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ORIGINAL RESEARCH

Bevacuzimab May Be Less Effective in Obese Metastatic Colorectal Cancer Patients

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Abstract

Purpose The purpose of this study was to investigate whether obesity affects survival in metastatic colorectal cancer (mCRC) patients treated with bevacizumab combined with chemotherapy.

Methods A total of 563 patients with mCRC who had received first-line chemotherapy in combination with bevacizumab were studied. Patients were grouped as obese (BMI levels > 30) or non-obese (BMI levels < 30). Progression-free survival (PFS) and overall survival (OS) were analyzed. Primary tumor location was also investigated in terms of PFS and OS.

Results The median age of the patients was 59 years. The non-obese group had longer PFS than the obese group ($P = 0.030$). The 2-year survival rate of the non-obese group was also significantly higher ($P = 0.036$). The median PFS of non-obese patients was significantly longer in Kras wild-type patients (10.1 vs. 8.1 months, $P = 0.010$). Among patients with left-sided primary tumor location, median PFS and OS were significantly higher in the non-obese group (PFS non-obese, 11.5 months; obese, 8.8 months; $P = 0.002$) (OS non-obese, 29.4 months; obese, 21.4 months; $P = 0.026$).

Conclusions Efficacy of bevacizumab may be lower in obese patients. Among patients with Kras wild-type left-sided tumors treated with bevacizumab-based regimens, the prognosis could be worse for obese patients than that for non-obese patients. There is a need for prospectively designed studies of obese patients to prove the efficacy and dosages of bevacizumab in treatment of mCRC.

Keywords Metastatic colorectal cancer · Bevacizumab · Body mass index · Obesity · K-ras

Introduction

Obesity is a well-known carcinogenic factor for colorectal cancer [1, 2]. However, the relationship between obesity and malignancy is still not well understood. Obesity can cause production of VEGF, angiopoietin-2, and other growth factors that induce tumor growth [3, 4]. It can also cause insulin resistance, hyperinsulinemia, and increased production of adipokines and proinflamatory cytokines that may be associated with tumor progression [5]. A recent study suggested a link between obesity and sporadic MSI-high colorectal cancer in women [6].

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Bevacizumab is an anti-angiogenic agent (targeting VEGF) used in metastatic colorectal cancer (mCRC) therapy [7]. Because whole VEGF forms are inhibited by bevacizumab, this process prevents VEGF/VEGF receptor binding [8].

Body mass index (BMI) is used to measure obesity. However, visceral fat area (VFA) and subcutaneous fat area (SFA), measured with computed tomography, can also be used for this purpose [9]. One study found that the survival outcomes of mCRC patients receiving bevacizumab combined with chemotherapy worsened as body fat ratio increased [10]. In a prospective cohort study, high BMI was associated with increased risk of Kras-mutated tumors in men but not in women [11]. In an EPIC cohort study, BMI and WC (waist circumference) were most strongly associated with survival in patients with left colon cancer [12]. In a recent analysis of the CALGB 80405 trial, Kras wild-type mCRC patients with left-sided tumors receiving either bevacizumab- or cetuximab-based therapies had a superior prognosis to those with right-sided tumors [13]. Therefore, it is important to know whether obesity can alter the effect of bevacizumab depending on tumor location.

We know that obese people have higher levels of circulating VEGF [14]. Thus, the affectivity of anti-VEGF treatments may vary according to patients' BMI. In one study, high BMI among mCRC patients treated with bevacizumab was associated with shorter time to tumor progression [15]. However, in the CAIRO study, high BMI was associated with better median overall survival [16]. In another retrospective study, bevacizumab was not associated with survival in high-BMI mCRC patients [17]. In contrast, another study found that obese patients treated with bevacizumab had poorer outcomes [18]. In a pooled analysis of 21,149 colorectal cancer patients, low BMI was found to be associated with increased risk of progressive disease [19]. As a result, there is no consensus about the impact of obesity in bevacizumab-treated mCRC patients. We need to learn more about the biological relationship between bevacizumab resistance and obesity.

In the present study, we aimed to investigate whether obesity affects survival in metastatic colorectal cancer patients treated with regimens containing bevacizumab.

Patients and Methods

We retrospectively analyzed data from 563 consecutive mCRC patients who received bevacizumab-based chemotherapies from nine centers belonging to the Turkish Oncology Group. The patients had been treated between January 2005 and December 2015. The study was approved by the ethics committee at Necmettin Erbakan University's Meram Faculty of Medicine and carried out in accordance with Declaration of Helsinki principles and all applicable regulations.

Patients were grouped as obese (BMI > 30) or non-obese (BMI < 30). Survival analyses were performed on the two groups. Additionally, three patient groups were identified based on their treatment regimens: irinotecan-fluropyrimidine (FI-bev)-based regimens (FOLFIRI-bev and XELIRI-bev); oxaliplatin (FO-bev)-based regimens (FOLFOX-bev and XELOX-bev); and fluoropyrimidine (F-bev)-based regimens (FUFA-bev and capecitabine-bev).

Table 1 Patient characteristics

	BMI < 30	BMI > 30	*P*
n (%)	474 (84%)	89 (16%)	
Age (years)	58 ± 12	58 ± 10	
ECOG			
≤ 1	402 (85%)	71 (80%)	0.151
> 1	72 (15%)	18 (20%)	
Female	175(77%)	53 (23%)	*< 0.001*
Male	299 (90%)	36 (10%)	
Kras status			
Wild	163 (81.5%)	37 (18.5%)	0.160
Mutant	157 (85.8%)	26 (14.2%)	
Primary tumor location			
0.160	120 (86%)	20 (14%)	0.388
Left	335 (84%)	63 (16%)	
Kras in female			
Wild	48 (39%)	23 (59%)	*0.023*
Mutant	75 (61%)	16 (41%)	
Kras in male			
Wild	115 (89%)	14 (11%)	0.581
Mutant	82 (89%)	10 (11%)	
Primary tumor location, Right			
Kras wild	36 (84%)	7 (16%)	0.476
Kras mutant	44 (86%)	14 (14%)	
Primary tumor location, Left			
Kras wild	120 (80%)	29 (20%)	0.114
Kras mutant	105 (87%)	16 (13%)	
Metastases			
Liver	215 (46%)	38 (43%)	0.487
Multiple	147 (31%)	25 (28%)	
The other sites	110 (23%)	26 (29%)	
Treatments			
FI+BEV	308 (65%)	52 (58%)	
FO+BEV	142 (30%)	33 (37%)	
F+BEV	24 (5%)	4 (5%)	

If the primary tumor location was the transverse colon, it was excluded. The transverse colon was the primary tumor location in 3.6% ($n = 20$) of the entire cohort

P values were italicized if they were statistically significant ($P < 0.05$)

FI+BEV, fluorouracil + irinotecan-based regimens; *FO+BEV*, fluorouracil + oxaliplatin-based regimens; *F+BEV*, fluorouracil-based regimens (5-FU or capecitabine); *n*, number of patients; *Left*, left colon (splenic flexure, descending colon, sigmoid colon, and rectum); *Right*: right colon (ascending colon, hepatic flexure)

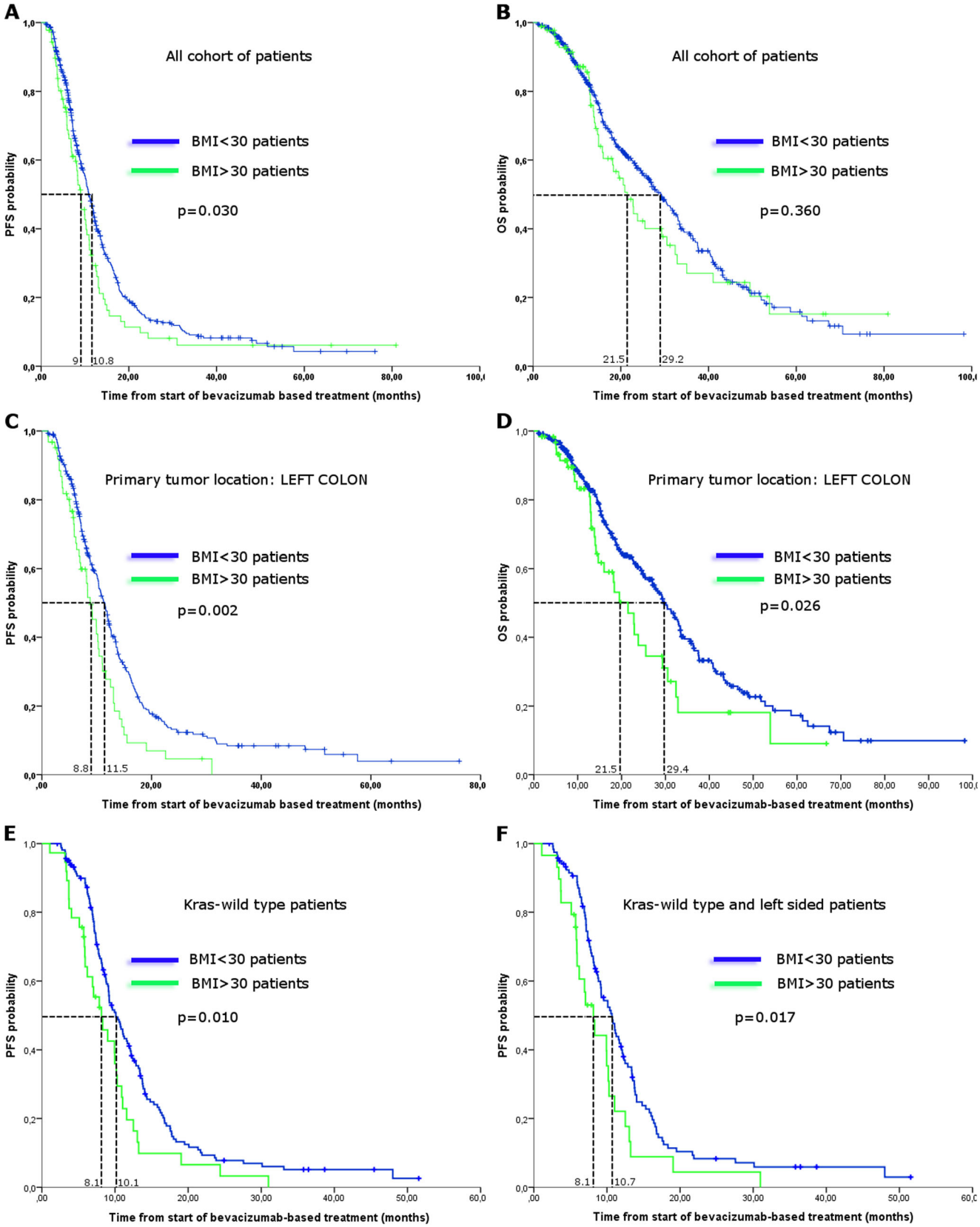

Fig. 1 **a** PFS of obese or not in all cohorts of patients. **b** OS of obese or not in all cohort of patients. **c** PFS of obese or not in patients who have left-sided primary tumor location. **d** OS of obese or not in patients who have left-sided primary tumor location. **e** PFS of obese or not in Kras wild type. **f** PFS of obese or not in Kras wild-type and left-sided primary tumor location

Kras mutational status and primary tumor location were evaluated to understand their relationship to obesity. Prevalence of positive Kras mutational status in obese and non-obese patients was analyzed. The patients were further categorized into two groups according to primary tumor location: left; left colon 71% ($n = 398$) (splenic flexure, descending colon, sigmoid colon, and rectum); and right: right colon 25% ($n = 140$) (ascending colon, hepatic flexure). If the primary tumor location was the transverse colon, it was excluded from the tumor location analysis. The transverse colon was the primary tumor location in 4% ($n = 20$) of the entire cohort. The primary tumor locations of five patients were unknown.

Statistical analysis was performed using SPSS version 20.0 software for Windows (SPSS, Chicago, IL). Standard descriptive statistics were used. Both OS and PFS were calculated from the start of administration of the bevacizumab-containing regimen. The Kaplan-Meier method was used to estimate survival. To compare OS and PFS in different groups, a log-rank test was used. Univariate and multivariate cox proportional hazards models were used to quantify the influence of the considered treatment modalities on survival in the presence of other potential predictive and prognostic factors. P values of < 0.05 were considered statistically significant. The association between dichotomized prognostic factors was evaluated by the chi-square test. Kras status, PFS, OS, and BMI were also analyzed using subgroups.

Results

The median age of the patients was 59 years (range 21–84). The cohort was 40% female and 60% male. The proportion of male patients was higher in the non-obese group (90 vs. 77%, $P < 0.001$). The prevalence of positive Kras mutational status in obese and non-obese patients was similar across the cohort ($P = 0.160$). However, the rate of Kras mutation was significantly higher in non-obese women than that in obese women (61 vs. 41%, respectively, $P = 0.023$). No such difference was found in men (42 vs. 42%, respectively, $P = 0.581$). Table 1 shows the clinical characteristics of the patients.

The non-obese group had longer PFS than the obese group (mPFSs 10.8 vs. 9 months, respectively, $P = 0.030$) (Fig. 1a). The 2-year survival rate of the non-obese group was also significantly higher (34 vs. 23%, respectively, $P = 0.036$) (Table 2). There was no statistically significant difference in terms of OS between the non-obese and obese groups (mOS 29.2 vs. 21.5 months, respectively, $P = 0.360$) (Fig. 1b). Among the non-obese patients, there was no difference between FI-bev, FO-bev, and F-bev groups in terms of PFS and OS analyses ($P = 0.493$, 0.643, respectively). In the obese group, PFS and OS of the FI-bev and FO-bev subgroups were longer than those of the F-bev subgroup. However, the number of patients in the F-bev subgroup was only five.

Table 2 Survival results in accordance with BMI

Survival (months)	BMI < 30	BMI > 30	*P*
PFS	10.8 (CI 9.9–11.6)	9 (CI 7.4–10.6)	*0.030*
OS	29.2 (CI 25.6–32.5)	21.5 (CI 16.7–26)	0.360
2 year OS (%)	34%	23%	*0.036*
5 year OS (%)	2.8%	3.5%	0.469
PFS			
FI-bev	11.2 (CI 10.2–12)	9 (CI 6.9–11)	0.300
FO-bev	9.6 (CI 8.3–10.9)	10.3 (CI 7.8–12.7)	0.126
F-bev	12.1 (CI 9–15.3)	4 (CI 1.7–6.3)	*0.001*
P	0.493	*0.030*	
OS			
FI-bev	29.2 (CI 25–33.4)	22.8 (CI 16.9–28.6)	0.982
FO-bev	27 (CI 24.2–29.8)	22.9 (CI 13–32.8)	0.229
F-bev	33.3 (CI 16–20.1)	9.8 (CI 2.2–17.4)	*0.003*
P	0.643	*0.030*	
PFS			
Kras wild	10.4 (CI 8.7–11.5)	8.1 (CI 5.6–10.6)	*0.013*
Kras mutant	11.5 (CI 10.2–12.9)	8.8 (CI 7.2–10.3)	0.375
P	0.659	0.379	
OS			
Kras wild	30.6 (CI 25.8–35.4)	30.4 (CI 26.6–34.1)	0.129
Kras mutant	31.9 (CI 27.3–36.5)	31.8 (CI 26.3–37.2)	0.962
P	0.293	0.474	
PFS			
Male	11.5 (CI 10.5–12.5)	9 (CI 7.2–10.8)	*0.005*
Female	10.2 (CI 9–11.4)	9.2 (CI 6.7–11.6)	0.983
P	*0.017*	0.302	
OS			
Male	27 (CI 21.5–32.5)	23.8 (CI 8.5–39.1)	0.925
Female	30.4 (CI 25.4–34.8)	20.9 (CI 17.9–23.9)	0155
P	0.343	0.613	
PFS, primary tumor location			
Right	9.6 (CI 7.9–11.4)	7.8 (CI 4.5–11.2)	0.442
Left	11.5 (CI 10.5–12.4)	8.8 (CI 6.9–10.7)	0.002
P	0.795	0.712	
OS, primary tumor location			
Right	26.1 (CI 20.5–31.6)	20.9 (CI 0.0–44.6)	0.552
Left	29.4 (CI 25.8–32.9)	21.4 (CI 15.5–27.4)	*0.026*
P	0.208	0.276	
PFS, primary tumor location: Right			
Kras wild	9.1 (CI 7.8–10.5)	7.8 (CI 0–17.6)	0.491
Kras mutant	10.6 (CI 7.6–13.6)	6.8 (CI 4.4–9.3)	0.148
P	0.664	0.705	
PFS, primary tumor location: Left			
Kras wild	10.7 (CI 8.9–12.4)	8.1 (CI 6.0–10.2)	*0.017*
Kras mutant	11.9 (CI 10.7–13.2)	8.8 (CI 6.1–11.5)	0.074
P	0.456	0.870	
OS, primary tumor location: Right			
Kras wild	26.6 (CI 20.4–32.8)	20.9 (CI 20.1–21.6)	0.992
Kras mutant	31.8 (CI 16.4–47.1)	14.9 (CI 0.3–29.5)	0.887
P	0.922	0.919	
OS, primary tumor location: Left			
Kras wild	31.3 (CI 26.4–36.2)	22.8 (CI 16.2–29.3)	0.069
Kras mutant	31.9 (CI 25.9–37.9)	19.5 (CI 16.6–22.3)	0.313
P	0.267	0.723	

If the primary tumor location was the transverse colon, it was excluded tumor location survival analyses

P values were italicized if they were statistically significant ($P < 0.05$)

CI, confidence interval (95%); *BMI*, body mass index; *Left*, left colon (splenic flexure, descending colon, sigmoid colon, rectum); *Right*, right colon (ascending colon, hepatic flexure)

Across the cohort, there were no PFS or OS differences between Kras mutant- and Kras wild-type groups (PFS 10.9 vs. 9.6 months, respectively, $P = 0.373$; OS: 31.8 vs. 30.4 months, respectively; $P = 0.474$). However, the median PFS of non-obese Kras wild-type patients was significantly longer than that of obese ones (10.1 vs. 8.1 months, $P = 0.010$) (Fig. 1e). There was no significant difference in Kras mutant-type patients (Table 2). In patients with right-sided primary tumor location, PFS and OS were not significantly different between the non-obese and obese groups. But among the patients with left-sided primary tumor location, PFS and OS were significantly higher in the non-obese group than that in the obese group (PFS non-obese, 11.5 months; obese, 8.8 months; $P = 0.002$) (OS non-obese, 29.4 months; obese, 21.4 months; $P = 0.026$) (Fig. 1c, d). Among the Kras wild-type patients with left-sided primary tumor location ($n = 149$), the median PFS of the non-obese group was significantly higher than that of the obese group (10.7 months vs. 8.1 months, respectively, $P = 0.017$) (Fig. 1f).

In the univariate cox regression analyses, multiple factors were analyzed (ECOG performance score, obesity, age, gender, chemotherapy combinations, and RAS mutational status) (Table 3). Of these, only three (ECOG, obesity, gender) significantly affected PFS univariately (HR 0.46, 0.81, and 0.75 respectively). In the multivariate analyses, ECOG performance status was found to be the most powerful prognostic factor for PFS (HR 0.47, $P < 0.001$).

Discussion

Obesity is associated with increased VEGF levels. Adipose tissue releases VEGF-like angiogenic factors into the blood. Therefore, therapy with bevacizumab may be affected [20]. We based our definition of obesity on BMI. Other measures can be used, however, such as SFA, VFA, and waist circumference.

In this study, median PFS was 10.8 and 9 months for the non-obese and obese groups, respectively. Two-year survival was higher in the non-obese group. There was no difference between the two groups in terms of OS. The rate of Kras mutation was significantly higher in non-obese than that in obese women. Among the non-obese patients, median PFS was significantly higher in Kras wild-type patients. In the non-obese group, median PFS and OS were significantly higher in patients with left-sided primary tumor location. In Kras wild-type patients with left-sided primary tumor location, the median PFS of the non-obese group was significantly higher than that of the obese group. These results may show that obesity could serve as a prognostic factor for mCRC patients treated with bevacizumab-based regimens. In particular, among Kras wild-type patients with left-sided tumors being treated with bevacizumab-based regimens, prognosis could be worse for obese patients than that for non-obese patients. This knowledge could be useful to clinicians when making treatment decisions for patients with Kras wild-type left-sided tumors. However, prospective studies would be required to validate these findings.

The CALBG/SWOG 80405 trial investigated the impact of primary tumor location (left-sided and right-sided) in mCRC. In Kras wild-type patients, the left-sided group had higher OS than the right-sided group (34.2 months vs. 19.4 months, respectively, $P < 0.0001$) [13]. Our study also investigated the relationship between Kras and BMI, dividing patients into left- and right-sided groups. The only association we found was in left-sided Kras wild-type patients; median PFS was significantly longer in the non-obese group than that in the obese group (10.7 vs. 8.1 months, respectively, $P = 0.017$).

In another study, VFA, BMI, and SFA were evaluated for survival analyses of mCRC patients treated with bevacizumab-based chemotherapy [10]. Time to progression (TTP) was shorter in patients whose BMI and VFA were higher than the median value. The present study considered whether obesity can predict the efficacy of bevacizumab-

Table 3 Univariate and multivariate cox regression analyses on PFS

Parameters	Progression-Free Survival					
	Univariate			Multivariate		
	HR	95% CI	*P*	HR	96% CI	*P*
ECOG ≤ 1 or not	0.46	0.36–0.59	*< 0.001*	*0.47*	*0.35–0.60*	*< 0.001*
Gender male or not	0.81	0.67–0.98	*0.035*	0.83	0.68–1.02	0.082
BMI < 30 or not	0.75	0.58–0.97	*0.030*	0.89	0.68–1.1	0.426
Kras wild or mutant	0.90	0.67–1.20	0.474			
Right- or left-sided*	0.91	0.69–1.20	0.498			

In parameters field, result is in favor of the first statement

P values were italicized if they were statistically significant ($P < 0.05$)

HR, hazard ratio; *ECOG*, Eastern Cooperative Oncology Group performance score; *BMI*, body mass index

*Right colon or left colon defined anatomically as in "Patients and Methods"

based treatments in mCRC patients. We could not find an OS-predictive role for obesity. Other factors may be more important than obesity for OS. In addition, most of our patients had received other treatments after experiencing progression with bevacizumab-based chemotherapies.

Berg and colleagues found that molecular changes related to Kras activation were more common in obese endometrial complex atypical hyperplasia patients, suggesting different prevention and systemic treatment strategies might be appropriate for obese and non-obese patients [21]. When the mutation threshold in colon cancer was investigated, fewer Kras mutations were detected in patients with high BMI [22]. While we did not find any difference in Kras mutation rates between obese and non-obese groups, we observed that in the Kras wild-type patients, the median PFS of non-obese patients was significantly longer than that of obese patients (10.4 vs. 8.1 months, respectively, $P = 0.013$). There was no significant difference between the groups among Kras mutant-type patients. In a study that evaluated associations of anthropometric factors with Kras and BRAF mutation status in primary CRC, high BMI was found to be associated with risk of Kras-mutated tumor in men, but not in women [11]. In the present study, conversely, the rate of Kras mutation was significantly higher in non-obese than that in obese women (61 vs. 41%, respectively, $P = 0.023$). No difference was found in men.

Simkens and colleagues [23] compared the impact of BMI on OS as seen in the results of two phase III studies (CAIRO trial [16]: advanced colorectal cancer patients were administered chemotherapy; CAIRO2 trial [24]: patients were administered chemotherapy plus bevacizumab). Patients with higher BMI in the CAIRO trial had significantly longer OS. However, no association between obesity and survival was found in the CAIRO2 trial. The present study found that PFS was worse for obese patients.

Anti-angiogenic agents (sunitinib, bevacizumab, and sorafenib) were investigated as to their effects on TTP and OS in metastatic renal cell carcinoma patients grouped according to BMI, SFA, and VFA [25]. Investigators found shorter OS and TTP in patients with higher SFA and VFA. This study supports our findings regarding the impact of obesity in mCRC. Survival may be predicted by obesity in patients treated with anti-angiogenic agents.

There were some limitations to our study. It was retrospectively designed. There is no data about expanded RAS mutation. We were unable to perform analyses using definitions of obesity based on measures other than BMI (e.g., VFA, waist circumference, SFA).

The efficacy of bevacizumab may be lower in obese patients. Standard bevacizumab dosages per kilogram may not be sufficient to antagonize the increased VEGF levels found in obese patients. Obesity-related factors such as insulin resistance and increased adipokine levels could constitute another cause of resistance to anti-angiogenic agents.

In conclusion, these results may show that obesity could serve as a prognostic factor for mCRC patients who have been treated with bevacizumab-based regimens. In particular, among Kras wild-type left-sided tumor patients with bevacizumab-based regimens, the prognosis could be worse for obese patients than that for non-obese patients. This knowledge could be of use to clinicians when making treatment decisions for patients with Kras wild-type left-sided tumors. However, prospective studies will be needed to validate these findings.

Compliance with Ethical Standards The study was approved by the ethics committee at Necmettin Erbakan University's Meram Faculty of Medicine and carried out in accordance with Declaration of Helsinki principles and all applicable regulations.

Conflict of Interest The authors declare that they have no conflict of interest.

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