly better for patients with left-sided tumors compared with right-sided tumors. On the other hand, according to targeted treatments, ORR was similar for patients receiving bevacizumab or cetuximab in the right-sided tumors, but it was better for patients treated with cetuximab in the left-sided tumors compared with bevacizumab arm (69.4 vs. 57.9%) [30]. There was no difference in terms of PFS and OS in the two treatment arms in RAS-wild type patients in the same trial. In the FIRE-3 study, its primary endpoint was ORR, FOLFIRI-cetuximab was compared with FOLFIRI-bevacizumab in patients with mCRC as first-line setting. This trial did not meet the endpoint but it showed superiority in terms of OS in patients receiving cetuximab compared with bevacizumab. This difference could not be clearly interpreted [34,35]. Our findings were thus compatible with the literature in terms of ORR [30,34].

In the present study, the relationship between targeted therapies and survivals were found to be different from the literature [5,7,9,11]. The median OS of the RAS wild type patients with bevacizumab as targeted agent was 50.7 months, while the median OS was 26.9 months in patients treated with anti-EGFR as the targeted agent. Thus, OS was significantly better in patients receiving bevacizumab-chemotherapy. However, response rates and PFS were similar in both groups. According to the literature this difference might be due to more frequent application of local ablative therapy/metastasectomies in the bevacizumab arm, as was the second lines treatment effects.

The pooled analysis was performed according to the primary tumor localization in these three important studies and the combination of anti-EGFR-chemotherapy was found to be significantly more effective in each of the tumors with left colon. Although bevacizumab-chemotherapy appeared to be slightly less effective in the left colon, it appeared to be more effective in tumors located in both colon and even more effective in patients with right colon than in anti-EGFR agents [12]. Recently a meta-analysis of FIRE-3, CALGB/SWOG80405 and PEAK studies was performed and the patients with the left-sided RAS wild type mCRC had significantly more benefit from anti-EGFR treatments than those with the right-sided tumors [11]. In our study, primary tumor localization was found to be an independent prognostic factor for both PFS and OS. According to our findings, the tumors located in the left colon had better survival than those localized on the right colon regardless of treatment. However, there was no difference in the combination of anti-EGFR and bevacizumab chemotherapy in the whole population. The probable cause may be related with the relatively low sample size of right colon tumors and the heterogeneous group of patients.

In a study of 194 patients with mCRC conducted by Zhang et al, palliative resection for 125 patients and treated with chemotherapy alone was performed. In that study, primary tumor location was found to be an independent risk factor for survival. However, subgroup analysis showed that palliative colon resection significantly prolonged OS in cancers located in the left colon. However, no similar benefit has been detected in the right-sided tumors. There was no statistically significant difference between the palliative resection and chemotherapy in patients with asymptomatic mCRC [39]. In our study, we also detected that the primary tumor resection was an independent prognostic factor for PFS, regardless of targeted treatments. In their SEER database analysis, Tarantino et al found a significant relationship between palliative resection and longer OS in patients with mCRC. Palliative primary tumor resection has been shown to reduce death risk by 60% [40]. In our study, analysis was performed independent of the RAS mutation status. There was a significant relationship between primary tumor resection, metastasectomy/local treatment and PFS. In other words, PFS was significantly prolonged in the presence of curative surgery of the primary tumor. However, OS was similar in both groups. In the RAS-wild type of patients, there was no significant relationship between PFS and OS with the use of curative surgery for primary tumor or metastasectomy/local treatment. This may be due to a low RAS wild type sample size.

The present study has several limitations. Its retrospective nature and short follow-up interval are important limitation, which might have influenced the results. The other limitation of this study is the relatively small sample size. Although our results should be confirmed using prospective studies with larger sample sizes that analyze curative (local treatment/metastasectomy, primary tumor resection) and paliative treatment options for patients with all RAS mCRC in terms of colon sidedness, we believe that our study is noteworthy and these results contribute to the knowledge of this disease because distinct prognostic factors including primary tumor resection and local treatments were analyzed for predicting relapse together with survival, unlike in previous studies.

In conclusion, it has been shown that primary tumor location is a prognostic factor in mCRC patients. Our study showed that the tumor location

might have different characteristics, especially in terms of genetic, prognostic and treatment efficacy. Although these differences appear to be generally compatible with the literature, it can be thought that the different results may result from the variability between the analysis methods and parameters in the studies. However, further development of genetic and embryological studies may clarify this issue. In addition, overcoming the difficulties in the diagnosis of tumors located in the right colon may clinically improve the existing significant differences.

Conflict of interests

The authors declare no conflict of interests.

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