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The Effect of the Mucinous Component Presence on the Clinical Outcomes of Colorectal Cancer

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Abstract

Background. The effect of colorectal cancer (CRC) histological subtypes on the prognosis is still a controversial issue. We aimed to compare clinical findings, histopathologic data, and survival outcomes in CRC patients with classical and mucinous subtypes.

Methods. Patients who were operated on for CRC between 2010 and 2017 were included in the study. Patients were classified into two groups according to the presence of a mucinous component: mucinous adenocarcinoma (MAC) – mucinous component $>$ 50% and classical adenocarcinoma (CAC). Clinical and histopathologic findings, recurrence, metastasis, and survival rates were compared.

Results. Data of the 484 CRC patients were documented. Sixty-nine patients (14.3%) were in the MAC group and 415 (85.7%) patients were in the CAC group. The mean age of patients with MAC and CAC was 63.4 $\pm$ 13.5 and 68.5 $\pm$ 12.7 years, respectively (p = 0.002). Proximal colon localization was found in 30 (43.5%) MAC patients and 123 (29.6%) CAC patients (p = 0.029). The number of patients with metastatic lymph nodes was higher in the MAC group (58% vs. 41.2%, p = 0.03). Nevertheless, there was no significant difference between the CAC and MAC groups in terms of disease-free survival (63.1% vs. 69.6%, p = 0.37) and disease-related mortality (23.6% vs. 23.2%, p = 0.94) over the follow-up period. Multivariate analysis showed that the presence of perineural invasion, patient's age, and disease stage were associated with mortality in CRC patients.

Conclusions. MACs occurred at a younger age than CACs and were more likely localized in the proximal colon as compared to CACs. Despite increased lymph node metastasis in MAC patients, no statistical significance was detected in overall survival or disease-free survival. Multivariate analysis revealed that age, perineural invasion, and disease stage were relevant to mortality in CRC patients.

Keywords

Colorectal Cancer; Mucinous Adenocarcinoma; Lymph Node Metastasis; Prognosis

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Introduction

Mucinous adenocarcinoma (MAC) is a distinct form of colorectal cancer (CRC). The World Health Organization classifies MAC as a histological subtype of CRC characterized by abundant extracellular mucinous accumulation that accounts for at least 50% of the tumor volume [1]. MACs have been shown to constitute 10-15% of CRCs worldwide and this rate has been observed to be lower in Asian regions [1, 2]. MACs occur at a younger age and are more common in the proximal colon [3]. In addition, some studies have found that MAC is more common in female patients [4]. The prognostic and predictive significance of MAC is still controversial. Although there is no consensus, there are reports that MACs are diagnosed at a more advanced stage and have a poorer prognosis than classical adenocarcinoma (CAC) [5, 6]. In addition, 5-year overall survival was found to be significantly lower (81.4%) for stage I, II, and III MAC patients as compared to CAC patients (87.4%) in case of adjuvant 5-fluorouracil-based chemotherapy treatment [7]. Moreover, MACs have a poor response to adjuvant chemotherapy treatments in comparison with CACs [3, 5, 6]. Patients with rectal MAC were more prone to have lower survival rates and poorer downstaging after preoperative chemotherapy [8]. Decreased chemosensitivity may be caused by the distinct genetic profiles and higher rates of microsatellite instability in MACs [5]. Despite these controversial factors, the same

treatment protocols are applied for MAC and CAC patients.

This study aimed to compare the MAC and CAC groups in terms of clinical and histopathological features that may have prognostic significance.

Materials and Methods

Study Design

Patients with colorectal cancer detected during colonoscopy and operated on at Istanbul Medeniyet University, Goztepe Education and Research Hospital between 2010 and 2017 were included in this retrospective study.

Study Population

Patients who met the criteria were evaluated in this single institution cohort. Patients who had an oncological follow-up in another centre, patients who refused or discontinued surgical and/or oncological treatment, and those with non-adenocarcinoma tumors were excluded from the study.

Patients were classified into two groups based on the presence of a mucinous component: the CAC group, where there was no mucinous component or the mucinous component was less than 50% of the tumor volume; the MAC group, where the mucinous component was more than 50% of tumor volume [1].

Analysis

Patient demographics, preoperative serum levels of tumor markers, tumor localization and size, TNM stages, the presence of perineural and lymphovascular invasion, and the number of harvested and metastatic lymph nodes were evaluated. Overall disease recurrence, disease-free survival, and mortality rates were analysed statistically.

Statistical Analysis

The R version 4.0.0 (Vienna, Austria; http://www.r-project.org/) was used in the statistical analysis. Descriptive statistics were presented as numbers and percentages (n, %) or Mean $\pm$ Standard Deviation. Normal distribution was examined using histograms and the Shapiro-Wilk test. Categorical variables were compared using the Pearson chi-square test with post hoc analysis or the Fisher's Exact test. Non-normal distributed variables were compared using the Mann-Whitney U test. The Kaplan Meier survival curve was illustrated for tumor subtype and the log-rank test was used to test the difference. The effects of patient characteristics on two-year and five-year survival were assessed using Cox proportional hazards regression. With clinically relevant variables that had significance in univariate analysis, multivariate models were illustrated separately for two-year and five-year survival. A value of $p < 0.05$ was considered statistically significant.

Results

Four hundred eighty-four of 523 patients operated on for colorectal adenocarcinoma between 2010 and 2017 and met the criteria were included in the study. Patients with MAC were statistically significantly younger than patients with CAC (Table 1). There was no statistical difference between the groups in terms of gender.

Tumor localization varied significantly between the CAC and MAC groups. Right-sided colon involvement was detected in 43.5% of patients with MAC and only 26.5% of patients with CAC. Post hoc analysis revealed that the incidence of right-sided colon involvement increased significantly in MAC groups ($p = 0.01$). Among right-sided colon cancers, 21.4% (n: 30) of tumors were MACs, while among left-sided colon cancers, only 9.7% (n=17) of tumors were MACs. MACs tumors are more often found in the right colon; however, left-sided colon involvement predominates in CAC.

At diagnosis, CA19-9 levels (> 37 U/mL) were higher in MAC patients as compared to CAC patients (26.2% versus 12.2%, respectively, $p = 0.04$). However, there was no statistical difference in preoperative CEA levels between the groups ($p = 0.80$).

Although tumor diameters were larger in patients with MAC, no statistically significant difference was found. There was no significant difference between the groups in tumor grade and the presence of perineural or lymphovascular invasion.

The total number of metastatic lymph nodes was significantly higher in the MAC group as compared to the CAC group. The number of patients with metastatic lymph nodes was documented, and metastatic lymph nodes were found in 58% of MAC and 41.2% of CAC patients ($p = 0.03$) (Table 1).

There was a significant relationship between tumor stage and histological subtype ($p = 0.02$). According to post hoc analysis, the prevalence of stage I and stage IV was statistically different between the CAC and MAC groups ($p = 0.03$). Stage IV disease was twice as common in patients with MAC and stage I disease was three times as common in patients with CAC. Although there was no difference between the groups in terms of tumor (T) and metastases (M) stage, more advanced lymph node (N) stages were detected in MAC patients ($p = 0.02$) (Table 1).

There was no statistically significant difference between the CAC and MAC groups in terms of disease-related mortality, overall survival, or disease-free survival rates (Table 2). Additionally, comparison of survival curves between two groups showed no significant difference in terms of the 2-year and 5-year mortality rates (both log rank $p = 0.7$, Fig. 1).

Table 3 presents univariate Cox regression models for 2-year and 5-year mortality. Age, tumor localization (rectum-colon), perineural invasion, and tumor stage were found to be statistically significant for 2-year and 5-year mortality in univariate analysis. Tumor subtype did not affect 2-year or 5-year survival. In multivariate analysis (Table 4), age (HR, 95% confidence interval (CI): 1.04, 1.02-1.07), perineural invasion (HR, 95% CI: 1.79, 1.09-2.94), and stage IV disease (HR, 95% CI: 3.85, 1.25-11.83) were found to be associated with 2-year mortality. Age (HR, 95% CI: 1.04, 1.03-1.06) and stage IV disease (HR, 95% CI: 3.69, 1.23-11.08) were found to be statistically significant for 5-year mortality (Table 4).

Survival of patients in the MAC and CAC groups was determined separately according to disease stage and tumor localization as well (Table 5). No statistically significant difference was found between the MAC and CAC group.

Table 1. Comparison of clinical and histopathological data in patients with classical adenocarcinoma and mucinous adenocarcinoma.

	CAC n=415	MAC n=69	Total n=484	p
Age[a]	68.5±12.7	63.4±13.5	67.8±12.9	**0.002**
Gender[b]				0.13
Male	245 (59)	34 (49.3)	279 (57.6)	
Female	170 (41)	35 (50.7)	205 (42.4)	
Tumor localization[b]				**0.03**
Right colon	110 (26.5)	30 (43.5)	140 (28.9)	
Transverse colon	27 (6.5)	4 (5.8)	31 (6.4)	
Left colon	158 (38.1)	17 (24.6)	175 (36.2)	
Rectum	120 (28.9)	18 (26.1)	138 (28.5)	
CA19-9 value[b]				
>37 U/mL	20 (12.2)	11 (26.2)	31 (15.0)	**0.02**
<37 U/mL	144 (87.8)	31 (73.8)	175 (85.0)	
CEA value[b]				
>5ug/L	59 (30.7)	15 (34.1)	74 (31.4)	0.8
<5ug/L	133 (69.3)	29 (65.9)	162 (68.6)	
Tumor size (cm) (mean±SD)[a]	4.93±2.27	5.31±2.18	4.99±2.26	0.12
Tumor stage[b]				**0.03**
Stage I	70 (16.9)	4 (5.8)	74 (15.3)	
Stage II	159 (38.3)	27 (39.1)	186 (38.4)	
Stage III	172 (41.4)	32 (46.4)	204 (42.1)	
Stage IV	14 (3.4)	6 (8.7)	20 (4.1)	
T stage[b]				0.14
T1	23 (5.5)	1 (1.4)	24 (5.0)	
T2	63 (15.2)	18 (26.1)	81 (16.7)	
T3	262 (63.1)	38 (55.1)	300 (62.0)	
T4	67 (16.2)	12 (17.4)	79 (16.3)	
N stage[b]				**0.02**
N0	234 (56.4)	29 (42.1)	263 (54.3)	
N1	103 (24.8)	21 (30.4)	124 (25.6)	
N2	78 (18.8)	19 (27.5)	97 (20.1)	
M stage[b]				0.05
M0	401 (96.6)	63 (91.3)	464 (95.9)	
M1	14 (3.4)	6 (8.7)	20 (4.1)	
Tumor grade[b]				0.07
Grade 1	58 (14.0)	5 (7.3)	63 (13.0)	
Grade 2	334 (80.5)	56 (81.2)	390 (80.6)	
Grade 3	23 (5.5)	8 (11.6)	31 (6.4)	
Perineural invasion[b]				0.27
Positive	123 (29.6)	16 (23.2)	139 (28.7)	
Negative	292 (70.4)	53 (76.8)	345 (71.3)	
Lymphovascular invasion[b]				0.98
Positive	187 (45.1)	31(44.9)	218 (45.0)	
Negative	228 (54.9)	38 (55.1)	266 (55.0)	
Harvested lymph nodes[a]	15.7±9.13	19.9±14.2	16.3±10.1	0.16
Metastatic lymph nodes (mean±SD)[a]	1.84±3.88	3.57±5.92	2.08±4.27	**0.002**
Patients with metastatic lymph nodes[b]	171 (41.2)	40 (58.0)	211 (43.6)	**0.03**
Synchronous tumor[c]	26 (6.3)	4 (5.8)	27 (5.6)	0.57

Notes: [a] – Mann-Whitney U test; [b] – Chi-square test; [c] – Fisher's Exact test;
CEA – carcinoembryonic antigen; CA19-9 – carbohydrate antigen 19-9.

Table 2. Comparison of 2-year and 5-year follow-up outcomes between patients with classical adenocarcinoma and mucinous adenocarcinoma.

	MAC n=69	CAC n=415	p
2-year follow-up outcome[a]			
- Overall survival	58 (84.1%)	356 (85.8%)	0.64
- Early (<30 days) postoperative mortality	2 (2.9%)	11 (2.7%)	>0.99
- Mortality not related to disease	0 (0%)	2 (0.5%)	>0.99
- Disease-related mortality	9 (13.0%)	46 (11.1%)	0.65
- Disease-free survival	54 (80.6%)	318 (79.1%)	0.91
5-year follow-up outcome[a]			
- Overall survival	50 (72.5%)	288 (69.4%)	0.84
- Early (<30 days) postoperative mortality	2 (2.9%)	11 (2.7%)	>0.99
- Mortality not related to disease	1 (1.5%)	18 (4.3%)	0.44
- Disease-related mortality	16 (23.2%)	98 (23.6%)	0.94
- Disease-free survival	48 (69.6%)	262 (63.1%)	0.37

Note: [a] – Pearson chi-square test.

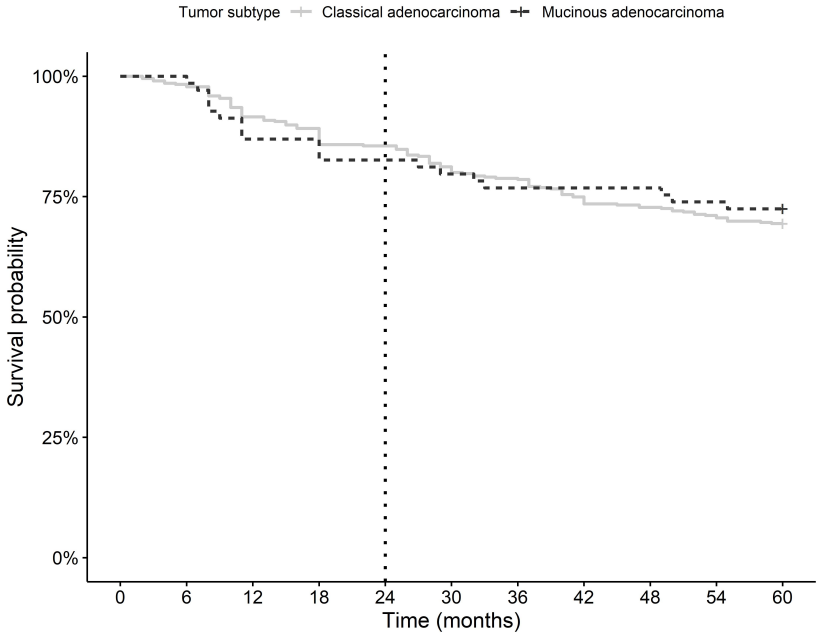

Figure 1. Kaplan-Meier survival curve for 2-year and 5-year survival data of patients with classical adenocarcinoma and mucinous adenocarcinoma.

Table 3. Univariate Cox regression models for 2-year and 5-year mortality.

	2-year mortality				5-year mortality			
	No, n=414	Yes, n=70	p	HR (95% CI)	No, n=338	Yes, n=146	p	HR (95% CI)
Age	66.8±13.0	73.6±11.2	**<0.001**	1.04 (1.02-1.07)	65.5 (13.1)	72.9 (11.2)	**<0.001**	1.04 (1.03-1.06)
Gender			0.89				0.99	
Male	239 (85.7)	40 (14.3)		Ref.	194 (69.5)	85 (30.5)		Ref.
Female	175 (85.4)	30 (14.6)		1.03 (0.64-1.66)	144 (70.2)	61 (29.8)		1.00 (0.72-1.39)
Tumor localization			0.13				0.17	
Right colon	120 (85.7)	20 (14.3)		Ref.	98 (70.0)	42 (30.0)		Ref.
Transverse colon	24 (77.4)	7 (22.6)		1.68 (0.71-3.98)	20 (64.5)	11 (35.5)		1.27 (0.65-2.47)
Left colon	145 (82.9)	30 (17.1)		1.21 (0.69-2.13)	115 (65.7)	60 (34.3)		1.17 (0.79-1.74)
Rectum	125 (90.6)	13 (9.42)		0.63 (0.32-1.28)	105 (76.1)	33 (23.9)		0.74 (0.47-1.17)
Tumor localization			**0.04**				**0.04**	
Rectum	125 (90.6)	13 (9.42)		Ref.	105 (76.1)	33 (23.9)		Ref.
Colon	289 (83.5)	57 (16.5)		1.84 (1.00-3.35)	233 (67.3)	113 (32.7)		1.49 (1.01-2.20)
Tumor grade			0.72				0.10	
Grade 1	56 (88.9)	7 (11.1)		Ref.	51 (81.0)	12 (19.0)		Ref.
Grade 2	332 (85.1)	58 (14.9)		1.36 (0.62-2.98)	268 (68.7)	122 (31.3)		1.75 (0.97-3.17)
Grade 3	26 (83.9)	5 (16.1)		1.46 (0.46-4.61)	19 (61.3)	12 (38.7)		2.24 (1.00-4.98)
Tumor size (cm)	4.91±2.14	5.45±2.82	0.06	1.09 (1.00-1.19)	4.89 (2.10)	5.21 (2.58)	0.11	1.06 (0.99-1.13)
Harvested lymph nodes	16.3±10.2	16.6±9.54	0.85	1.00 (0.98-1.03)	16.9 (10.2)	15.1 (9.83)	0.12	0.99 (0.97-1.00)
Total number of metastatic lymph nodes	1.97±3.99	2.79±5.63	0.16	1.03 (0.99-1.07)	1.68 (3.55)	3.02 (5.48)	**0.001**	1.05 (1.02-1.08)
Lymph node metastasis			0.74				**0.03**	
No	235 (86.1)	38 (13.9)		Ref.	202 (74.0)	71 (26.0)		Ref.
Yes	179 (84.8)	32 (15.2)		1.08 (0.68-1.74)	136 (64.5)	75 (35.5)		1.42 (1.03-1.97)
Lymphovascular invasion			0.16				**0.008**	
Negative	233 (87.6)	33 (12.4)		Ref.	199 (74.8)	67 (25.2)		Ref.
Positive	181 (83.0)	37 (17.0)		1.40 (0.88-2.24)	139 (63.8)	79 (36.2)		1.55 (1.12-2.15)
Perineural invasion			**0.002**				**0.001**	
Negative	306 (88.7)	39 (11.3)		Ref.	255 (73.9)	90 (26.1)		Ref.
Positive	108 (77.7)	31 (22.3)		2.08 (1.29-3.33)	83 (59.7)	56 (40.3)		1.74 (1.24-2.43)
Tumor stage			**0.003**				**0.002**	
Stage I	68 (91.9)	6 (8.11)		Ref.	60 (81.1)	14 (18.9)		Ref.
Stage II	159 (85.5)	27 (14.5)		1.84 (0.76-4.47)	135 (72.6)	51 (27.4)		1.54 (0.85-2.77)
Stage III	175 (85.8)	29 (14.2)		1.79 (0.74-4.31)	134 (65.7)	70 (34.3)		1.97 (1.11-3.50)
Stage IV	12 (60.0)	8 (40.0)		5.76 (2.00-16.6)	9 (45.0)	11 (55.0)		4.19 (1.90-9.25)
Tumor subtype			0.731				0.692	
CAC	356 (85.8)	59 (14.2)		Ref.	288 (69.4)	127 (30.6)		Ref.
MAC	58 (84.1)	11 (15.9)		1.12 (0.59-2.13)	50 (72.5)	19 (27.5)		0.91 (0.56-1.47)

Note: HR – hazard ratio; Ref. – reference.

Table 4. Univariate and multivariate Cox regression models for 2-year and 5-year mortality.

	2-year mortality		5-year mortality	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age	1.04 (1.02-1.07)	1.04 (1.02-1.07)	1.04 (1.03-1.06)	1.04 (1.03-1.06)
Tumor localization				
Rectum	Ref.	Ref.	Ref.	Ref.
Colon	1.84 (1.00-3.35)	1.41 (0.76-2.61)	1.49 (1.01-2.20)	1.21 (0.82-1.81)
Lymph node metastases				
No	Ref.	-	Ref.	Ref.
Yes	1.08 (0.68-1.74)	-	1.42 (1.03-1.97)	0.82 (0.37-1.83)
Lymphovascular invasion				
No	Ref.	-	Ref.	Ref.
Yes	1.40 (0.88-2.24)	-	1.55 (1.12-2.15)	1.22 (0.84-1.76)
Perineural invasion				
No	Ref.	Ref.	Ref.	Ref.
Yes	2.08 (1.29-3.33)	1.79 (1.09-2.94)	1.74 (1.24-2.43)	1.41 (0.98-2.04)
Tumor stage				
Stage I	Ref.	Ref.	Ref.	Ref.
Stage II	1.84 (0.76-4.47)	1.32 (0.53-3.26)	1.54 (0.85-2.77)	1.12 (0.61-2.08)
Stage III	1.79 (0.74-4.31)	1.31 (0.53-3.27)	1.97 (1.11-3.50)	1.76 (0.66-4.68)
Stage IV	5.76 (2.00-16.6)	3.85 (1.25-11.83)	4.19 (1.90-9.25)	3.69 (1.23-11.08)

Notes: HR – hazard ratio; Ref. – Reference.
The multivariate model for 2-year mortality included age, tumor localization, perineural invasion, and tumor stage. The multivariate model for 5-year mortality included age, tumor localization, lymph node metastases, lymphovascular invasion, perineural invasion, and tumor stage.

Table 5. Univariate Cox regression models for patients with classical adenocarcinoma and mucinous adenocarcinoma stratified by tumor stage and tumor localization.

	2-year mortality				5-year mortality			
	No, n=414	Yes, n=70	p	HR (95% CI)	No, n=338	Yes, n=146	p	HR (95% CI)
Tumor stage								
Stage I (n=74)			>0.99				0.16	
CAC, n (%)	64 (91.4)	6 (8.6)		Ref	58 (82.9)	12 (17.1)		Ref
MAC, n (%)	4 (100)	0 (0)		-*	2 (50.0)	2 (50.0)		2.84 (0.64-12.72)
Stage II (n=186)			>0.99				0.67	
CAC, n (%)	136 (85.5)	23 (14.5)		Ref	114 (71.7)	45 (28.3)		Ref
MAC, n (%)	23 (85.2)	4 (14.8)		1.07 (0.37-3.09)	21 (77.8)	6 (22.2)		0.82 (0.35-1.93)
Stage III (n=204)			>0.99				0.31	
CAC, n (%)	147 (85.5)	25 (14.5)		Ref	110 (64)	62 (36)		Ref
MAC, n (%)	28 (87.5)	4 (12.5)		0.82 (0.29-2.37)	24 (75)	8 (25)		0.65 (0.31-1.35)
Stage IV (n=20)			0.64				>0.99	
CAC, n (%)	9 (64.3)	5 (35.7)		Ref	6 (42.9)	8 (57.1)		Ref
MAC, n (%)	3 (50.0)	3 (50.0)		1.37 (0.33-5.76)	3 (50.0)	3 (50.0)		0.89 (0.24-3.36)
Tumor localization								
Colon Tumors (n=346)			0.65				0.71	
CAC, n (%)	248 (84.1)	47 (15.9)		Ref	197 (66.8)	98 (33.2)		Ref
MAC, n (%)	41 (80.4)	10 (19.6)		1.24 (0.62-2.44)	36 (70.6)	15 (29.4)		0.92 (0.53-1.58)
Rectum Tumors (n=138)			>0.99				>0.99	
CAC, n (%)	108 (90.0)	12 (10.0)		Ref	91 (75.8)	29 (24.2)		Ref
MAC, n (%)	17 (94.4)	1 (5.56)		0.55 (0.07-4.21)	14 (77.8)	4 (22.2)		0.55 (0.07-4.21)

Note: * – Model did not converge, so hazard ratio could not be calculated.

Discussion

MACs constitute approximately 10-15% of CRCs. MACs are thought to have poorer prognosis than non-mucinous tumors and are more common in the proximal colon [1]. In addition, they are associated with a higher rate of metastases in peritoneal and lymph nodes, more frequent local recurrence, larger tumor diameters, and more advanced stage at diagnosis [9, 10]. MACs were reported to show different genetic profiles and higher rates of microsatellite instability, and a poor response to chemotherapy treatment in comparison to CACs [6]. The MAC rate was 14.3% in the assessed cohort, which was similar to other studies reporting results ranging from 3.9% to 19% [1, 5]. In our cohort, younger age, greater number of metastatic lymph nodes, and higher proportion of stage IV tumors were observed in MAC patients.

According to Yu F *et al.*, MACs are more common in females [3]. Ott C *et al.* observed a significant difference in gender specificity, with women having an increased tendency to develop mucinous CRC [10]. There was no difference between the groups in terms of gender in our cohort. We identified that MAC patients were diagnosed at a significantly younger age and had more tumors localized in the right colon as compared to CAC patients, which is consistent with the literature [9, 10].

There is disagreement in the literature regarding the effects of MAC on overall and disease-free survival in CRC patients. Some studies have identified an inverse relationship between MAC and overall survival [11]. Kim *et al.* observed the 3-year disease-free survival rate of 56.9% and 79.2% in stage III CRC patients with MAC and CAC, respectively. These findings revealed a poorer prognosis in MAC patients as compared to CAC patients [12]. This relationship could not be fully confirmed in other studies [13, 14]. Kang *et al.* demonstrated that MACs had worse overall five-year survival than CACs (58.1% vs. 62.9%), but there was no statistical difference between stage-specific survivals for all stages [13]. In our cohort, the two- and five-year follow-ups showed no significant difference between CAC and MAC patients in terms of overall survival and disease-free survival. There was no statistical difference in stage-specific survivals between MAC and CAC in our cohort. It has been stated that the change in gene expression leading to the increase in extracellular mucin increases the migration of neoplastic cells from the extracellular matrix to the lymphatics, and that barrier function may then be protected against cellular migration and inhibits the systemic circulation [15]. The relationship between MACs and local-systemic recurrence has not been reported in most studies [2, 5]. When all covariates are included in a multivariate model, the relationship between overall survival and MAC remains uncertain [16]. Inconsistent results may be due to inadequately powered studies or from not applying a multivariate analysis when studying the results. The uncertainty may arise from combining both colon and rectal cancer patients in the same study. A study of 435 colon cancer patients by Hogan *et al.* included 77 individuals with MACs, and it was observed that patients with MACs had higher overall survival rates than those with non-mucinous adenocarcinomas [17]. In another study by Park *et al.*, a subgroup analysis of colon cancer patients was performed on 6,475 CRC patients. The presence of MAC was found at more advanced stages and indicated a worse prognosis for colon cancer [7]. We performed subgroup analysis for rectal and colon tumors and significant survival difference was not detected between both MAC and CAC groups. Consistent with our study, Hu X *et al.* [18] revealed that MAC patients presented with advanced tumor categories, worse grade of differentiation, and larger tumor size than CAC patients; nevertheless, there was no significant difference in overall survival between groups.

Although the number of patients with lymph node metastases was statistically significantly higher in the MAC group, we did not detect a statistically significant difference in 2-year and 5-year survival between MAC and CAC patients. Subgroup analysis was performed for each stage of the disease. MAC patients had slightly better survival in stage II (77.8% vs. 71.7%) and stage III (75% vs. 64%), which provided a relatively sufficient number of patients for statistical analysis, but no statistically significant difference was obtained between MAC and CAC groups for each stage of disease in our cohort. As in similar studies in the literature, no difference in survival was found between MAC and CAC patients in this study. Huang L *et al.* [1] revealed that the MAC group had more T2 patients in stage I CRC at presentation, but the presence of a mucinous component did not affect recurrence and prognosis, as in our cohort. Although lymph node metastasis rates were high in the MAC group, the lack of statistical difference between groups in terms of T and M stages may explain the lack of survival difference.

Tumor size and differentiation grade were identified as independent prognostic factors for MAC patients in previous studies [19]. The presence of perineural invasion, patient's age, tumor localization (rectum-colon), and advanced tumor stage were found to be statistically significant for 2-year and 5-year mortality in univariate analysis of our cohort. In multivariate analysis, the presence of perineural invasion, patient's age, and stage IV disease were found to be associated with 2-year mortality. Age and stage IV disease were found to be statistically significant for 5-year mortality. Consistent with our study, Enblad *et al.* found perineural invasion, lymph node metastasis, and tumor deposits to be associated with recurrence in their study as well [20].

In clinical practice, tumor markers such as CEA and CA19-9 are frequently used for the detection of recurrence or metastasis in the follow-up process [21]. Generally, higher CEA levels indicate recurrence; therefore, this parameter is widely considered as a marker for postoperative surveillance in CRC patients. Additionally, serum CEA, CA24-2, and CA19-9 were found to be valuable indicators for predicting the risk of colorectal cancer; although the specificity of CA19-9, CEA, and CA72-4 in detecting CRC was more than 92% [22]. Gao Y *et al.* [23] demonstrated that patients who had positive preoperative serum CEA or CA19-9 were more likely to have lymph node invasion. In addition, positive CA19-9, CA72-4, or CA125

were associated with poorly differentiated tumor, and positively correlated with pathological tumor-node-metastasis stages. In our cohort, the elevated serum CA19-9 levels were more common in MAC patients as compared to CAC patients (26% versus 12%) but most individuals with elevated CA19-9 had neither MAC nor CAC. There was no significant difference between groups according to CEA levels. Although the number of studies on this subject is limited, in a study by Catalano V *et al.*, no significant difference was found in pre-operative CEA and CA19-9 levels between MAC and non-mucinous CRC patients [6]. In another study, preoperative CEA levels in MAC were significantly higher than in non-mucinous CRCs [7]. In a study by Cheng *et al.*, a mucinous component and preoperative CA19-9 elevation were observed in CRC patients with BRAF-V600E mutation [24]. Although its usefulness in predicting prognosis remains controversial [25], higher preoperative CA19-9 levels might have been observed due to more frequent lymph node metastases of MAC and MAC diagnosis at a more advanced stage.

Limitations

The limitations of this study include the small number of patients in the subgroups of the cohort, the retrospective nature of the study, and the fact that it included single-center patients.

Conclusions

Assessing colorectal cancer cohort revealed that MAC occurred more commonly at a younger age than CAC and was more commonly located in the proximal colon. CA19-9 levels were found to be more sensitive for MAC patients. There was no survival difference between MAC and CAC patients, though lymph node metastasis occurred more frequently in patients with MAC. Although the presence of the mucinous component did not affect survival in CRC patients, multivariate analysis showed that the presence of perineural invasion, patient's age, and disease stage were associated with mortality.

Ethical Statement & Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Scientific Ethics Committee of the Istanbul Medeniyet University School of Medicine and informed consent was obtained from the study participants prospectively at the admission stage.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

All authors declare that no conflict of interest exists, and that they have no direct or indirect commercial financial incentive associated with publishing this article.

Financial Disclosure

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