ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2025.2025-3-22
J Oncol Sci 2025;11(2):96-103

Comparison of First-Line FOLFOX versus FOLFIRI in RAS Mutant Metastatic Colorectal Cancer Patients

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ABSTRACT

Objective: Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality, with rat sarcoma (RAS) and proto-oncogene B-raf (BRAF) mutations associated with worse prognosis in metastatic settings. Despite advances in treatment, the optimal chemotherapy backbone combined with bevacizumab in RAS/BRAF-mutant metastatic CRC remains unclear. Our study aimed to investigate the best chemotherapy backbone in this patient group.

Material and Methods: This retrospective study compared the efficacy and safety of first-line infused 5-fluorouracil, folinic acid and oxaliplatin (mFOLFOX6)+bevacizumab versus infused 5-fluorouracil, folinic acid and irinotecan (FOLFIRI)+bevacizumab in patients with RAS/BRAF-mutant metastatic CRC treated between November 2016 and January 2024. Overall survival (OS), progression-free survival, and clinical characteristics were evaluated. Statistical analyses included Kaplan-Meier survival estimates, Cox regression models, and subgroup analyses.

Results: Among 130 patients, the median OS was significantly longer in the mFOLFOX6+bevacizumab group [22.6 months, 95% confidence interval (CI): 16.0-29.2] compared to the FOLFIRI+bevacizumab group (15.8 months, 95% CI: 10.7-20.8). ECOG performance status and chemotherapy backbone were significant prognostic factors for OS. Subgroup analysis revealed that patients with Eastern Cooperative Oncology Group performance status 2-4, and those with *de novo* metastases had worse outcomes, while younger patients (<60 years) benefited more from FOLFIRI+bevacizumab.

Conclusion: mFOLFOX6+bevacizumab demonstrated superior survival outcomes compared to FOLFIRI+bevacizumab in first-line treatment of RAS/BRAF-mutant metastatic CRC. These findings highlight the need for further randomized, prospective trials to validate these results and inform treatment strategies for this challenging patient population.

Keywords: Colorectal cancer; KRAS; BRAF; FOLFOX; FOLFIRI; bevacizumab

INTRODUCTION

Globally, colorectal cancer (CRC) continues to rank among the top causes for morbidity and death.[1] About 20% of CRC patients had metastases at the moment of diagnosis, making the disease's stage one of the most crucial determinants of prognosis, and approximately half of those with localised disease will progress to the metastatic stage.[2-4] In metastatic patients, 5-year survival is less than 20%.[5]

For metastatic disease, the backbone of treatment is 5-fluorouracil (5-FU)-based regimens. These include 5-FU+irinotecan (FOLFIRI), capecitabine+oxaliplatin, and 5-FU+oxaliplatin (FOLFOX).[6] In selected patients, triplet

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Received: 27.03.2025 **Accepted:** 23.06.2025 **Publication Date:** 28.08.2025

Cite this article as: Topal A, Akdağ G, Dumludağ A, et al. Comparison of first-line FOLFOX versus FOLFIRI in RAS mutant metastatic colorectal cancer patients. J Oncol Sci. 2025;11(2):96-103

Available at journalofoncology.org

therapy with FOLFOXIRI could be favored.[7] In patients with metastatic CRC, epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) inhibitory monoclonal antibodies are added to the backbone chemotherapy regimen depending on tumour location (left or right side), proto-oncogene B-Raf (BRAF) and rat sarcoma (RAS) mutations.[8,9]

RAS (KRAS/NRAS) mutations are the most common mutations found in patients with metastatic CRC. The frequency is approximately 40-45%. The frequency of the BRAF mutation is approximately 6.5%.[10,11] The presence of KRAS and BRAF mutations has been associated with an increased risk of death.[4] Bevacizumab, an anti-VEGF monoclonal antibody, was added to first-line chemotherapy in patients with these mutations, extending both overall survival (OS) and progression-free survival (PFS). Bevacizumab has also shown efficacy in patients with RAS mutations and outperforms anti-EGFR treatments.[12,13]

The purpose of this research was to compare first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab regimens in terms of PFS, OS, and safety in individuals with metastatic RAS/BRAF mutant CRC.

MATERIAL AND METHODS

We compared the OS of first-line mFOLFOX6[14]+bevacizumab and FOLFIRI[15]+bevacizumab regimens in individuals with RAS- or BRAF-mutated mCRC in this retrospective analysis. mFOLFOX6 + bevacizumab (bevacizumab 5 mg/kg on day 1, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, fluorouracil 400 mg/m^2, followed by fluorouracil 2400 mg/m^2 continuous infusion over 46 hours, every 2 weeks) and FOLFIRI + bevacizumab (bevacizumab 5 mg/kg on day 1, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2, followed by fluorouracil 2400 mg/m^2 continuous infusion over 46 hours, every 2 weeks) were administered between November 2016 and January 2024. The clinician's expertise determined whether to use FOLFOX or FOLFIRI. The trial excluded patients who were less than 18 years old, did not have BRAF or RAS mutations, were non-metastatic, or were not given FOLFOX/FOLFIRI, bevacizumab as first-line therapy. Clinical traits, pathological features, and test results were gathered from medical records and the hospital's computerized system.

OS served as the study's main outcome. OS was defined as the interval from the onset of first-line therapy to the date of last follow-up or death from any cause. Every three months, patients were evaluated using the imaging modalities that their doctors had selected. The RECIST 1.1 criteria were followed for performing the radiological evaluation.

All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. G**ü**lhane Ethics Committee, G**ü**lhane Research & Training Hospital, Ankara, approved the research (approval number: 2024/507, date: 05.11.2024). Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

Statistical Analysis

IBM SPSS Statistics version 25 software (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analyses. The descriptive data were displayed as either median [range (minimum-maximum)] or frequency (%). The Fisher exact test or the chi-squared test was used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables between two groups. Absolute frequencies and percentages were used to represent categorical data. The 95% confidence interval (CI) and survival outcomes were estimated using the Kaplan-Meier model. To assess differences across survival curves, the log-rank test was employed, with a two-sided significance threshold of 0.05. Multivariate analysis was performed using Cox regression.

RESULTS

There were 130 patients in the research. The patients' median age was 62 years (minimum-maximum: 25-85). Male patients there were 78 (60%) and female patients 52 (40%). One hundred and eighty-eight patients (88.5%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1. At the time of diagnosis, 89 patients (68.5%) presented with *de novo* metastases. Of the patients, 118 (90.8%) had adenocarcinoma histology. The remaining 12 patients (9.2%) had mucinous adenocarcinoma histology. In terms of location, 46 patients (35.4%) were located in the right colon, 74 patients (56.9%) in the left colon, and 10 patients (7.7%) in the transverse colon. The number of patients who underwent metastasectomy at the time of diagnosis was 12 (9.2%). The most common mutation was KRAS, found in 122 patients (93.8%), while NRAS was identified in 8 patients (6.2%). BRAF mutation was present in 1 patient (0.8%), human epidermal growth factor receptor 2 (HER2) mutation in 3 patients (2.3%), and 3 patients (2.3%) were microstallite instability-high. Eighty-three patients (63.8%) received first-line mFOLFOX6+bevacizumab, while 47 patients (36.2%) received FOLFIRI+bevacizumab; clinicopathological characteristics are shown in Table 1.

Age, sex, ECOG PS, histological tumour type, stage at diagnosis, number of metastatic sites, primary tumour location, mutation status, and albumin levels were compared between the mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab groups (Table 2). There were differences in gender (p=0.005), histological type (p=0.03), and *de novo*/recurrent metastasis (p=0.002). The distributions of other parameters were similar.

TABLE 1: Baseline characteristics of the patients.

Variables, n=130	n (%)
Age, years, median (minimum-maximum)	63 (25-85)
≤60	57 (43.8)
>60	73 (56.2)
Gender	
Male	78 (60)
Female	52 (40)
ECOG, n=122	
0-1	108 (88.5)
2-4	14 (11.5)
Stage at diagnosis	
II	10 (7.7)
III	31 (23.8)
IV	89 (68.5)
Histology	
Adenocarcinoma	118 (90.8)
Mucinous adenocarcinoma	12 (9.2)
Tumor localization	
Right colon	46 (35.4)
Left colon	74 (56.9)
Transvers colon	10 (7.7)
Surgery, primary ± metastasectomy	
Yes	24 (18.5)
No	106 (81.5)
Mutation	
KRAS	122 (93.8)
NRAS	8 (6.2))
BRAF	1 (0.8)
MSI-H	3 (2.3)
HER2	3 (2.3)
Adjuvant therapy	
Yes	38 (29.2)
No	92 (70.8)
First-line treatment	
FOLFOX+bevacizumab	83 (63.8)
FOLFIRI+bevacizumab	47 (36.2)

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; HER2: Human epidermal growth factor receptor 2.

The follow-up period has a median of 43.9 months. mOS of patients receiving mFOLFOX6+bevacizumab was 22.6 months (95% CI: 16.0-29.2), while mOS of participants receiving FOLFIRI+bevacizumab was 15.8 months (95% CI: 10.7-20.8) (Figure 1). According to univariate analyses, ECOG PS (p=0.012) and chemotherapy backbone (p=0.049) were observed to be the elements affecting OS (Table 3). The mOS of participants with ECOG PS 0-1 was 22.6 months (95% CI: 18.6-26.5), while the mOS of participants with ECOG PS 2-4 was 12.4 months (95% CI: 4.9-19.8) (Figure 1). Other patient characteristics did not affect OS.

To understand the subgroups of patients who benefited according to chemotherapy backbone, univariate/multivariate analyses were performed, and patient subgroups were examined (Table 4). Patients with ECOG PS 2-4 who received mFOLFOX6+bevacizumab [hazard ratio (HR): 3.66 (1.64-8.16)] and those with de novo metastases [HR: 0.37 (0.16-0.83)] had statistically significantly shorter survival. The mOS of participants having ECOG PS 2-4 was 11.2 months (95% CI: 7.65-14.75), while the mOS of participants having ECOG PS 0-1 was 26.7 months (95% CI: 20.42-33.13) (Figure 2). The mOS of participants having de novo metastases was 20.4 months (95% CI: 16.15-24.70), while the mOS of patients with recurrent metastases was not reached. Among patients who received FOLFIRI+bevacizumab, survival was statistically significantly shorter in patients older than 60 years [HR: 2.49 (1.09-5.64)] (Figure 3). Participants 60 years of age and younger had a mOS of 24.7 months (95% CI: 5.94-18.89), while the mOS for patients aged 60 years and older was 12.4 months (95% CI: 17.24-31.31). The treatments received by the patients in the subsequent lines are presented in Table 5.

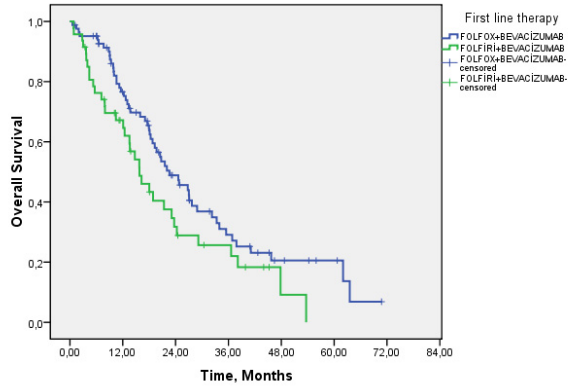

FIGURE 1: Kaplan-Meier OS curves according to chemotherapy backbones.

OS: Overall survival; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan

TABLE 2: The features of FOLFOX and FOLFIRI groups.

Patient characteristics				
Variables		**Folfox+bevacizumab (83)**	**Folfiri+bevacizumab (47)**	**p**
Age	≤60 years	39 (47.0)	18 (38.3)	0.363
	>60 years	44 (53.0)	29 (61.7)	
Gender	Male	41 (49.4)	11 (23.4)	**0.005***
	Female	42 (50.6)	36 (76.6)	
ECOG	0-1	67 (88.2)	41 (91.1)	0.765
	2-4	9 (11.8)	4 (8.9)	
Histological type	Adenocarcinoma	79 (95.2)	39 (83.0)	**0.028***
	Mucinous	4 (4.8)	8 (17.0)	
Metastatic status	Recurrent	18 (21.7)	23 (48.9)	**0.002***
	Denovo	65 (78.3)	24 (51.1)	
Number of metastatic site before treatment	Single	25 (30.1)	18 (38.3)	0.438
	Multiple	58 (69.9)	29 (61.7)	
Primary tumor site	Right	28 (33.7)	18 (38.3)	0.519
	Left	47 (56.6)	27 (57.4)	
	Transvers	8 (9.6)	2 (4.3)	
KRAS mutation	Present	78 (94.0)	44 (93.6)	0.999
	Absent	5 (6.0)	3 (6.4)	
NRAS mutation	Present	5 (8.9)	3 (11.5)	0.770
	Absent	34 (60.7)	17 (65.4)	
BRAF mutation	Present	1 (1.9)	-	0.756
	Absent	38 (71.7)	20 (71.4)	
MSI status	MSS	37 (63.8)	25 (80.6)	0.125
	MSI_H	1 (1.7)	2 (6.5)	
Albumin	≤4.0	38 (49.4)	21 (46.7)	0.852
	>4.0	39 (50.6)	24 (53.3)	

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability, MSS: Microstallite stable.

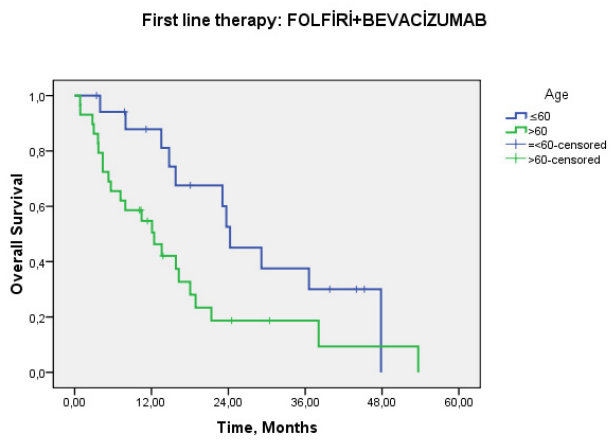

FIGURE 2: Kaplan-Meier OS curves according to age in patients receiving FOLFIRI+bevacizumab.

OS: Overall survival; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan

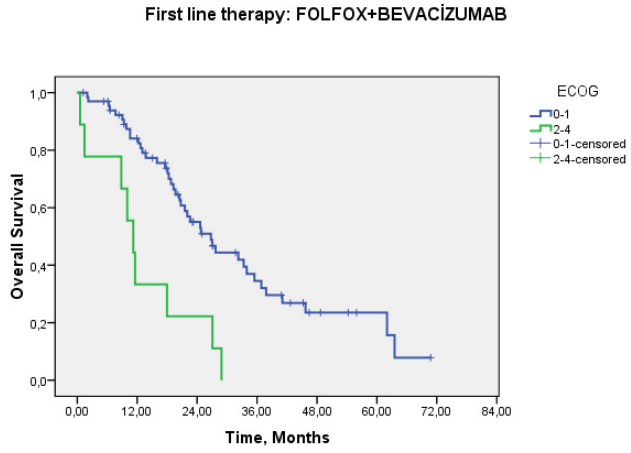

FIGURE 3: Kaplan-Meier OS curves of patients receiving FOLFOX+bevacizumab according to ECOG.

OS: Overall survival; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; ECOG: The Eastern Cooperative Oncology Group

TABLE 3: OS results according to patient characteristics.

Variables		Event/total	mOS, HR (95% CI)	p*
Age	≤60 years	36/57	23.6 (19.7-27.5)	0.088
	>60 years	52/73	17.9 (12.0-23.9)	
Sex	Male	53/78	18.8 (15.3-22.4)	0.866
	Female	35/52	22.0 (15.8-28.2)	
ECOG	0-1	71 /108	22.6 (18.6- 26.5)	**0.012***
	2-4	11/13	12.4 (4.9-19.8)	
Histological type	Adenocarcinoma	80/118	30.4 (16.6-24.3)	0.886
	Mucinous	8/12	14.7 (0-42.1)	
Metastatic status	Recurrent	23/41	18.8 (12.1-25.6)	0.426
	De novo	65/89	20.7 (16.4-24.9)	
Number of metastatic site before treatment	Single	31/43	21.5 (17.2-25.9)	0.850
	Multiple	57/87	17.0 (9.7-24.3)	
Primary tumor site	Right	27/46	22.6 (17.0-28.1)	0.138
	Left	53/74	20.4 (14.0-26.8)	
	Transvers	8/10	12.0 (8.7-15.4)	
KRAS mutation	Present	82/122	20.7 (16.7-24.6)	0.247
	Absent	6/8	12.2 (7.2-17.2)	
NRAS mutation	Present	6/8	12.2 (7.2-17.2)	0.430
	Absent	35/51	20.4 (17.2-23.6)	
BRAF mutation	Present	1/1	18.7 (-)	0.736
	Absent	39/58	19.6 (15.4-23.8)	
MSI status	MSS	41/62	19.6 (14.4-24.8)	0.207
	MSI_H	2/3	24.2 (-)	
Albumin	≤4.0	42/59	18.0 (25.0-21.0)	0.724
	>4.0	39/63	22.6 (18.8-26.3)	
Chemotherapy backbone	FOLFOX	54/83	22.6 (16.0-29.2)	**0.049***
	FOLFIRI	34/47	15.8 (10.7-20.8)	

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; MSS: Microstallite stable; HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

To our knowledge, there is a limited number of studies in the literature comparing first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab in individuals having RAS-mutant mCRC. They have generally been analysed as subgroups within trials.[16,17] Our study's objective was to analyse whether the chemotherapy backbone makes a difference in patients with RAS-mutated mCRC and compared the efficacy of first-line mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab treatment. The results of first-line mFOLFOX6+bevacizumab were better than those of FOLFIRI+bevacizumab. The mOS for patients who received mFOLFOX6+bevacizumab was 22.6 months in comparison to 15.8 months for patients who received FOLFIRI+bevacizumab.

RAS and BRAF mutations are associated with anti-EGFR resistance and worse survival in patients with mCRC.[18] In a meta-analysis, bevacizumab was associated with better survival than cetuximab in patients with RAS-mutated mCRC.[13] Similarly, the inclusion of cetuximab did not prove beneficial in the OPUS and CRYSTAL trials, with patients having KRAS-mutant mCRC.[19,20] In the PRIME trial, the addition of panitumumab in 440 patients with KRAS exon mutations was linked to worse PFS without improvement in mOS.[21]

The phase II MAVERICC trial enrolled 376 patients with mCRC. Approximately 1/3 of patients had RAS mutations. There was no difference in OS between mFOLFOX6+bevacizumab and FOLFIRI+bevacizumab. The mOS of patients receiving FOLFOX was 24 months, while that of patients receiving FOLFIRI was 27.5 months. Subgroup analysis by RAS status was not performed. In the phase III study by Yamazaki et al with the same

TABLE 4: Univariate and multivariate analysis of patients with metastatic CRC for overall survival.

Variable		Folfox+bevacizumab			Folfiri+bevacizumab				
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		
	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	
Age (years)	≤60 >60	1.0 (0.62- 1.82)	0.80			2.20 (1.05-4.61)	0.03	2.49 (1.09- 5.64)	**0.029**
Gender	Male Female	0.99 (0.57-1.70)	0.97			0.79 (0.36- 1.72)	0.56		
ECOG	0-1 2-4	3.50 (1.70- 7.59)	**0.001**	3.66 (1.64-8.16)	**0.001**	0.75 (0.17- 3.22)	0.70		
Histological type	Adenocarcinoma Mucinous	0.69 (0.21- 2.24)	0.54			1.40 (0.53- 3.69)	0.49		
Metastatic status	Recurrent *De novo*	0.36 (0.16- 0.80)	**0.013**	0.37 (0.16-0.83)	**0.017**	1.47 (0.73- 2.99)	0.27		
Number of metastatic site before treatment	Single Multiple	1.58 (0.84- 2.99)	0.15			0.52 (0.26- 1.05)	0.06		
Primary tumor site	Right Left Transvers	0.94 (0.60- 1.48)	0.81			1.13 (0.61- 2.05)	0.69		
KRAS mutation	Present Absent	0.74 (0.26- 2.07)	0.57			0.22 (0.04- 1.01)	0.06		
NRAS mutation	Present Absent	1.20 (0.82- 1.75)	0.33			1.20 (0.72- 1.99)	0.47		
BRAF mutation	Present Absent	1.18 (0.80- 1.74)	0.39			0.96 (0.57- 1.62)	0.89		
MSI status	MSS MSI_H	0.67 (0.37- 1.20)	0.17			0.90 (0.50- 1.64)	0.75		
Albumin	≤4.0 >4.0	0.62 (0.35- 1.09)	0.10			2.04 (0.97- 4.28)	0.06		

CRC: Colorectal cancer; FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; ECOG: The Eastern Cooperative Oncology Group; RAS: Rat sarcoma; BRAF: Proto-oncogene B-raf; MSI: Microstallite instability; MSS: Microstallite stable; CI: Confidence interval; HR: Hazard ratio; Statistically significant p values are written in bold.
*Analysis was performed using Cox proportional hazards model to evaluate the effect of prognostic factors on.

TABLE 5: Subsequent therapies.

First line therapy, (n)	Second line therapy, (n)	Third line therapy, (n)
FOLFOX+bevacizumab (83)	FOLFIRI+bevacizumab, (26) FOLFIRI+aflibercept, (10) FOLFIRI, (5)	Regorafenib, (15) FOLFOX+bevacizumab, (2) FOLFIRI+bevacizumab, (2) FOLFOXIRI, (2) FOLFOX, (1) Capecitabine, (1)
FOLFIRI+bevacizumab (47)	FOLFOX+bevacizumab, (12) FOLFOX/XELOX, (5)	Regorafenib, (5) FOLFIRI+bevacizumab, (4) Capecitabine, (1)

FOLFOX: Infused 5-fluorouracil, folinic acid and oxaliplatin; FOLFIRI: Infused 5-fluorouracil, folinic acid and irinotecan; XELOX: Oral capecitabine and infused oxaliplatin; FOLFOXIRI: Infused 5-fluorouracil, folinic acid, irinotecan and oxaliplatin.

design, 402 patients were included. Similarly, the rate of RAS mutant patients in this study was approximately 1/3. The mOS of patients receiving FOLFIRI+bevacizumab was 31.4 months, while that of patients receiving mFOLFOX6+bevacizumab was 30.4 months, which was not statistically significant. The inclusion of only patients with ECOG PS 0-1 in these two prospective studies, which are very similar to each other, may have led to better survival rates than in our study. In our study, the number of patients with ECOG PS 2-4 was approximately 10% and individuals having ECOG PS 2-4 were shown to have worse survival. The FOCUS trial included 711 patients. KRAS/BRAF mutant patients (43%) were shown to have worse survival than wild-type patients. Again, no difference was found with respect to the chemotherapy backbone (FOLFOX/FOLFIRI).[22] In a Chinese study, similar PFS and OS were observed in sequential use of CAPOX/CAPIRI+bevacizumab treatments.[23] In the HORG study, first-line FOLFOXIRI and FOLFIRI were compared in patients with mCRC. In patients receiving FOLFIRI, similar survival was observed in the group aged under and over 65 years.[24] In our study, it was observed that patients who received FOLFIRI+bevacizumab had better survival in patients under 65 years of age. The STEAM study compared sequential/concurrent FOLFOXIRI+bevacizumab treatment with FOLFOX+bevacizumab treatment. There was no difference in OS among the groups, regardless of RAS status. The study was closed early because it did not meet its primary endpoint.[7] The CAIRO-5 study aimed to find the optimal conversion regimen in patients who were initially unresectable. In this study, no difference was shown between FOLFOX/FOLFIRI+bevacizumab (93% preferred oxaliplatin) and FOLFOXIRI+bevacizumab treatments in terms of mOS, regardless of RAS status.[25] When we look at the two studies mentioned above, the similar results of triplet+bevacizumab treatment and FOLFOX+bevacizumab treatment suggest that FOLFOX+bevacizumab treatment may be an appropriate initial treatment in accordance with the results of our study.

Study Limitations

When interpreting the results of our study, several limitations should be considered. Firstly, the retrospective nature and single-centre design of the study may limit the generalisability of our findings to larger populations. Secondly, the relatively small sample size may affect the statistical power of multivariate analyses and may also require careful interpretation. Despite these limitations, we believe that our study provides valuable real-world data on the selection of first-line treatment in patients with metastatic BRAF/RAS mutant CRC.

CONCLUSION

In summary, RAS/BRAF mutant patients represent approximately half of all mCRC patients and have a worse prognosis than RAS/BRAF WT patients. Our study raised the question of which treatment regimen should be the initial treatment in this group of those and showed that those who were given mFOLFOX6+bevacizumab had better survival outcomes than those who received FOLFIRI+bevacizumab. Our study is valuable because it is one of the few studies in the literature addressing this specific issue. However, more prospective, randomized clinical studies are required in this field.

Ethics

Ethics Committee Approval: All procedures conducted in this study involving human participants complied with the ethical standards of the institutional and national research committee, in addition to the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical norms. Gülhane Ethics Committee, Gülhane Research & Training Hospital, Ankara, approved the research (approval number: 2024/507, date: 05.11.2024).

Informed Consent: Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., G.A., A.D., Ç.K., Ö.F.K., H.A., B.C.A., G.Y., S.Y., H.Ş.Y., G.Y.K., N.K., Concept: A.T., G.Y.K., N.K., Design: A.T., Data Collection or Processing: A.T., A.D., Ç.K., Ö.F.K., B.C.A., G.Y., S.Y., H.Ş.Y., Analysis or Interpretation: G.A., H.A., Literature Search: Ö.B., E.A., Writing: A.T., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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