ORIGINAL RESEARCH

DOI: 10.37047/jos.2022-94250

Prognostic Significance of Mucinous Histology in Metastatic Colorectal Cancer Patients Treated with Regorafenib

Rukiye ARIKAN[a], Hilal SAĞIROĞLU ÜSTÜN[b], Nazım Can DEMİRCAN[c], Selver IŞIK[a], Tuğba AKIN TELLİ[a], Alper YAŞAR[a], Abdussamet ÇELEBİ[a], Nargiz MAJİDOVA[a], Nadiye SEVER[a], Çiğdem ÇELİKEL[d], Murat SARI[a], Özlem ERCELEP[a], Osman KÖSTEK[a], İbrahim Vedat BAYOĞLU[a]

[a]Division of Medical Oncology, Marmara University Faculty of Medicine, İstanbul, Türkiye
[b]Department of Internal Medicine, Marmara University Faculty of Medicine, İstanbul, Türkiye
[c]Clinic of Medical Oncology, Erzurum Training and Research Hospital, Erzurum, Türkiye
[d]Department of Pathology, Marmara University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT Objective: Prognostic factors for regorafenib therapy have not been fully defined. Mucinous adenocarcinoma (MAC) is a distinct subtype of colorectal cancer (CRC). We investigated the significance of mucinous histology in patients treated with regorafenib for metastatic CRC (mCRC). **Material and Methods:** In this retrospective study, patients were stratified according to the presence of mucinous histology; >1% extracellular mucin was defined as mucinous component adenocarcinoma (MCAC), and containing no mucin was defined as non-MAC. The prognostic significance of mucinous histology for progression-free survival (PFS) and overall survival (OS) was evaluated by univariate and multivariate analyses. **Results:** A total of 103 patients were included, including 20 (19.4%) patients with MCAC and 83 (80.6%) patients with non-MAC. The median follow-up time was 8.6 months (range 1.8-31.6 months). The median PFS was lower in cases with MCAC than those with non-MAC (3.2 months vs. 3.6 months, respectively, p=0.01). Median OS was lower in MCAC patients than in non-MAC patients (4.3 months vs. 9.6 months, respectively, p=0.008). In multivariate analyses, mucinous histology was an independent risk factor [hazard ratio (HR): 2.2, p=0.003] for PFS and Eastern Cooperative Oncology Group-Performance Status (HR: 2.2, p=0.01), cancer antigen 19-9 (HR: 1.7, p=0.03), and mucinous histology (HR: 1.9, p=0.02) were independent risk factors for OS. **Conclusion:** This study revealed the prognostic value of mucinous histology in mCRC patients treated with regorafenib. Consideration of histologic features may be helpful in selecting patients for regorafenib therapy.

Keywords: Mucinous adenocarcinoma; colorectal neoplasms; regorafenib; prognosis

Colorectal carcinoma (CRC) is one of the most common types of cancer.[1] Five-year survival rate declines to 14% in patients with metastatic disease.[2] The prognosis of metastatic disease has improved in recent years with effective systemic therapies. First- and second-line setting regimens include fluorouracil (5-FU) combined with oxaliplatin and/or irinotecan and an appropriate biological agent.[3] However, the third-line and subsequent treatment options are less effective and include rechallenge with 5-FU-based chemotherapy (CT) regimen or using new agents, such as regorafenib.[4,5]

Regorafenib is a multi-kinase inhibitor that affects protein kinases involved in oncogenesis, angiogenesis, and tumor microenvironment.[6] In the international multicenter Phase 3 CORRECT trial, regorafenib showed a significant survival benefit versus best supportive care in metastatic CRC (mCRC) patients who had progressed under multiple lines of treatment. Asian patients in the CONCUR trial achieved survival benefits, as well.[4,5] On the other hand, appropriate patient selection and predictive and prognostic factors affecting regorafenib therapy in real life are unknown and usually under investigation.[7-9]

Correspondence: Rukiye ARIKAN
Division of Medical Oncology, Marmara University Faculty of Medicine, İstanbul, Türkiye
E-mail: dr_rukiyearikan@hotmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 09 Nov 2022 ***Received in revised form:*** 15 Mar 2023 ***Accepted:*** 27 Mar 2023 ***Available online:*** 10 Apr 2023

Histological features can be an appropriate guide in patient selection for third-line and further treatment. Mucinous adenocarcinoma (MAC) is defined as a histologic subtype characterized by the presence of extracellular mucin in more than 50% of tumor volume and accounts for 10-20% of all colorectal adenocarcinomas.[10] However, mucinous histology may be present in different proportions in the tumor volume and is generally defined as the mucinous component when mucin constitutes 1-50% of tumor volume.[11-13] Mucinous component adenocarcinoma (MCAC) has different clinicopathological and molecular features associated with poor prognosis at metastatic stage.[14,15] However, there are conflicting results regarding whether it represents resistance to standard CT regimens and/or biological agents.[11-13] In addition, limited and conflicting information is available about its predictive and prognostic value for regorafenib. Although Ayhan et al. emphasized that mucinous histology is associated with poor treatment response and prognosis in patients receiving regorafenib, Hsu et al. reported no significant effect of mucinous histology on patients' outcomes.[16,17] Assessing the prognosis of mucinous mCRC patients receiving regorafenib can be important for appropriate patient selection.

The present study sought to investigate the prognostic value of mucinous histology in mCRC patients treated with regorafenib.

MATERIAL AND METHODS

STUDY POPULATION AND DATA COLLECTION

This study included mCRC patients who were followed up from 2011 to 2020 and received at least one cycle of regorafenib. Data were retrospectively reviewed using patients' files. Baseline characteristics, performance status, metastatic sites, and tumor markers [cancer embryonic antigen (CEA) and cancer antigen (CA) 19-9] were recorded considering the regorafenib treatment onset. Tumor mutation status, tumor sidedness, previous surgical histology, and previous treatments were also recorded. During the study, histologic examinations were performed by pathologists with more than f5 years of experience in our center. Mucinous histology was assessed according to standardized protocols based on international guidelines.[18] Histological re-evaluation was not performed. The research protocol was approved by the Marmara University Clinical Research Ethics Committee (date: February 11, 2022, no: 09.2022.316] of our center in accordance with the Helsinki Declaration.

RESPONSE ASSESSMENT AND SURVIVAL OUTCOMES

Patients received regorafenib daily for the first three weeks of each four-week cycle until disease progression, death, or unacceptable toxicity. In our center, physicians evaluate the patients weekly in the first cycle and every two weeks after that. A dose escalation strategy was implemented for regorafenib therapy based on the physician's judgment, patient compliance, and adverse events. Response assessment was performed 8 weeks after the initiation of regorafenib therapy and every 8-12 weeks after that by conventional cross-sectional imaging. Treatment responses were evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 in radiological imaging.

Disease control rate (DCR) was described as the percentage of patients with the best overall response, including complete response, partial response, or stable disease during regorafenib therapy, and referred to as DCR+ patients. Patients with progressive disease as their best response were referred to as DCR- patients. Progression-free survival (PFS) was described as the time between regorafenib treatment onset and disease progression (evaluated by radiologic imaging or observing intolerable adverse effects) or the last medical examination in patients still using regorafenib or death. Overall survival (OS) was described as the time from initiation of regorafenib therapy to death or last medical examination (live patients).

STATISTICAL ANALYSES

Study groups were stratified as MCAC and non-MAC patients. MCAC was defined as tumors containing more than 1% extracellular mucin, and non-MAC was defined as tumors containing no mucin component. CEA was evaluated using the me-

dian value because most patients had high CEA according to the cut-off value of our laboratory (5 µg/L). CA 19-9 was evaluated using the cut-off value of our laboratory (34 U/mL). A chi-square test was used to compare categorical variables. Survival was estimated with Kaplan-Meier. The Cox proportional model was used to detect variables significantly affecting the outcomes or those tending toward significance (p<0.25) in univariate analyses. The backward-stepwise method was used to determine independent prognostic indicators in multivariate analysis. The confidence interval (CI) and p-value were accepted as 95% and <0.05, respectively, for statistical significance.

RESULTS

The baseline characteristics and treatment outcomes of 103 patients are shown in Table 1. All patients had adenocarcinoma histology. Twenty (19.4%) patients

TABLE 1: Demographic and clinical characteristics of the study subjects.

	All (n=103)	MCAC (n=20)	Non-MCAC (n=83)	p value
Age, years				
Median (IQRs)	58 (50-66)	61 (55-64)	57 (50-66)	0.25
Gender, n (%)				
Female	39 (37.9)	6 (30.0)	33 (39.8)	0.41
Male	64 (62.1)	14 (70.0)	50 (60.2)	
ECOG-PS, n (%)				
0-1	86 (83.5)	17 (85.0)	69 (83.1)	0.84
2	17 (16.5)	3 (15.0)	14 (16.9)	
Primary tumor location, n (%)				
Right	22 (21.3)	5 (25.0)	17 (20.5)	0.65
Left	81 (78.6)	15 (75.0)	66 (79.5)	
Primary resection, n (%)	84 (81.5)	16 (80.0)	68 (81.9)	0.84
Grade, n (%)				
1	11 (10.7)	1 (5.0)	10 (12.0)	0.62
2-3	75 (72.8)	15 (75.0)	60 (72.3)	
Unknown	17 (16.5)	4 (20.0)	13 (15.7)	
Liver metastasis, n (%)	83 (80.6)	16 (80.0)	67 (80.7)	0.94
Peritoneal metastasis, n (%)	13 (12.6)	2 (10.0)	11 (13.3)	0.69
Metastatic site number, n (%)				
1	28 (27.2)	9 (45.0)	19 (22.9)	**0.04**
≥2	75 (72.8)	11 (55.0)	64 (77.1)	
KRAS/NRAS				
Mutant	60 (58.3)	12 (60.0)	48 (57.8)	0.86
Wild type	43 (41.7)	8 (40.0)	35 (42.2)	
BRAF				
Mutant	14 (13.6)	5 (25.0)	9 (10.8)	0.23
Wild	63 (61.2)	10 (50.0)	53 (63.9)	
Unknown	26 (25.2)	5 (25.0)	21 (25.3)	
Regorafenib tolerable dose, n (%)				
80 mg	19 (18.4)	7 (35.0)	12 (14.5)	0.06
120 mg	46 (44.7)	9 (45.0)	37 (44.6)	
160 mg	38 (36.9)	4 (20.0)	34 (41.0)	
Regorafenib treatment line, n (%)				
Third line	72 (69.9)	13 (65.0)	59 (71.1)	0.59
≥Fourth line	31 (30.1)	7 (35.0)	24 (28.9)	

MCAC: Mucinous component adenocarcinoma; IQR: Interquartile range; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status.

had MCAC, and 83 (80.6%) had non-MAC. Although MCAC was defined as patients with mucinous histology of more than 1% of tumor volume, no patient with less than 20% mucinous histology was found in the retrospective data. Sixty-two (60.2%) patients had de novo metastatic disease, and 41 (39.8%) patients developed metastatic disease during the follow-up period. Curative or palliative surgery was performed in 84 (81.5%) patients. Median age, gender, primary tumor sidedness, history of primary tumor resection, grade, *KRAS*/*NRAS*/*BRAF* mutation status, and Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) showed no difference between the study groups. The number of patients with ≥2 metastatic sites in the non-MAC group was more than in the MCAC group (p=0.04).

All patients had previously received 5-FU-based CT regimens combined with an appropriate biologic agent according to tumor and tumor mutation status. Regorafenib was applied as a third-line or subsequent therapy in mCRC. Seventy-two (69.9%) patients received regorafenib in the third line. Thirty-one (30.1%) patients, who had a good response and PFS using CT in the first/second line CT, received rechallenge with CT; therefore, they received regorafenib beyond third-line therapy. The number of patients in the MCAC group who could tolerate the standard 160 mg dose was less than in the non-MCAC group, but the difference was not statistically significant (p=0.06).

The median follow-up period was 8.6 months (range: 1.8-31.6 months). DCR was 15.0% in MCAC patients and 38.6% in non-MAC patients (p=0.04). The best responses and DCR in the groups are presented in Table 2. Median PFS was 3.5 months (95% CI: 3.3-3.7) in all patients, 3.2 months (95% CI: 2.4-3.9), and 3.6 months (95% CI: 3.4-3.8) in MCAC and non-MAC patients, respectively. In univariate analyses, elevated CA 19-9 and mucinous histology were associated with poor PFS (p=0.03 and p=0.01, respectively). In multivariate analysis, mucinous histology was associated with poor PFS [hazard ratio (HR): 2.2 (95% CI: 1.3-3.7), p=0.003], and the presence of liver metastasis was close to the significance level (p=0.05). The Kaplan-Meier curve and univariate and multivariate analyses for PFS are shown in Figure 1 and Table 3, respectively.

TABLE 2: Treatment responses and DCR.

	All	MCAC	Non-MAC
Best response, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	14 (13.6)	1 (5.0)	13 (15.7)
SD	21 (20.4)	2 (10.0)	19 (22.9)
PD	68 (66.0)	17 (85.0)	51 (61.4)
DCR+, n (%)	35 (34.0)	3 (15.0)	32 (38.6)
p value (chi-square)		0.04	

DCR: Disease control rate; MCAC: Mucinous component adenocarcinoma; MAC: Mucinous adenocarcinoma; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

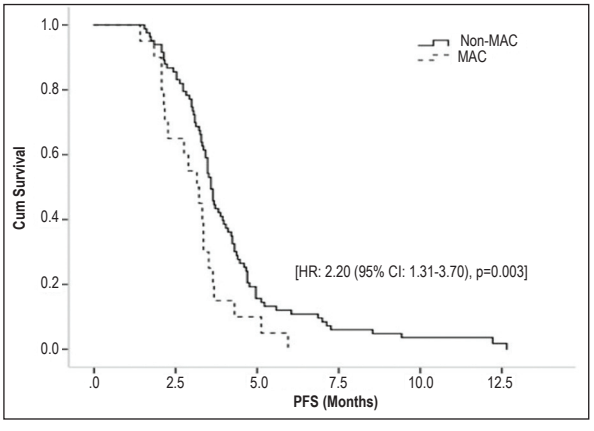

FIGURE 1: Kaplan-Meier curve for PFS according to mucinous histology. MAC: Mucinous adenocarcinoma; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval.

Ninety-two (89.3%) patients died during the follow-up period. Median OS was 9.1 months (95% CI: 8.18-10.02) in all patients; 4.3 months (95% CI: 2.3-6.4) in MCAC and 9.6 months (95% CI: 8.4-10.7) in non-MAC patients. In univariate analyses, ECOG-PS, liver metastasis, elevated CA 19-9 levels, and mucinous histology were associated with OS (p=0.03, p=0.03, p=0.01, and p=0.008, respectively). In multivariate analysis, ECOG-PS [HR: 2.2 (95% CI: 1.2-3.9), p=0.01], elevated CA 19-9 levels [HR: 1.7 (95% CI: 1.1-2.6), p=0.03], and mucinous histology [HR: 1.9 (95% CI: 1.1-3.3), p=0.02] were associated with OS. The Kaplan-Meier curve and univariate and multivariate analyses for OS are shown in Figure 2 and Table 4, respectively.

TABLE 3: Univariate and multivariate analyses for PFS.

	Univariate analyses		Multivariate analysis	
	Median PFS (mos) (95% CI)	**p value**	**HR (95% CI)**	**p value**
Age, years				
<58	3.5 (3.2-3.9)	0.63		
≥58	3.4 (3.1-3.7)			
Gender				
Female	3.5 (3.3-3.7)	0.77		
Male	3.5 (3.2-3.7)			
ECOG-PS				
0-1	3.5 (3.3-3.7)	0.60		
2	3.1 (2.0-4.3)			
Primary tumor location				
Right	3.6 (3.4-3.8)	0.66		
Left	3.5 (3.3-3.7)			
Primary resection				
(+)	3.5 (3.3-3.7)	0.60		
(-)	3.4 (2.1-4.8)			
Grade				
1	3.9 (3.2-4.7)	0.47		
2-3	3.5 (3.3-3.7)			
Unknown	3.2 (2.0-4.4)			
Liver metastasis				
(+)	3.5 (3.3-3.7)	**0.09**	1.7 (0.9-2.8)	0.05
(-)	3.7 (2.6-4.7)		Ref.	
Peritoneal metastasis				
(+)	3.7 (3.2-4.1)	0.94		
(-)	3.5 (3.3-3.7)			
Metastatic site number				
1	3.5 (3.1-3.9)	0.40		
≥2	3.5 (3.3-3.7)			
KRAS/NRAS				
Mutant	3.6 (3.4-3.8)	**0.18**	0.7 (0.5-1.1)	0.09
Wild type	3.3 (3.1-3.5)		Ref.	
BRAF				
Mutant	3.5 (3.2-3.8)		0.8 (0.4-1.6)	
Wild	3.5 (3.3-3.7)	**0.15**	Ref.	0.44
Unknown	3.8 (2.7-4.9)		0.7 (0.4-1.2)	
CEA				
<38 (µg/L)	3.2 (3.2-3.8)	0.73		
≥38 (µg/L)	3.5 (3.2-3.8)			
CA 19-9				
<36.9 (U/mL)	3.6 (3.3-3.9)	**0.03**	Ref.	0.18
≥36.9 (U/mL)	3.5 (3.3-3.7)		1.3 (0.9-2.1)	
Regorafenib tolerable dose				
80 mg	3.4 (2.3-4.4)			
120 mg	3.5 (3.2-3.8)	0.33		
160 mg	3.4 (3.1-3.8)			
Regorafenib treatment line				
Third line	3.5 (3.3-3.7)	0.69		
≥Fourth line	3.7 (3.3-4.0)			
Histology				
MCAC	3.2 (2.4-3.9)	**0.01**	2.2 (1.3-3.7)	**0.003**
Non-MAC	3.6 (3.4-3.8)		Ref.	

PFS: Progression-free survival; Mos: Months; CI: Confidence interval; HR: Hazard ratio; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; CEA: Cancer embryonic antigen; CA: Cancer antigen; MCAC: Mucinous component adenocarcinoma; MAC: Mucinous adenocarcinoma.

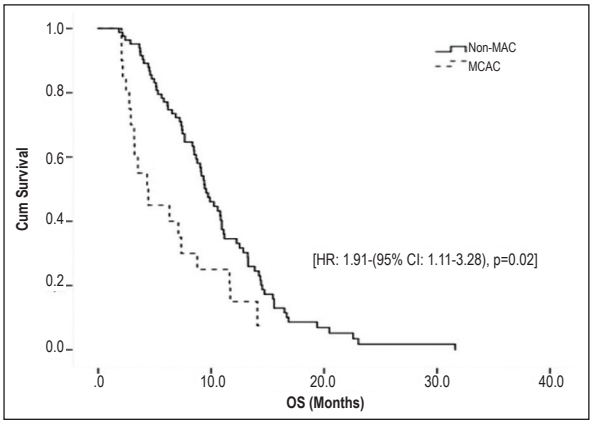

FIGURE 2: Kaplan-Meier curve for OS according to mucinous histology.
MAC: Mucinous adenocarcinoma; MCAC: Mucinous component adenocarcinoma; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

This study analyzed the prognostic significance of mucinous histology in mCRC patients treated with regorafenib and revealed its association with worse survival outcomes compared to non-mucinous histology. Also, patients with MCAC were found with poor treatment responses. Additionally, ECOG-PS and elevated CA 19-9 levels were independent poor risk factors for OS.

Recently, the prognostic significance of mucinous histology has been widely demonstrated in CRC patients.[14,15,19,20] In almost all studies investigating mucinous histology in CRC, patients received conventional CT and biological agents.[21,22] Although poor prognostic value has been commonly confirmed in the literature, some studies have concluded that prognosis may differ according to treatment agents. Catalano et al. studied mCRC patients who received irinotecan- or oxaliplatin-based CT. They revealed that mucinous histology was associated with poor prognosis only in patients receiving oxaliplatin-based CT compared to non-mucinous histology.[11] Similarly, they emphasized that mucinous histology was a negative independent prognostic factor only in those receiving oxaliplatin-based CT and biological agents.[11] Studies on regorafenib, in which patients are stratified according to mucinous histology, are rare. Hsu et al. analyzed the factors affecting outcomes in 613 patients receiving regorafenib and demonstrated no predictive or prognostic value of mucinous histology.[17] On the other hand, Ayhan et al. classified the studied population according to histology and revealed that mucinous histology was associated with PFS and OS in patients receiving regorafenib.[16] We found mucinous histology as an independent prognostic factor in patients treated with regorafenib.

Treatment resistance remains unclear in MCAC. DCR has been reported to be 41% and 51% in Phase 3 randomized trials of regorafenib, regardless of histological features.[4,5] In addition, it has been reported to be about 36-38% in retrospective analyses examining real-life data.[16,17] There are very few studies on the response rate for regorafenib in terms of histologic features. Ayhan et al. found that DCR for regorafenib was 36% in all patients and 5.6% in patients with mucinous histology.[16] In the current study, DCR was lower than its value in the Phase 3 trials; however, it was similar to the values reported in retrospective analyses in all patients regardless of histology. It is an expected result due to the appropriate patient selection of Phase 3 trials. In addition, mucinous histology was associated with low DCR, which is consistent with the literature, suggesting that mucinous histology is associated with regorafenib resistance. Considering baseline characteristics, the studied patients differed from those in the literature in terms of de novo metastasis and *BRAF* mutation. In the literature, de novo metastasis and *BRAF* mutation have been reported around 25-30% and 5-10%, respectively.[23,24] Seligmann et al. analyzed the patients included in 3 randomized trials and reported a prevalence of 9.1% for *BRAF* mutation in CRC.[25] The reasons for a high incidence of de novo metastasis and *BRAF* mutation in the current study can be the expected bias due to its retrospective nature and because the studied subjects were a group of patients with relative resistance and poor prognosis receiving at least 2 lines of treatment.

The survival time with regorafenib varies even between randomized clinical trials. Although PFS and OS were 3.2 months and 8.8 months in the CONCUR trial, they were 1.7 months and 6.4 months in the CORRECT trial, respectively.[4,5] According to real-life data and retrospective analyses, PFS was about 2.7-2.9 months, and OS was about 5.5-7.7

TABLE 4: Univariate and multivariate analyses for OS.

	Univariate analyses		Multivariate analysis	
	Median OS (mos) (95% CI)	**p value**	**HR (95% CI)**	**p value**
Age, years				
<58	9.1 (8-10.3)	0.81		
≥58	9.0 (7.5-10.6)			
Gender				
Female	9.1 (7.7-10.6)	0.32		
Male	9.0 (6.9-11.2)			
ECOG-PS				
0-1	9.3 (8.3-10.4)	**0.03**	Ref.	0.01
2	6.3 (3.7-8.9)		2.2 (1.2-3.9)	
Primary tumor location				
Right	8.3 (5.1-11.6)	0.70		
Left	9.1 (8.3-9.9)			
Primary resection				
(+)	9.1 (8.2-10.0)	0.15	0.7 (0.4-1.3)	0.25
(-)	7.7 (3.0-12.3)		Ref.	
Grade				
1	13.2 (10.9-15.6)			
2-3	8.8 (8-9.6)	0.41		
Unknown	7.7 (3.5-11.8)			
Liver metastasis				
(+)	9.1 (8.1-10.1)	**0.03**	1.7 (0.9-2.9)	0.07
(-)	9.0 (6.7-11.3)		Ref.	
Peritoneal metastasis				
(+)	7.4 (2.6-12.3)	0.82		
(-)	9.1 (8.2-10.0)			
Metastatic site number				
1	7.7 (5.1-10.3)	0.33		
≥2	9.3 (8.2-10.5)			
KRAS/NRAS				
Mutant	9.7 (7.7-11.7)	0.22	0.7 (0.5-1.1)	0.10
Wild type	8.5 (6.9-10.1)		Ref.	
BRAF				
Mutant	8.3 (5.2-11.5)		1.7 (0.8-3.4)	
Wild	8.5 (7.2-9.9)	0.22	Ref.	0.26
Unknown	10.8 (8.4-13.3)		0.9 (0.6-1.6)	
CEA				
<38 (µg/L)	9.6 (7.1-12.1)	0.11	Ref.	0.26
≥38 (µg/L)	8.8 (6.7-10.8)		1.3 (0.8-2.2)	
CA 19-9				
<36.9 (U/mL)	9.6 (7.6-11.5)	**0.01**	Ref.	**0.03**
≥36.9 (U/mL)	8.3 (6.5-10.2)		1.7 (1.1-2.6)	
Regorafenib tolerable dose				
80 mg	8.8 (5.5-12.1)			
120 mg	8.5 (6.6-10.3)	0.66		
160 mg	9.9 (8.1-11.7)			
Regorafenib treatment line				
Third line	9.4 (8.0-10.8)	0.36		
≥Fourth line	8.8 (6.9-10.7)			
Histology				
MCAC	4.3 (2.3-6.4)	**0.008**	1.9 (1.1-3.3)	**0.02**
Non-MAC	9.6 (8.4-10.7)		Ref.	

OS: Overall survival; Mos: Months; CI: Confidence interval; HR: Hazard ratio; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; CEA: Cancer embryonic antigen; CA: Cancer antigen; MCAC: Mucinous component adenocarcinoma; MAC: Mucinous adenocarcinoma.

months, respectively.[7,16,17] In the current study, median PFS and OS were similar to the CONCUR trial but longer than the CORRECT trial and other retrospective analyses. Although we found some poor prognostic features, such as de novo metastatic dizease and *BRAF* mutation, the long-term survival outcomes were remarkable and possibly affected by the number of previous treatments. In our study, regorafenib was administered in earlier lines of treatment (70% of patients received a third-line therapy) than in the randomized trials. Poor ECOG-PS and elevated CA19-9 levels were independent risk factors for poor OS, which is consistent with the literature. It was an expected result as both reflect tumor burden. Similarly, Hsu et al. found high levels of serum tumor markers (CEA>50 ng/mL) as an independent poor prognostic factor for OS in a retrospective analysis of patients receiving regorafenib.[17] The status of *KRAS* and *BRAF* mutations did not affect the outcomes, which is consistent with the CONCUR and CORRECT trials.[4,5] The presence of liver metastasis was close to the statistical significance level for poor PFS and OS, which is in line with other studies. In the REBECCA and CORRECT trials, which evaluated regorafenib therapy in real-life conditions, liver metastasis was determined as a poor prognostic factor. Likewise, Hsu et al. found liver metastasis associated with both PFS and OS.[17]

Our study has significant limitations, primarily due to its retrospective nature and small sample size. Also, it was not possible to control all potential confounding biases. Additionally, the MCAC group showed a wide range (20%-80%) of mucinous histology.

CONCLUSION

The results indicated mucinous histology associated with poor response and prognosis in mCRC patients treated with regorafenib. Factors affecting appropriate patient selection for regorafenib therapy have yet to be identified. According to our findings, consideration of histologic features may be helpful in selecting patients for regorafenib therapy. However, because of our small sample size, the results should be supported by further studies with larger sample sizes.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Rukiye Arıkan;* ***Design:*** *Rukiye Arıkan;* ***Data Collection and/or Processing:*** *Hilal Sağıroğlu Üstün, Abdussamet Çelebi, Alper Yaşar, Nargiz Majidova, Nadiye Sever;* ***Analysis and/or Interpretation:*** *Nazım Can Demircan, Rukiye Arıkan;* ***Literature Review:*** *Tuğba Akın Telli, Selver Işık;* ***Writing the Article:*** *Rukiye Arıkan;* ***Critical Review:*** *Murat Sarı, Özlem ercelep, Osman Köstek, İbrahim Vedat Bayoğlu;* ***Materials:*** *Çiğdem Çelikel.*

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. [Crossref] [PubMed]
2. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93. [Crossref] [PubMed]
3. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386-422. [Crossref] [PubMed]
4. Grothey A, Cutsem E Van, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12. [Crossref] [PubMed]
5. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16(6):619-29. [Crossref] [PubMed]
6. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245-55. [Crossref] [PubMed]
7. Adenis A, de la Fouchardiere C, Paule B, et al. Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBECCA) nested within a compassionate use program. BMC Cancer. 2016;16(1):412. [Crossref]
8. Yoon SE, Lee SJ, Lee J, et al. The Impact of Primary Tumor Sidedness on the Effect of Regorafenib in Refractory Metastatic Colorectal Cancer. J Cancer. 2019;10(7):1611-1615. [Crossref] [PubMed] [PMC]
9. UNSELD M, FILIP M, SEIRL S, et al. Regorafenib therapy in metastatic colorectal cancer patients: markers and outcome in an actual clinical setting. Neoplasma. 2018;65(04):599-603. [Crossref] [PubMed]
10. World Health Organization. Classification of Tumours of the Digestive System Fourth Edition-WHO-OMS, Vol. 3. press, Geneva, Switzerland: WHO; 2010.
11. Catalano V, Bergamo F, Cremolini C, et al. Clinical impact of first-line bevacizumab plus chemotherapy in metastatic colorectal cancer of mucinous histology: a multicenter, retrospective analysis on 685 patients. J Cancer Res Clin Oncol. 2020;146(2):493-501. [Crossref] [PubMed]
12. Moretto R, Morano F, Ongaro E, et al. Lack of Benefit From Anti-EGFR Treatment in RAS and BRAF Wild-type Metastatic Colorectal Cancer With Mucinous Histology or Mucinous Component. Clin Colorectal Cancer. 2019;18(2):116-24. [Crossref] [PubMed]
13. Zhou Y, Long Y, Chen Y, et al. First-line therapy of bevacizumab plus chemotherapy versus cetuximab plus chemotherapy for metastatic colorectal cancer patients with mucinous adenocarcinoma or mucinous component. Cancer Med. 2021;10(10):3388-402. [Crossref] [PubMed] [PMC]
14. Ott C, Gerken M, Hirsch D, et al. Advanced Mucinous Colorectal Cancer: Epidemiology, Prognosis and Efficacy of Chemotherapeutic Treatment. Digestion. 2018;98(3):143-52. [Crossref] [PubMed]
15. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. J Clin Pathol. 2012;65(5):381-8. [Crossref] [PubMed]
16. Ayhan M, Turan N, Köstek O, et al. Does the efficacy of regorafenib differ in chemotherapy refractory metastatic colorectal cancer patients who had mucinous pathology compared to those who had non-mucinous pathology? Curr Probl Cancer. 2021;45(3):100670. [Crossref] [PubMed]
17. Hsu H-C, Huang K-C, Chen W-S, et al. Preference criteria for regorafenib in treating refractory metastatic colorectal cancer are the small tumor burden, slow growth and poor/scanty spread. Sci Rep. 2021;11(1):15370. [Crossref] [PubMed] [PMC]
18. Washington K. Excisional biopsy (polypectomy), local excision (transanal disk excision), colectomy (total, partial, or segmental resection), rectal resection (low anterior resection or abdominoperineal resection). College of American Pathologists, 2012.
19. Huang A, Yang Y, Shi J-Y, et al. Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer. World J Gastrointest Surg. 2021;13(12):1567-83. [Crossref] [PubMed] [PMC]
20. Miyakawa T, Kawamura H, Honda M, et al. Impact of histological subtype on prognosis in stage IV colorectal cancer: A population-based cohort study. Chou W-C, ed. PLoS One. 2022;17(3):e0264652. [Crossref] [PubMed] [PMC]
21. Catalano V, Loupakis F, Graziano F, et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. Br J Cancer. 2009;100(6):881-7. [Crossref] [PubMed] [PMC]
22. Maisano R, Azzarello D, Maisano M, et al. Mucinous histology of colon cancer predicts poor outcomes with FOLFOX regimen in metastatic colon cancer. J Chemother. 2012;24(4):212-6. [Crossref] [PubMed]
23. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64. [Crossref] [PubMed]
24. Chiu JW, Krzyzanowska MK, Serra S, et al. Molecular Profiling of Patients With Advanced Colorectal Cancer: Princess Margaret Cancer Centre Experience. Clin Colorectal Cancer. 2018;17(1):73-9. [Crossref] [PubMed]
25. Seligmann JF, Fisher D, Smith CG, et al. Investigating the poor outcomes ofBRAF-mutant advanced colorectal cancer: analysis from 2530 patients in randomised clinical trials. Ann Oncol. 2017;28(3):562-8. [Crossref] [PubMed]