

Prognostic significance of mucinous histology in left-sided metastatic colorectal cancers with wild-type RAS and evaluation of backbone chemotherapy regimens

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Abstract. Mucinous colorectal adenocarcinoma (MCAC) is a distinct subtype of colorectal carcinoma (CRC). The prognostic and predictive significance of mucinous histology remains controversial. It was aimed to investigate the prognostic and/or predictive role of mucinous histology in left-sided metastatic

CRC (mCRC) with wild-type RAS. This is a retrospective multicenter study of mCRC treated with first line anti-EGFR combined 5-fluorouracil based chemotherapy (CT). Patients were stratified according to presence (>50% extracellular mucin) or absence of mucinous histology. Survival analyses were performed firstly regardless of treatment options and then performed as separating according to CT regimens. Additional analyses were performed for MCAC patients considering backbone CT regimens. A total of 125 patients were included, consisting of 40 (32.0%) patients with MCAC and 85 (68.0%) patients with non-MCAC. Median follow-up time was 19.7 months. Median progression-free survival (PFS) was 10.7 months in all patients, and PFS was lower in MCAC than non-MCAC (9.9 vs. 12.0 months, respectively, $P=0.005$). Median overall survival (OS) was 25.7 months in all patients. OS was lower in MCAC than non-MCAC (22.8 vs. 29.7 months, respectively, $P=0.005$). When considering backbone CT regimens, in multivariate analyses, mucinous histology was an independent prognostic factor for OS in both for mFOLFOX6 (HR: 1.92, $P=0.04$) and FOLFIRI (HR: 2.04, $P=0.04$) groups and was associated with poor PFS in only mFOLFOX6 (HR: 3.86, $P<0.001$) group. When outcomes were analyzed for the MCAC group, median OS of MCAC patients receiving mFOLFOX6 and FOLFIRI was 22.47 and 14.22 months, respectively ($P=0.41$). Median PFS of MCAC patients receiving mFOLFOX6 and FOLFIRI was 10.15 and 8.11 months, respectively ($P=0.73$). The study revealed poor prognosis of mucinous histology, both in whole study population and in backbone CT groups. Moreover, lower PFS of MCAC patients was revealed in only mFOLFOX6 group and this finding may be a valuable issue for the future research. However, considering all analyses, the present results did not indicate a special benefit of any backbone CT regimen for MCAC patients.

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Abbreviations: anti-EGFR, anti-epidermal growth factor receptor; BRAF, v-RAS murine sarcoma viral oncogene homolog B1; CI, confidence interval; CIMP-H, CpG island methylator phenotype-high; CR, complete response; CRC, colorectal carcinoma; ECOG-PS, Eastern cooperative oncology group-performance status; HR, hazard ratio; Iri, irinotecan; mCRC, metastatic colorectal carcinoma; CT, chemotherapy; FU, fluorouracil; IQR, interquartile ranges; KRAS, Kirsten rat sarcoma; MCAC, mucinous colorectal adenocarcinoma; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; MSI, microsatellite instable; MSS, microsatellite stable; Non-MCAC, non-mucinous colorectal adenocarcinoma; NRAS, neuroblastoma rat sarcoma; OS, overall survival; Oxa, oxaliplatin; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-Bisphosphate-3-kinase catalytic subunit alpha; PFS, progression-free survival; PR, partial response; RAS, rat sarcoma; RECIST, response evaluation criteria in solid tumors; SD, stable disease; SLD, Sum of the longest diameters; TNM, Tumor-Node-Metastasis

Key words: metastatic colorectal cancer, mucinous histology, prognosis, backbone chemotherapy

Introduction

Mucinous colorectal adenocarcinoma (MCAC) is defined as a histologic subtype characterized by the presence of extracellular mucin >50% of tumor volume and constitutes 10-20% of all colorectal carcinomas (CRCs) (1). MCAC has specific clinicopathological features including larger tumor size, poor differentiation, is commonly located in proximal colon, associated with peritoneal infiltration and synchronous metastases (2-4). Molecularly, MCAC is more likely to have aberrations in the MAPK [Rat Sarcoma (RAS) and v-RAF Murine Sarcoma Viral Oncogene Homolog B1 (BRAF)] and Phosphatidylinositol-4,5-Bisphosphate-3-Kinase Catalytic Subunit Alpha (PIK3CA) pathways and associated with increased microsatellite instability (MSI) and CpG island methylator phenotype-high (CIMP-H), and less likely to have p53 mutations when compared with non-MCAC (5-7).

Different clinicopathological and molecular features of MCAC are associated with poor prognosis in metastatic setting (8,9). Various hypotheses have been claimed about the poor prognosis of MCAC patients and mostly emphasized causes were metastasis pattern, tumor sidedness and MSI status (4,10,11). In a recent study, primary tumor was mostly located in proximal colon and had RAS mutation (12). On the other hand, proximal location and RAS mutation are characteristics that are well known to be associated with poor prognosis in metastatic CRC (mCRC) (13,14). It is an important question whether the mucinous tumor that is located in the left colon and has wild-type RAS is associated with poor prognosis or not. Additionally, almost in all recent studies heterogeneous patient groups are included. Therefore, it would be useful to evaluate mucinous histology in a relatively homogeneous patient group, independently of poor prognostic features such as proximal location and RAS mutation.

Treatment resistance is another issue that remains unclear in MCAC. The number of studies evaluating the survival outcomes in terms of backbone chemotherapy (CT) regimens in MCAC patients is limited (10,15,16). Previously, a few studies emphasized the predictive value of mucinous histology particularly for biological agents (17-19). However, in these studies since primary tumors were mostly located in the proximal colon, bevacizumab was used as the standard first line therapy.

In the present study, it was aimed to clarify whether mucinous histology has prognostic and/or predictive role in mCRC patients treated with standard first-line therapy included anti- Epidermal Growth Factor Receptor (EGFR) agents, when primary tumor has wild-type RAS and located in left-side colon. In addition, it was aimed to investigate whether the backbone CT regimen made a difference in terms of survival outcomes in MCAC and non-MCAC patients.

Materials and methods

Patient population. A total of 125 patients with histologically proven mCRC who were followed up in the medical oncology department of four institutions between 2012 and 2020 were evaluated retrospectively. Inclusion criteria were as follows: i) Patients with histologically confirmed mCRC in the pathology department of involved institutes; ii) Who had

stage 4 [according to AJCC Tumor-Node-Metastasis (TNM) Staging System], left-sided (splenic flexure, descending colon, sigmoid colon, and rectum), measurable disease, and Kirsten Rat Sarcoma/Neuroblastoma Rat Sarcoma (KRAS/NRAS) wild-type tumor; iii) Who received anti-EGFR containing regimens as first-line therapy; iv) Who underwent palliative or curative resection of primary tumor in order to accurately evaluate the mucinous histology percentage. The histologic examinations were performed by pathologists with more than five years of working experience in our centers. Patients with secondary malignancy were excluded. Data were retrospectively reviewed from patients' files. Mucinous histology was assessed as per standardized protocols according to international guidelines (20). The present study protocol was reviewed and approved (approval no. 09.2021.490) by Local Research Ethics Committee of Marmara University School of Medicine (Istanbul, Turkey).

Treatment protocols. Modified FOLFOX6 (mFOLFOX6) and FOLFIRI were used as backbone CT regimens. mFOLFOX6 was applied as follows: Oxaliplatin (oxa) 85 mg/m² on day 1, leucovorin 400 mg/m² on day 1 and 5-fluorouracil (FU) 400 mg/m² bolus on day 1, followed by continuous infusion of 2,400 mg/m² over 48 h, repeated every 2 weeks. FOLFIRI was applied as follows: Irinotecan (iri) 180 mg/m² on day 1, leucovorin 400 mg/m² on day 1 and 5-FU 400 mg/m² bolus on day 1, followed by continuous infusion of 2,400 mg/m² over 48 h, repeated every 2 weeks. Cetuximab (500 mg/m²) or panitumumab (6 mg/kg) were administered on day 1 and was repeated every 2 weeks.

Patients who achieved disease control after 12-cycles of anti-EGFR and CT combination were continued with maintenance therapy (consisted of anti-EGFR agent, 5-FU 400 mg/m² bolus, leucovorin 400 mg/m², 5-FU 2,400 mg/m² infusion over 48 h on day 1, which was repeated every two weeks) until disease progression or unacceptable toxicity.

Response assessment. Response assessment was performed within 10 to 15 days following the initial sixth administration and every six cycles of the 14-day regimens by conventional cross-sectional imaging. Treatment Response was assessed with using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in radiological imaging (21).

Response criteria for targeted lesions according to RECIST 1.1 were defined as follows; Complete Response (CR): Disappearance of all targeted lesions and reduction of all pathological lymph nodes' axis to <10 mm, Partial Response (PR): ≥30% decrease in sum of the longest diameters (SLD) from baseline, Stable Disease (SD): Neither PR nor Progressive Disease (PD) with the Nadir as reference point, PD: ≥20% increase in SLD from Nadir with an absolute sum of diameter increase ≥5 mm. Or appearance of one or more new lesions. Response criteria for non-targeted lesions according to RECIST 1.1 were defined as follows; CR: Disappearance of all targeted lesions and normalization of tumor marker levels, PR: No progression, SD: Persistence of one or more non-target lesions and/or continuation to be above normal of tumor markers, PD: Unequivocally progression in lesion size.

Progression-free survival (PFS) was defined as the time interval in months between start of first line therapy and

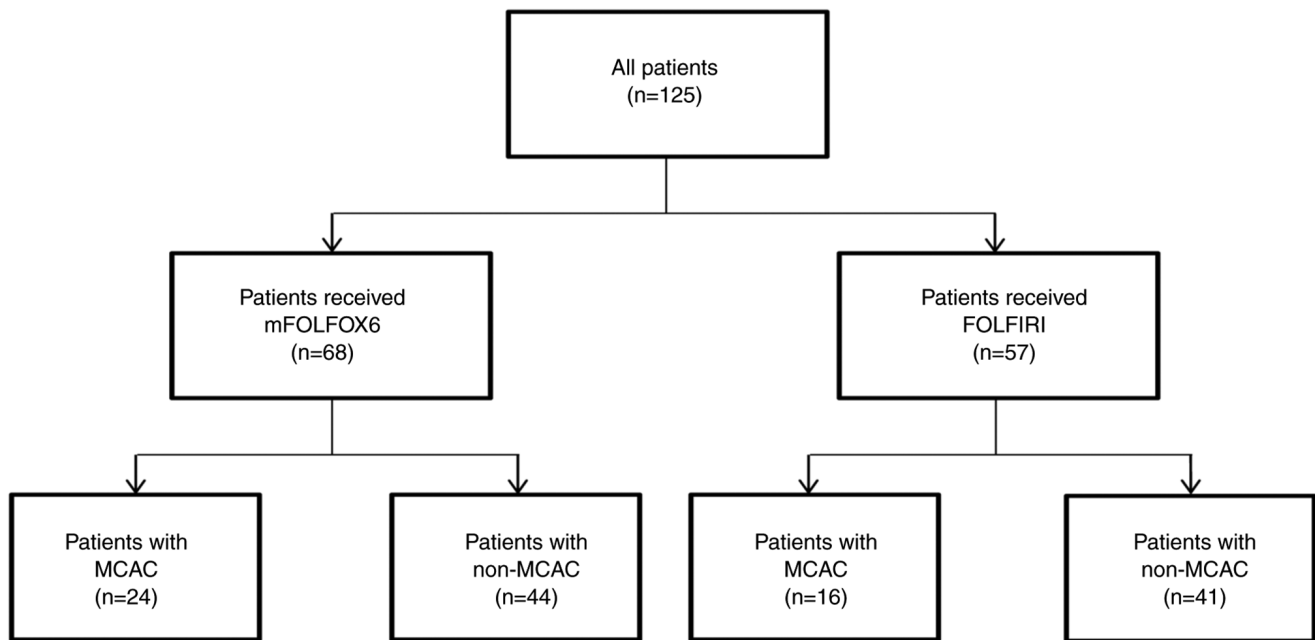


Figure 1. Flow chart of study population. MCAC, mucinous colorectal adenocarcinoma.

disease progression, death or last visit if the patient was still on treatment. Overall survival (OS) was characterized as the time interval in months between the start of first line therapy and death or last visit if the patient was still alive.

Study design. Study groups were stratified as MCAC and non-MCAC patients. MCAC was defined as tumors containing >50% extracellular mucin, and non-MCAC was defined as tumors containing no mucin component. Survival analyses were performed firstly regardless of treatment options and then performed as separating according to backbone CT regimens. The flow chart of the study population is shown in Fig. 1. Furthermore, additional survival analyses were performed for the MCAC patients considering backbone CT regimens. Flow chart of MCAC patients according to CT regimens is presented in Fig. 2.

Statistical analysis. Descriptive data were recorded as frequencies and percentages. Continuous variables were presented as median values with interquartile ranges (IQRs). Chi-square test was used to compare categorical variables. Survival was estimated with Kaplan-Meier method and log-rank test. Cox proportional models were conducted to select factors affecting survival significantly or with a trend toward significance ($P < 0.25$) in univariate analyses and to determine independent prognostic indicators in multivariate analyses using a backward stepwise method. Confidence interval (CI) was accepted as 95% and $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS version 22.0 (IBM Corp.).

Results

Baseline characteristics and treatments of 125 patients (78 males and 47 females) with a median age of 60 years (IQR, 52–68) are summarized in Table I. A total of 40 patients (32.0%)

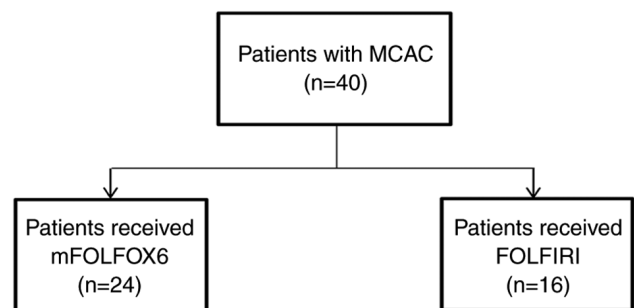


Figure 2. Flow chart of MCAC patients according to chemotherapy regimens. MCAC, mucinous colorectal adenocarcinoma.

had MCAC and 85 (68.0%) patients had non-MCAC. Among the entire study population, MCAC and non-MCAC patients were similar in age, sex, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), tumor differentiation, primary tumor location, number of metastatic sites, BRAF mutation and mismatch repair (MMR) status ($P > 0.05$ for all). While *de novo* metastasis and liver metastasis were more common in non-MCAC ($P < 0.001$ for both), peritoneal carcinomatosis was more common in MCAC ($P = 0.02$). All patients received oxa-based or iri-based CT and anti-EGFR agent in first line setting. Baseline characteristics of patients according to backbone CT regimen are shown in Table II. In both backbone CT groups, MCAC and non-MCAC patients were similar in terms of age, sex, ECOG-PS, tumor differentiation and number of metastatic sites ($P > 0.05$ for all). In the mFOLFOX6 group; *de novo* metastasis, rectum location and liver metastasis were more frequent in non-MCAC patients ($P < 0.001$, $P = 0.01$ and $P = 0.001$, respectively). The FOLFIRI group was relatively more homogeneous and only metastasis pattern was different between non-MCAC and MCAC patients. Additionally, among MCAC patients who received FOLFIRI, there were no patients

Table I. Demographic and clinical characteristics of the study subjects.

Characteristics	All (n=125)	MCAC (n=40)	Non-MCAC (n=85)	P-value
Age, years [Median (IQR)]	60 (52-68)	56 (45-63)	61 (53-68)	0.08
Sex				
Female	47 (37.6)	19 (47.5)	28 (32.9)	0.11
Male	78 (62.4)	21 (52.5)	57 (67.1)	
ECOG-PS, n (%)				
0-1	118 (94.4)	37 (92.5)	81 (95.3)	0.67
2	7 (5.6)	3 (7.5)	4 (4.7)	
<i>De novo</i> metastasis (%)	40 (32.0)	4 (10%)	36 (42.4)	<0.001
Tumor differentiation, n (%)				
Well	10 (8.0)	2 (5.0)	8 (9.0)	0.15
Moderate	81 (64.8)	22 (55.0)	59 (69.4)	
Poor	22 (17.6)	11 (27.5)	11 (12.9)	
Unknown	12 (9.6)	5 (12.5)	7 (8.2)	
Tumor differentiation group, n (%)				
Well	10 (8.8)	2 (5.7)	8 (10.2)	0.72
Moderate and poor	103 (91.2)	33 (94.3)	70 (89.7)	
Metastasectomy, n (%)	4 (3.2)	-	4 (4.7)	0.3
Primary tumor location, n (%)				
Rectum	46 (36.8)	10 (25.0)	36 (42.4)	0.06
Sigmoid or descending colon	79 (63.2)	30 (75.0)	49 (57.6)	
Metastatic site, n (%)				
Liver	82 (65.6)	17 (42.5)	65 (76.5)	<0.001
Lung	23 (26.4)	9 (22.5)	24 (28.2)	
Lymph node	39 (31.2)	14 (35.0)	25 (29.4)	0.52
Carcinomatosis peritoneal	31 (24.8)	15 (37.5)	16 (18.8)	0.02
Metastatic site number, n (%)				
≥2	61 (48.8)	18 (45.0)	43 (50.5)	0.48
First-line CT regimen, n (%)				
mFOLFOX6	68 (54.4)	24 (60.0)	44 (51.8)	0.38
FOLFIRI	57 (45.6)	16 (40.0)	41 (48.2)	
Anti-EGFR agent, n (%)				
Cetuximab	69 (55.2)	18 (45.0)	51 (60.0)	0.11
Panitumumab	56 (44.8)	22 (55.0)	34 (40.0)	
Maintenance, n (%)	67 (53.6)	17 (42.5)	50 (58.8)	0.08
BRAF, n (%)				
Mutant	6 (4.0)	1 (2.0)	5 (6.0)	0.39
Wild	119 (96.0)	39 (98.0)	80 (94.0)	
MMR status, n (%)				
MSI	5 (4.0)	3 (7.0)	2 (2.0)	0.64
MSS	120 (96.0)	37 (92.0)	83 (97.0)	

IQR, interquartile range; ECOG-PS, Eastern cooperative oncology group-performance status; CT, chemotherapy, EGFR, epidermal growth factor receptor; BRAF, V-Raf murine sarcoma Viral Oncogene Homolog B1; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable.

with BRAF mutation or MSI tumor, but no statistical difference was identified.

In the whole group without separating backbone CT regimen, MCAC group had poor OS and PFS. Median follow-up

period was 19.7 months (range 2.2-77.3) and during this time, disease progression and death occurred in 107 (85.6%) and 86 (68.8%) patients, respectively. Median PFS with first line treatment was 10.7 (95% CI: 9.3-12.1) months. PFS was

Table II. Demographic and clinical characteristics according to chemotherapy regimens.

Characteristics	Patients received FOLFOX + anti-EGFR			Patients received FOLFIRI + anti-EGFR		
	MCAC (n=24)	Non-MCAC (n=44)	P-value	MCAC (n=16)	Non-MCAC (n=41)	P-value
Age, years [Median (IQR)]	59 (46-62)	62 (53-70)	0.21	52 (44-66)	59 (52-68)	0.15
Sex						
Female	10 (41.7)	15 (34.1)	0.53	9 (56.3)	13 (31.7)	0.08
Male	14 (58.3)	29 (65.9)		7 (43.8)	28 (68.3)	
ECOG-PS, n (%)						
0-1	22 (91.7)	42 (95.5)	0.52	15 (93.8)	39 (95.1)	0.83
2	2 (8.3)	2 (4.5)		1 (6.3)	2 (4.9)	
<i>De novo</i> metastasis, n (%)	2 (8.3)	25 (56.8)	<0.001	2 (12.5)	11 (26.8)	0.24
Tumor differentiation, n (%)						
Well	1 (4.2)	4 (9.1)	0.39	1 (6.3)	4 (9.8)	0.28
Moderate	14 (58.3)	31 (70.5)		8 (50.0)	28 (68.3)	
Poor	7 (29.2)	8 (18.2)		4 (25.0)	3 (7.3)	
Unknown	2 (8.3)	1 (2.3)		3 (18.8)	6 (14.6)	
Metastasectomy, n (%)	-	2 (4.5)	0.28	-	2 (4.9)	0.36
Primary tumor location, n (%)						
Rectum	2 (8.3)	15 (34.1)	0.01	8 (50.0)	21 (51.2)	0.93
Sigmoid or descending colon	22 (91.7)	29 (65.9)		8 (50.0)	20 (48.8)	
Metastatic site, n (%)						
Liver	11 (45.8)	37 (84.1)	0.001	6 (37.5)	28 (68.3)	0.03
Lung	6 (25.0)	9 (20.5)	0.66	3 (18.8)	15 (36.6)	0.19
Lymph node	8 (33.3)	14 (31.8)	0.89	6 (37.5)	11 (26.8)	0.42
Carcinomatosis peritoneal	9 (37.5)	11 (25.0)	0.28	6 (37.5)	5 (12.2)	0.03
Metastatic site number, n (%)						
≥2	13 (54.2)	26 (59.1)	0.69	5 (31.3)	18 (43.9)	0.38
Anti-EGFR agent, n (%)						
Cetuximab	9 (37.5)	25 (56.8)	0.12	9 (56.2)	26 (63.4)	0.61
Panitumumab	15 (62.5)	19 (43.2)		7 (43.8)	15 (36.6)	
Maintenance, n (%)	11 (45.8)	29 (65.9)	0.10	6 (37.5)	21 (51.2)	0.35
BRAF, n (%)						
Mutant	1 (4.2)	3 (6.8)	0.65	0 (0.0)	1 (2.4)	0.52
Wild	23 (95.8)	41 (93.2)		16 (100.0)	40 (97.6)	
MMR status, n (%)						
MSI	3 (12.5)	1 (2.3)	0.08	0 (0.0)	2 (4.9)	0.36
MSS	21 (87.5)	43 (97.7)		16 (100.0)	39 (95.1)	

IQR, interquartile range; ECOG-PS, Eastern cooperative oncology group-performance status; EGFR, epidermal growth factor receptor; BRAF, V-Raf murine sarcoma Viral Oncogene Homolog B1; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable.

significantly lower in MCAC [9.9 months (95% CI: 9.4-10.3)] than non-MCAC patients [12.0 months (95% CI: 10.2-13.7)] ($P=0.005$). Median OS was 25.7 months (95% CI: 22.4-29.1) and was significantly lower in MCAC [22.8 months (95% CI: 14.5-31.2)] than non-MCAC patients [29.7 months (95% CI: 22.1-37.3)] ($P=0.005$). Kaplan-Meier curves for OS and PFS according to mucinous histology are presented in Fig. 3.

When survival outcomes were evaluated according to two backbone CT regimens, patients with mucinous histology had

poorer OS in both of regimens. In mFOLFOX6 group, 41 (60.3%) patients died. Median OS was 26.84 months (95% CI: 20.47-33.21) and lower in MCAC patients [22.47 months (95% CI: 17.11-27.82)] than non-MCAC patients [30.85 months (95% CI: 20.98-40.71)] ($P=0.03$). Moreover, in multivariate analysis mucinous histology was an independent prognostic factor for poor OS in mFOLFOX6 group [Hazard Ratio (HR): 1.92, (95% CI: 1.03-3.61), $P=0.04$]. Univariate and multivariate analyses for OS in mFOLFOX6 group are demonstrated in

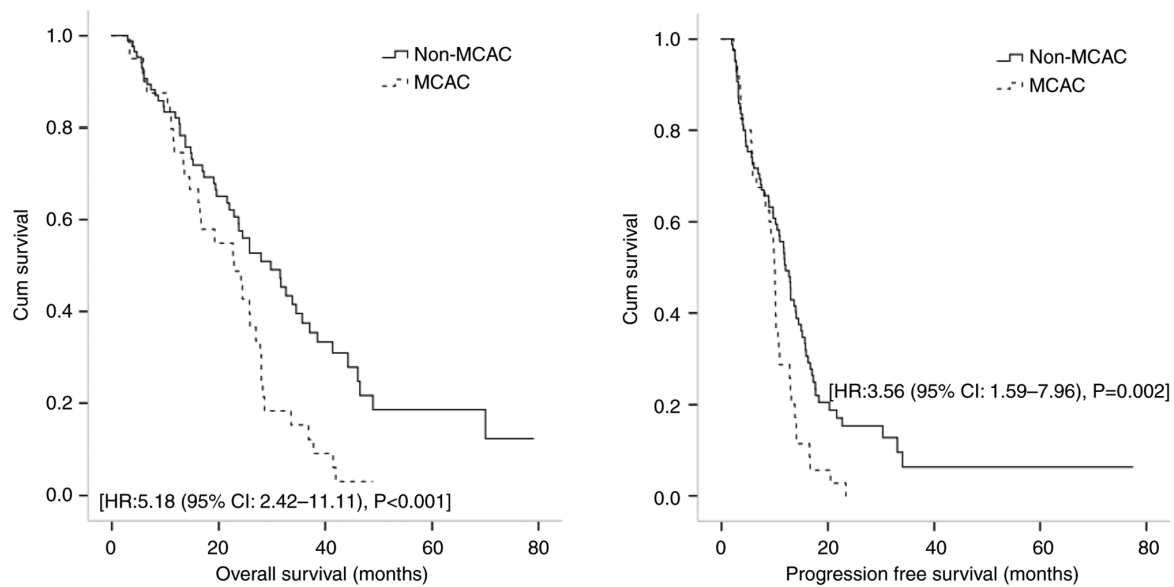


Figure 3. Kaplan-Meier curve for overall survival and progression-free survival according to mucinous histology. MCAC, mucinous colorectal adenocarcinoma; HR, hazard ratio; CI, confidence interval.

Table III. In FOLFIRI group, 44 (77.2%) patients succumbed. Median OS was 21.38 months (95% CI: 13.69-29.08) and lower in MCAC [14.22 months (95% CI: 0.00-36.24)] patients than non-MCAC patients [21.38 months (95% CI: 13.18-29.59)], $P=0.08$. In multivariate analysis, ECOG-PS [HR: 6.28, (95% CI: 1.39-28.51), $P=0.01$], *de novo* metastasis [HR: 2.53 (1.18-5.46), $P=0.01$], MMR status [HR: 26.00 (95% CI: 2.76-244.95), $P=0.004$] and mucinous histology [HR: 4.29 (95% CI: 0.54-33.88), $P=0.04$] were independent prognostic factors for OS. Univariate and multivariate analyses for OS in FOLFIRI group are revealed in Table IV. Kaplan-Meier curves for OS in mFOLFOX6 and FOLFIRI group according to mucinous histology are shown in Fig. 4.

When evaluating PFS by separating backbone CT regimens, in only mFOLFOX6 group, MCAC was found to be poor prognostic. In patients receiving mFOLFOX6, disease progression occurred in 56 (82.3%) patients. Median PFS was 11.86 months (95% CI: 9.68-14.04) and lower in MCAC patients [10.15 months (95% CI: 9.65-10.64)] than non-MCAC patients [13.01 months (95% CI: 10.74-15.27)], $P=0.008$. After correcting for significant prognostic factors by multivariate analysis, ECOG-PS [HR: 22.77 (95% CI: 3.12-166.22), $P=0.002$] and mucinous histology [HR: 3.86 (95% CI: 1.85-8.10), $P<0.001$] were revealed to be associated with poor PFS. Univariate and multivariate analyses for PFS in mFOLFOX6 group are shown in Table III. In FOLFIRI group, disease progression occurred in 51 (89.5%) patients. Median PFS was 9.82 months (95% CI: 7.73-11.91) and numerically shorter in MCAC group [8.11 months (95% CI: 3.41-12.82)] than non-MCAC group [10.87 months (95% CI: 8.98-12.77)], $P=0.18$. In multivariate analysis, *de novo* metastasis [HR: 2.02, (95% CI: 1.04-3.94), $P=0.03$] and rectum location [HR: 1.77, (95% CI: 1.00-3.12), $P=0.04$] were independent prognostic factors. PFS was comparable between MCAC and non-MCAC patients [HR: 1.57, (95% CI: 0.85-2.92), $P=0.15$]. Univariate and multivariate analyses for PFS in FOLFIRI group are shown in Table IV. Kaplan-Meier curves for PFS in mFOLFOX6 and FOLFIRI

group according to mucinous histology are demonstrated in Fig. 5.

When survival outcomes were analyzed in the MCAC group, backbone CT regimens did not make a significant difference. Median OS of MCAC patients receiving mFOLFOX6 and FOLFIRI was 22.47 months (95% CI: 17.12-27.38) and 14.22 months (95% CI: 0.00-36.25), respectively ($P=0.41$). Median PFS of MCAC patients receiving mFOLFOX6 and FOLFIRI was 10.15 months (95% CI: 9.65-10.64) and 8.11 months (95% CI: 3.41-12.82), respectively ($P=0.73$). Kaplan-Meier curves for PFS and OS in MCAC group according to backbone CT regimens are revealed in Fig. 6.

Any grade toxicity was similar between treatment groups ($P=0.39$) and observed in 72.0% (49/68 patients) in mFOLFOX6 + anti-EGFR group and 64.9% (37/57 patients) in FOLFIRI + anti-EGFR group. Moreover, any grade toxicity rate of MCAC and non-MCAC patients was similar in treatment groups (83.3 and 65.9%, $P=0.13$ in mFOLFOX6 + anti-EGFR group, 68.7 and 63.4%, $P=0.70$ in FOLFIRI + anti-EGFR group, respectively). In mFOLFOX6 + anti-EGFR group, while the most common grade 1-2 toxicities were neuropathy (30.1%), skin toxicity (29.4%), asthenia (27.9%) and anemia (27.9%), grade 3-4 toxicities were neutropenia (10.3%), nausea (8.8%) and neuropathy (8.8%). In FOLFIRI + anti-EGFR group, the most common grade 1-2 toxicities were anemia (26.3%), skin toxicity (26.3%), asthenia (24.6%) and nausea (21.0%), whereas grade 3-4 toxicities were neutropenia (12.2%), skin toxicity (5.3%) and diarrhea (5.3%). Neuropathy was higher in mFOLFOX6 + anti-EGFR group ($P=0.001$) and diarrhea was higher in FOLFIRI + anti-EGFR group ($P=0.003$). There was no statistically difference in terms of other toxicities between treatment groups.

Discussion

The present study revealed that mucinous histology is associated with worse survival outcomes than non-mucinous

Table III. Univariate and multivariate analyses for PFS and OS in mFOLFOX6 group.

Characteristics	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	Median (95% CI)	P-value	HR (95% CI)	P-value	Median (95% CI)	P-value	HR (95% CI)	P-value
Age, years								
<61	10.61(9.59-11.62)	0.73			23.06 (15.92-30.20)	0.43		
≥61	12.81 (11.52-14.10)				28.25 (18.77-37.74)			
Sex								
Female	11.86 (8.91-14.80)	0.30			20.69 (14.60-26.79)	0.04	Ref.	0.05
Male	12.68 (9.87-15.48)				30.25 (25.43-35.08)		0.52 (0.27-1.00)	
ECOG-PS, n (%)								
0-1	12.02 (9.63-14.41)	0.003	Ref.	0.002	27.76 (21.18-34.34)	0.09	Ref.	0.12
2	2.89 (2.44-3.34)		22.27 (3.12-166.22)		6.60 (0.00-23.63)		2.25 (0.79-6.44)	
<i>De novo</i> metastasis								
(+)	12.91 (10.42-15.40)	0.50			30.25 (17.64-42.88)	0.85		
(-)	11.72 (9.46-13.99)				26.84 (20.37-33.31)			
Metastasectomy								
(+)	13.96 (NE-NE)	0.16	1.57 (0.18-13.95)	0.68	22.20 (NE-NE)	0.34		
(-)	11.82 (9.68-13.98)		Ref.		26.84 (20.67-33.01)			
Primary tumor location								
Rectum	8.93 (6.77-11.10)	0.28			23.06 (12.37-33.75)	0.78		
Non-rectum	12.68 (11.21-14.16)				27.76 (20.69-34.83)			
Metastatic site								
Liver	12.68 (10.32-15.03)	0.02	0.54 (0.25-1.20)	0.13	28.25 (20.16-36.34)	0.80		
Lung	13.10 (10.63-15.58)	0.80			28.25 (25.93-30.57)	0.54		
Lymph node	11.82 (9.26-14.39)	0.50			40.90 (13.02-68.78)	0.23		
Carcinomatosis peritoneal	10.25 (9.26-11.24)	0.37			22.20 (13.71-30.70)	0.15	1.78 (0.88-3.59)	0.10
Anti-EGFR agent								
Cetuximab	12.68 (9.43-15.93)	0.34			23.98 (13.31-34.66)	0.75		
Panitumumab	11.28 (10.38-13.28)				27.76 (20.36-35.16)			
Histopathology								
Mucinous	10.15 (9.65-10.64)	0.008	3.86 (1.85-8.10)	<0.001	22.47 (17.11-27.82)	0.03	1.92 (1.03-3.61)	0.04
Non-mucinous	13.01 (10.74-15.27)		Ref.		30.85 (20.98-40.71)		Ref.	
BRAF								
Mutant	3.58 (0.00-10.60)	0.27			6.43 (0.00-33.10)	0.46		
Wild-type	11.86 (9.58-14.14)				27.76 (21.46-34.06)			

Table III. Continued.

Characteristics	PFS			OS		
	Univariate		Multivariate	Univariate		Multivariate
	Median (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
MMR status						
MSI	3.58 (0.00-10.23)	0.14	1.29 (0.37-4.57)	6.43 (NE-NE)		0.76
MSS	13.66 (11.08-16.25)		Ref.	27.76 (21.45-34.07)		

PFS, Progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern cooperative oncology group-performance status; EGFR, epidermal growth factor receptor; BRAF, V-Raf murine sarcoma Viral Oncogene Homolog B1; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable; Ref., reference.

histology in left-sided mCRC patients with wild-type RAS who treated with standard first line therapy. Additionally, in terms of backbone CT regimens, MCAC patients had poor OS than non-MCAC patients in both mFOLFOX6 and FOLFIRI groups, and MCAC patients had poor PFS than non-MCAC patients only in mFOLFOX6 group. However, when survival analyses were performed for only MCAC group, backbone CT option did not significantly affect PFS or OS in this distinct histologic subgroup of mCRC.

Previously, although increasing evidence has indicated that mucinous histology is a poor prognostic factor in CRC patients, prognosis and treatment strategy remain conflicting (3,9,11). Maisano *et al* (16), Negri *et al* (22) and Mekenkamp *et al* (23) demonstrated poor prognosis of patients with mucinous histology who were treated with different CT regimens. Conversely, Catalano *et al* (10) evaluated both all mCRCs and only the left-sided ones separately and revealed that prognosis of patients with mucinous histology was not significantly different from that with non-mucinous histology. In the aforementioned studies, study populations were heterogeneous in terms of tumor location and RAS mutation and were mostly located in right colon. Lan *et al* (24) analyzed survival of right- and left-sided CRCs according to histologic subtype and identified that mucinous histology was associated with worse 5-year OS compared with non-mucinous histology only in left-sided CRCs, not in right-sided. The present study included a relatively homogeneous group of patients compared with the literature and revealed that among left-sided mCRC patients, OS of MCAC patients was worse than non-MCAC patients. Prognostic difference was remarkable, despite the presence of more *de novo* metastasis in the non-MCAC group.

There are also several studies investigating the prognostic importance of mucinous histology according to backbone CT regimens. Catalano *et al* (10) compared fluoropyrimidine-based, oxa-based, and iri-based CT and all regimens included bevacizumab. They found that in only oxa-based CT group, mucinous histology was associated with worse prognosis. Zhou *et al* (18) compared CT plus bevacizumab with CT plus cetuximab in the first line setting and also analyzed backbone CT regimens. In patients with mucinous histology, FOLFIRI combined with bevacizumab or cetuximab indicated an improved prognosis than oxa-based regimens. In the current study, when OS was analyzed over backbone CT regimens among patients receiving mFOLFOX6, although baseline characteristics of the MCAC group indicated an improved prognosis, mucinous histology was still found to be associated with poorer OS. Baseline characteristics of patients who received FOLFIRI were relatively homogeneous. Otherwise, there was no BRAF mutant or MSI tumor in the MCAC group. Despite the absence of these features indicating poor prognosis and treatment resistance, MCAC was also associated with poor prognosis in the FOLFIRI group.

Predictive value of mucinous histology remains controversial. Several studies emphasized that mucinous and non-mucinous CRCs show differential expression of CT metabolism and resistance genes (25,26). Furthermore, Cantero-Recasens *et al* (27) suggested that controlling mucin secretion may reverse chemo-refraction in CRC cells. Among studies investigating backbone CT and mucinous histology, Catalano *et al* (15) included patients receiving

Table IV. Univariate and multivariate analyses for PFS and OS in FOLFIRI group.

Characteristics	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	Median (95% CI)	P-value	HR (95% CI)	P-value	Median (95% CI)	P-value	HR (95% CI)	P-value
Age, years								
<57	9.69 (7.12-12.27)	0.80			26.08 (15.70-36.47)	0.97		
≥57	10.05 (6.95-13.16)				20.20 (10.67-29.74)			
Sex								
Female	8.11 (0.81-15.42)	0.38			20.20 (9.57-30.14)	0.10		
Male	10.05 (8.20-11.91)				22.43 (13.58-31.30)			
ECOG-PS, n (%)								
0-1	9.82 (7.27-12.37)	0.14	Ref.	0.44	22.43 (17.48-27.39)	<0.001	Ref.	0.01
2	4.60 (3.49-5.70)		1.72 (0.42-7.10)		6.07 (3.71-8.44)		6.28 (1.39-28.51)	
<i>De novo</i> metastasis								
(+)	8.01 (3.35-12.68)	0.04	2.02 (1.04-3.94)	0.03	13.27 (6.09-20.44)	0.01	2.53 (1.18-5.46)	0.01
(-)	10.94 (7.56-14.32)		Ref.		24.67 (19.02-30.32)		Ref.	
Metastasectomy								
(+)	9.69 (NE-NE)	0.68			20.33 (NE-NE)	0.92		
(-)	9.82 (7.59-12.06)				21.38 (11.39-31.38)			
Primary tumor location								
Rectum	8.27 (4.39-12.17)	0.05	1.77 (1.00-3.12)	0.04	20.20 (11.39-29.01)	0.14		
Non-rectum	10.94 (7.35-14.53)		Ref.		24.67 (11.20-38.13)			
Metastatic site								
Liver	7.16 (2.75-11.57)	0.79			17.51 (9.99-25.03)	0.44		
Lung	5.78 (0.00-13.44)	0.63			20.20 (7.88-32.53)	0.46		
Lymph node	10.05 (1.13-18.98)	0.40			21.38 (11.30-31.46)	0.62		
Carcinomatosis peritoneal	10.05 (8.41-11.70)	0.28			22.43 (10.17-34.70)	0.19		
Anti-EGFR agent								
Cetuximab	9.82 (8.18-11.47)	0.62			24.67 (18.41-30.93)	0.44		
Panitumumab	8.27 (4.04-12.52)				15.14 (13.62-16.67)			
Histopathology								
Mucinous	8.11 (3.41-12.82)	0.18	1.57 (0.85-2.92)	0.15	14.22 (0.00-36.24)	0.08	2.04 (1.02-4.08)	0.04
Non-mucinous	10.87 (8.98-12.77)		Ref.		21.38 (13.18-29.59)		Ref.	
BRAF								
Mutant	4.53 (NE-NE)	0.58			5.91 (NE-NE)	0.05	4.29 (0.54-33.88)	0.16
Wild-type	9.82 (7.77-11.88)				22.43 (16.07-28.80)		Ref.	

Table IV. Continued.

Characteristics	PFS			OS		
	Univariate		Multivariate	Univariate		Multivariate
	Median (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
MMR status						
MSI	4.53 (NE-NE)	0.19	4.21 (0.52-33.78)	0.17	5.91 (NE-NE)	0.007
MSS	9.82 (7.91-11.73)		Ref.		21.38 (14.98-27.79)	0.004
PFS, Progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern cooperative oncology group-performance status; EGFR, epidermal growth factor receptor; BRAF, V-Raf murine sarcoma Viral Oncogene Homolog B1; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable; Ref., reference.						

oxa-based or iri-based CT but not biological agent, in 2009. It was found that mucinous histology was associated with a low response rate for both CT regimens. In the following years, Catalano *et al* (10) studied with patients receiving CT plus bevacizumab for the first line. They found that PFS was comparable between mucinous and non-mucinous histology in either CT regimens, but only in the oxa-based CT group, PFS was numerically notably lower in patients with mucinous histology. Few studies have been conducted on its predictive significance for biological agents. Moretto *et al* (17), in the left-sided mCRCs, Zhou *et al* (18), regardless of tumor sidedness, emphasized that mucinous histology was a negative predictive factor for anti-EGFR agents. Wang *et al* (19) included left-sided RAS/BRAF wild-type mucinous and non-mucinous mCRC patients. They analyzed mucinous mCRC patients according to first line treatment and they revealed that patients who received CT plus bevacizumab had improved PFS compared with patients who received CT plus anti-EGFR agent. However, there were only seven patients in each group and the study did not include analysis for backbone CT regimens. Since the present study did not include a group who did not receive anti-EGFR agent, it was not possible to evaluate the effectiveness of the biological agent. In the present study, mucinous histology was significantly associated with worse PFS in the mFOLFOX6 group, but was not in the FOLFIRI group and consistent with the literature.

Further findings are needed to clarify in terms of whether there is an extra benefit of a specific CT regimen for the MCAC patients. Nearly all previous studies compared mucinous histology with non-mucinous histology. However, Zhou *et al* (18) included mucinous and non-mucinous patients and performed a separate analysis for patients with mucinous histology according to CT regimens. Patients received FOLFIRI or oxa-based CT regimens combined with bevacizumab or cetuximab. For patients with mucinous histology, while in patients who received bevacizumab, median OS was significantly longer in combination to FOLFIRI than oxa-based regimens, in patients who received cetuximab, median OS was comparable between FOLFIRI and oxa-based regimens. The present study included patients receiving CT combined with anti-EGFR agents and there was no statistically significant difference between iri-based or oxa-based regimens in MCAC patients consistent with the literature.

There are certain major limitations to the present study. Clinical data based on the retrospective nature have certain disadvantages to control for all potential confounding bias. The study included a small number of patients and there were no patients who had mucinous component (<50% extracellular mucin) and therefore analyses did not include a comparison between MCAC and mucinous component. Since the study included only left-sided mCRC, also no comparison could be made between left-sided and right-sided MCAC. Single-center histologic revision was not applied. At the time interval in which data were collected, the association of BRAF mutation with anti-EGFR resistance was not a well-known entity. Therefore, the present study included a small proportion of patients with BRAF mutations, which may partly explain the poor prognosis and anti-EGFR combined CT resistance. Additionally, there was a small number of patients who had MMR-deficient tumor and there was no information about

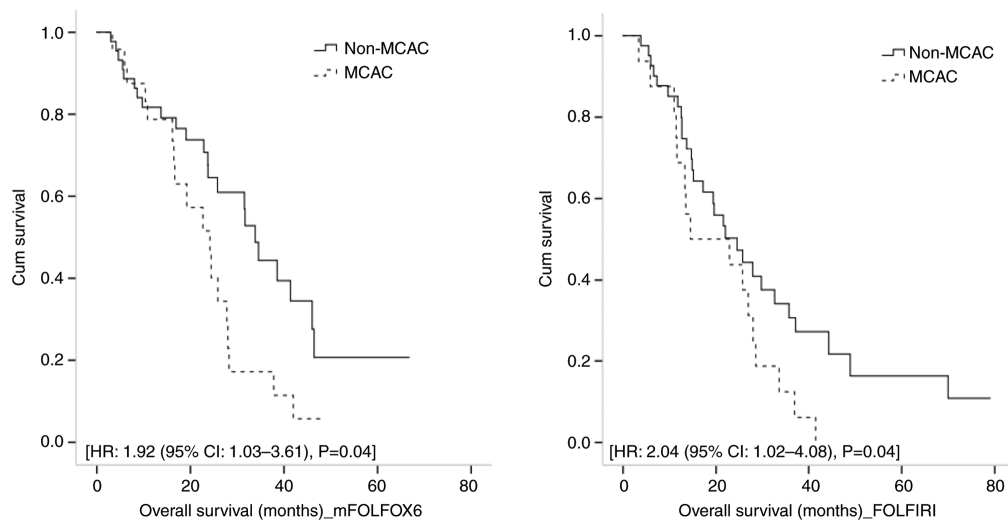


Figure 4. Kaplan-Meier curve for overall survival in mFOLFOX6 and FOLFIRI groups according to mucinous histology. MCAC, mucinous colorectal adenocarcinoma; HR, hazard ratio; CI, confidence interval.

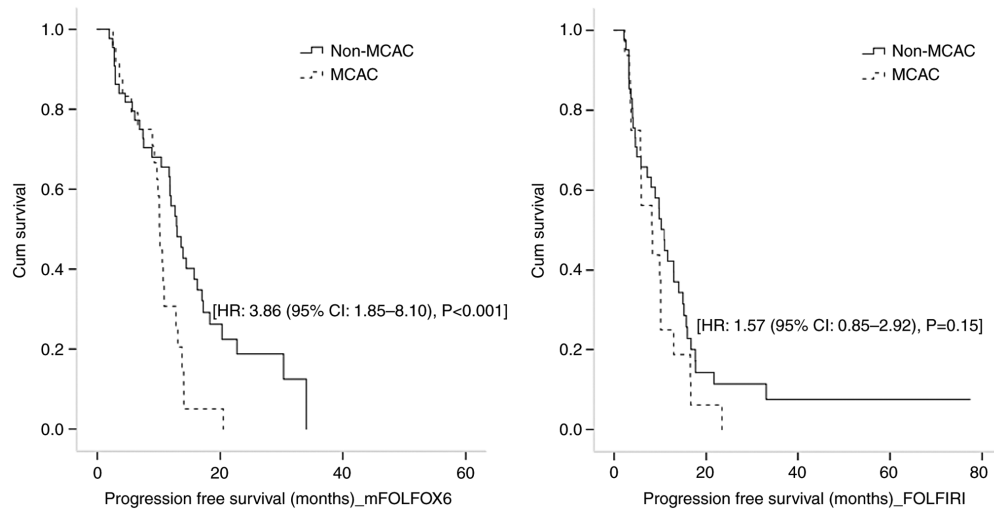


Figure 5. Kaplan-Meier curve for progression-free survival in mFOLFOX6 and FOLFIRI groups according to mucinous histology. MCAC, mucinous colorectal adenocarcinoma; HR, hazard ratio; CI, confidence interval.

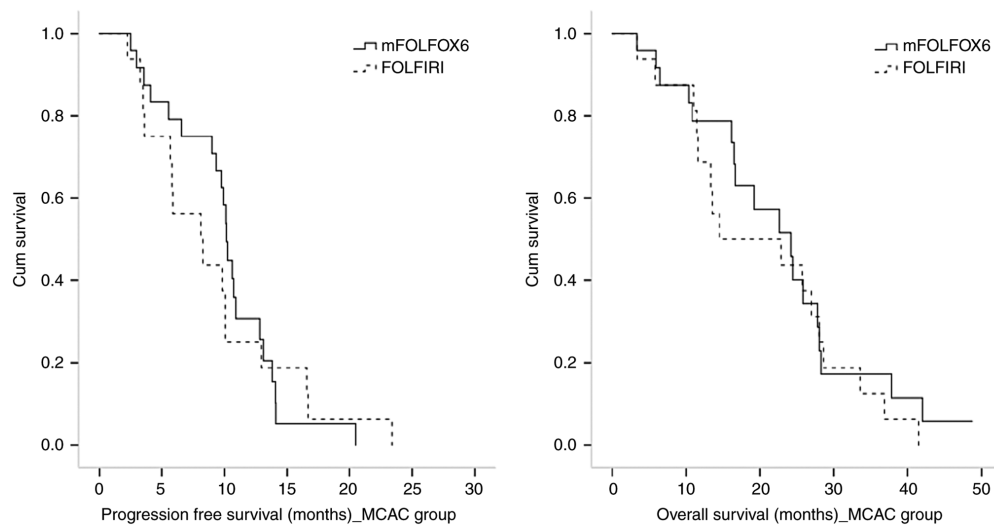


Figure 6. Kaplan-Meier curve for progression-free survival and overall survival in MCAC group according to backbone CT regimens. MCAC, mucinous colorectal adenocarcinoma.

consensus molecular subtypes, which are other factors that may affect prognosis.

In conclusion, the present study revealed that mucinous histology is associated with poor prognosis in left-sided mCRC with wild-type RAS. Considering analyses of MCAC group, the results did not indicate an extra benefit of a specific backbone CT regimen in patients with mucinous mCRC. However, the poor prognostic role of mucinous histology should be kept in mind. Additionally, considering analyses of backbone CT groups, poor PFS of MCAC patients was shown in only among patients receiving mFOLFOX6 and this finding may be an important issue that needs to be clarified in future studies.

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Availability of data and materials

The data that support the findings of this study may be available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions

RA conceptualized the study, conducted investigation and formal analysis, wrote the original draft, developed the study concept, designed and monitored the study, and collected the data. MMA, SA, MA, AC and AY collected data. CC performed pathology review. NCD and OK performed statistical analyses. TAT and SI collected data, and reviewed and edited the manuscript. OB, IVB, FD and PFY developed methodology, supervised the study, reviewed and edited the manuscript. FD and PFY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent is not required for the study due to retrospective design. The present study protocol was reviewed and approved (approval no. 09.2021.490) by Local Research Ethics Committee of Marmara University School of Medicine (Istanbul, Turkey).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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