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ORIGINAL ARTICLE

Clinicopathologic features and prognosis of histologic subtypes in the right-sided colon cancer

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Summary

Purpose: *Differentiation of the histopathologic subtypes can be clinically important as it can affect the course of treatment and the prognosis. The aim of this study was to investigate both the clinicopathological features and prognosis of histologic subtypes in right-sided colon cancer.*

Methods: *This study included 138 patients who underwent surgery for right-sided colon cancer. The patients were divided into three groups according to histopathological subtypes as follows: medullary carcinoma (MC, n=11), mucinous adenocarcinoma (MAC, n=29), and classic adenocarcinoma (AC, n=98). The groups were compared in terms of demographic characteristics, type of surgery, pathological outcomes and survival.*

Results: *The rate of laparoscopic surgery was significantly lower in the MC group compared with MAC and AC groups (45.4% vs 54.5% vs 35.7%, respectively, p=0.001). In MC group, T4 stage was significantly higher than in other groups (90.0% vs 34.5% vs 35.7%, respectively, p=0.001). While patients with MAC had no distant metastasis, 18.2% and 15.3% of patients with MC and AC respectively, had distant metastasis (p=0.07). MAC vs MC, p=0.01, MAC vs AC, p=0.03). Tumor size, tumor volume, and the rate of microsatellite instability were found significantly higher in the MC group (p<0.05). The 5-year overall (OS) and disease-free survival (DFS) were better in the MAC group compared with MC and AC groups, but these differences did not reach statistical significance (OS: 92.8% vs 72.7% and 68.7%, p=0.16 and DFS 87.3% vs 58.2% and 64%, p=0.10, respectively).*

Conclusion: *MC is associated with more advanced tumor size and T stages, and therefore entails reduced rate of minimally invasive procedures. In our series, the absence of distant metastasis in the patients of MAC also had a positive effect on survival.*

Key words: *histologic subtype, medullary carcinoma, mucinous adenocarcinoma, right colon cancer*

Introduction

Colorectal cancer (CRC) has become a major health problem globally since it is the third most common cancer in males and second most common in females. In 2015, the number of CRC cases was 1.65 million and this disease was responsible for 835.000 deaths [1,2]. The tumor location, histopathologic characteristics, and the TNM staging of the tumor are important prognostic factors to consider in CRC. In 1990, Bufill et al firstly described different characteristics of CRC according to the exact anatomical location of the tumor [3]. Some studies have shown that right-sided colon cancer differs from left-sided colon and rectal cancers in terms of embryological development, anatomical, microscopic, genetic, and immunological characteristics [3-5].

According to World Health Organization, CRCs are classified based on their histological characteristics as classical adenocarcinoma (AC), mucinous adenocarcinoma (MAC), medullary carcinoma

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(MC), signet-ring cell carcinoma, squamous cell carcinoma, small cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinoma [6].

In order for a tumor to be considered as MAC, its histological characteristics should include mucinous pattern greater than 50% [6,7]. MC is quite a rare type of CRC; it has mostly solid growth pattern and does not show any glandular differentiation [8]. In general, MAC constitutes 5-15% and MC is approximately 1% of all CRC [9,10]. Because of their rarity, it is difficult to assess the clinical effects of these subtypes on patients. However, there are some differences between subtypes such as age, gender, tumor location, prognosis, and molecular pattern [11-14]. Although MAC has been shown to be a poor prognostic factor in some studies [11,12,15], others have shown no efficacy on prognosis [16-18].

The aim of this study was to investigate both the clinicopathological features and prognosis of histologic subtypes in right colon cancer.

Methods

Patients and study design

One hundred thirty-eight patients who underwent surgery for right-sided colon cancer in the General Surgery Department of the American Hospital between January 2011 and August 2017, were included in this study. The data of the patients was registered prospectively and the results were evaluated retrospectively. In accordance with embryological plans, standard colon surgery was performed with dissection and selective central ligation by the same surgeon who was experienced in colorectal surgery.

The patients were divided into three groups according to their histopathological subtypes of tumor: medullary carcinoma (MC, n=11), mucinous adenocarcinoma (MAC, n=29), and classic adenocarcinoma (AC, n=98). Other pathological diagnoses mentioned above were excluded. Patients with concomitant malignancy, patients undergoing cytoreductive surgery, palliative operations, or patients with inflammatory bowel disease were excluded.

The groups were compared in terms of demographic characteristics, type of surgical procedure, pathological outcomes, overall survival (OS) and disease-free survival (DFS). Demographic characteristics included gender, age, body mass index (BMI), and tumor location. The histopathologic results, including lymphatic invasion, vascular invasion, perineural invasion, number of harvested lymph nodes, tumor size, tumor volume, and pathological TNM stage were recorded. The patients were followed up at 3-month intervals for 2 years, at 6-month intervals for the next 3 years, and then annually. Recurrence was determined by clinical and radiologic examination or histopathological confirmation. The main pattern of recurrence was recorded as the first site of detectable failure during the follow-up period.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Pathological evaluation

Pathological diagnosis was based on the findings of the resected specimens and evaluations were performed by the same experienced gastrointestinal pathology team. Pathological TNM stage was recorded according to the 7th edition of the American Joint Committee on Cancer's staging manual [19].

MAC was defined as a tumor containing more than half mucin by volume on histologic examination with pools of extracellular mucin containing malignant epithelium as acinar structure, strips of cells, or single cells [20]. MC was defined by large cells that proliferate in large trabeculae or layers that have definite nucleoli, eosinophilic cytoplasm and vesicular nuclei [8].

Statistics

Descriptive and comparative statistics were performed using SPSS 24.0 software package (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were defined as the mean standard deviation unless otherwise stated. Categorical variables were described as n (%). The associations between different groups of histological subtype and baseline characteristics were determined using the chi-square test for qualitative variables and Student t-test for quantitative ones. Kaplan-Meier survival analysis was performed for OS and DFS and log-rank test was utilized to compare survival differences between two groups. A p value <0.05 was regarded significant. When significant results were obtained, comparisons were done between the two groups or *post-hoc* analyses were performed.

Results

The rate of female patients was higher in the MC group than in MAC and AC groups (90.9% vs 58.6% and 43.9%, p=0.008, MC vs MAC, p=0.03, MC vs AC, p=0.003)). There were no statistically significant differences between the three groups in terms of the age, BMI, and tumor location, while the rate of laparoscopic surgery was 89.7% and 78.6% in the MAC and AC groups respectively. This rate decreased to 45.4% in the MC group (p=0.01, MC vs MAC, p=0.03, MC vs AC, p=0.01) (Table 1).

In the MC group, 90.9% of the patients had T4 stage, and this rate was significantly higher than in the other groups (p=0.001, MC vs MAC, p=0.001, MC vs AC, p=0.001). While patients with MAC had no distant metastasis, 18.2% and 15.3% of patients with MC and AC respectively, had distant metastasis in our series (p=0.07, MAC vs MC, p=0.01, MAC vs AC, p=0.03). Both the tumor size and tumor volume were significantly higher in the MC

group than in the others (p=0.001 and p=0.03, respectively). There were no statistically significant differences between the three groups in terms of other prognostic factors except vascular invasion which was less frequently seen in both MC and MAC groups. The rate of high level of microsatellite instability (MSI-H) was significantly higher in the MC group (p=0.001, MC vs MAC, p=0.03, MC vs AC, p<0.01). (Table 2).

The 5-year OS and DFS were better in the MAC group compared with MC and AC groups, but these differences did not reach statistical significance (OS; 92.8% vs 72.7% and 68.7%, p=0.16 and DFS; 87.3% vs 58.2 and 64%, p=0.10, respectively (Figures 1 and 2).

Table 1. Comparison of the demographic, clinical, and surgical characteristics of patients with medullary carcinoma, mucinous adenocarcinoma, and adenocarcinoma

Characteristics	*MC*	*MAC*	*AC*	*p value*
Number of patients, n (%)	11 (8)	29 (21)	98 (71)	
Gender, n (%)			43 (43.9)	0.008
Female	10 (90.9)	17 (58.6)		
Male	1 (9.1)	12 (41.4)	55 (56.1)	
Age (years), mean ± SD	61 ± 18	63 ± 12	65 ± 12	0.51
BMI (kg/m^2), mean ± SD	28,1 ± 7.6	28.8 ± 6.2	27.5 ± 4.9	0.62
Operative procedure, n (%)				0.03
Open	5 (45.4)	3 (10.3)	17 (17.3)	
Laparoscopic	5 (45.4)	26 (89.7)	77 (78.6)	0.01
Conversion	1 (9.2)	0	4 (4.1)	
Operative time, min, mean ± SD	107 ± 29	132 ± 29	144 ± 60	0.10
Length of hospital stay, days, mean ± SD	9 ± 3	8 ± 4	7 ± 3	0.11
Tumor location, n (%)				0.26
Cecum, ascending colon	7 (63.6)	22 (75.9)	71 (72.4)	
Hepatic flexure	3 (27.3)	7 (24.1)	15 (15.3)	
Transverse colon	1 (9.1)	0	12 (12.3)	

BMI: body mass index; min: minutes; SD: standard deviation; MC: medullary carcinoma; MAC: mucinous adenocarcinoma; AC: adenocarcinoma

Table 2. Comparison of the pathological outcomes of patients with medullary carcinoma, mucinous adenocarcinoma, and adenocarcinoma

Variables	*MC*	*MAC*	*AC*	*p value*
T stage, n (%)				0.01
T1	1 (9.1)	2 (6.9)	11 (11.2)	
T2	0	1 (3.4)	9 (9.2)	
T3	0	16 (55.2)	43 (43.9)	
T4	10 (90.9)	10 (34.5)	35 (35.7)	0.001
Lymph node positivity, n (%)	6 (54.5)	15 (51.7)	44 (44.9)	0.71
Distant metastasis, n (%)	2 (18.2)	0	15 (15.3)	0.07
pTNM stage, n (%)				0.34
I	1 (9.1)	2 (6.9)	15 (15.3)	
II	3 (27.3)	12 (41.4)	36 (36.7)	
III	5 (45.5)	15 (51.7)	32 (32.7)	
IV	2 (18.2)	0	15 (15.3)	
Lymphatic invasion, n (%)	8 (72.7)	19 (65.5)	64 (65.3)	0.88
Vascular invasion, n (%)	2 (18.2)	3 (10.3)	37 (37.8)	0.01
Perineural invasion, n (%)	5 (45.5)	7 (24.1)	31 (31.6)	0.42
Tumor volume, cm^3, mean ± SD	133 ± 130	106 ± 220	50 ± 77	0.03
Tumor size, mm, mean ± SD	69 ± 30	53 ± 28	42 ± 20	0.001
Microsatellite instability rate, %	90.9	44.8	27.5	0.001

SD: standard deviation; M: medullary carcinoma; MAC: mucinous adenocarcinoma; AC: adenocarcinoma

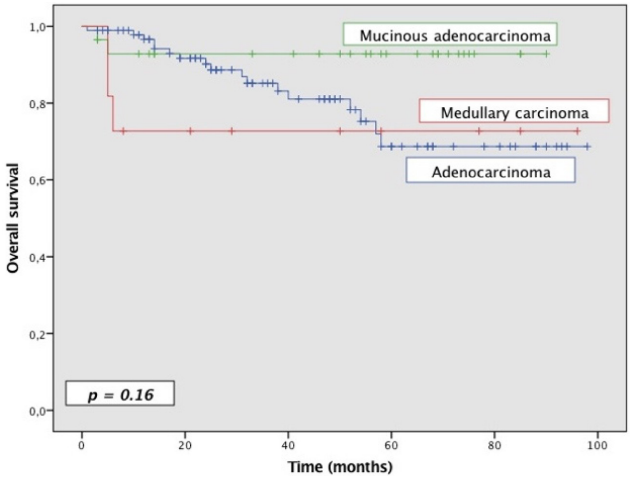


Figure 1. Kaplan-Meier survival curves for overall survival categorized according to histopathological subtypes in right colon cancer.

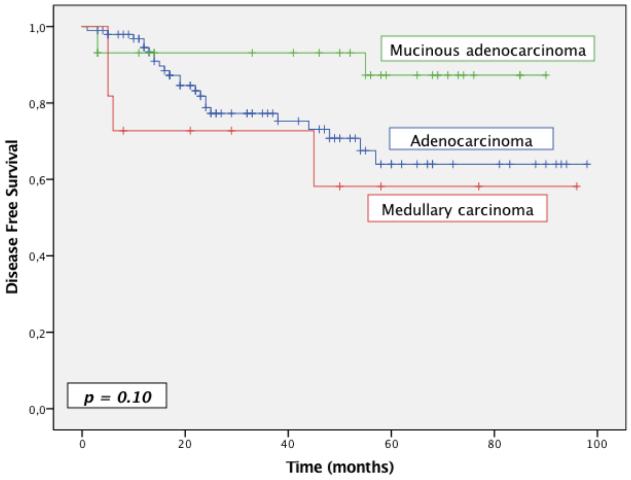


Figure 2. Kaplan-Meier survival curves for disease-free survival categorized according to histopathological subtypes in right colon cancer.

Discussion

Right and left colon have different embriyological origins and physiological features. Therefore, many studies have shown differences between right-sided colon cancer and left-sided colon cancer in terms of epidemiology, pathogenesis, embryological development, genetics, and molecular characteristics and oncologic results [3,5,21]. Some studies have shown right-sided colon cancer is mostly diploid, and contains MSI-H, CpG island methylation, and BRAF mutation. On the contrary, left-sided colon cancer is more likely to be aneuploid and mostly shows chromosomal instability [3,5,21-23]. Some other studies have shown that patients with right-sided colon cancer were most likely to be older, more often to be females diagnosed as to be females, at advance stage with a higher tumor size and to show different molecule characteristics [4,21,26,27].

Many studies have revealed that different types of CRC play a role in tumor biology and prognosis [26,27]. In general, 5-15 % are MAC, and about 1 % are MC of all CRC [9,10]. In the SEER database, 9.3% of CRC patients were diagnosed with MAC [28]. Knox et al have studied 102 MC patients and found the incidence of MC to be 2.8% [13]. In our all colorectal series, we found 3.1% in MC and 9.8 % in MAC, but when we investigated only right colon cancer cases, these rates were found to be 8% and 21%, respectively. The rarity of these subtypes makes it difficult to assess the effect on patients, but there are some differences between subtypes in terms of age, gender, tumor location, molecular pattern and prognosis [11-14].

MC is a CRC subtype that is most commonly seen in older females and is mostly localized in the right colon, but left colon and rectal localization are rare [13,14,29,30]. Some studies have shown that MC cases are most likely to be in T3 or T4 stages [13,14]. In our study, the number of female patients and T4 stage rates were higher in the MC group than in others.

The prognostic value of the histologic subtypes of CRC is still not clear. Some authors have indeed shown a worse survival in mucinous cancers [11,12,15,33,34] while others did not find any adverse prognostic effect [16-18,35,36]. In some studies which included mainly rectal carcinoma, MAC was considered to be an independent worse prognostic factor for survival [30,37]. In a large study of Hugen et al with MAC patients (n=3052), poor prognosis was only reported in rectal cancer cases [38]. Recently published studies concluded that mucinous tumors have poorer response to adjuvant chemotherapy [39,40] and chemoradiotherapy [41]. In our study, there was no distant metastasis in the MAC group and the 5-year OS and DFS rates were higher than the others, but without statistical significance.

It is indicated that MC has a better prognosis compared with the other poorly differentiated cancers [14,31,32]. Knox et al have made a large-scale survival analysis and indicated that the 5-year overall survival rate was 67.5% in MC group [13]. Pyo et al also suggested that the overall survival rate in the MC group was significantly better than the poorly differentiated CRCs, but there was no statistically significant difference compared to the CRCs in general [32]. In our series, the 5-year OS rate of MC was 72.7%.

Microsatellite instability (MSI) has a positive effect on the prognosis of CRC; however, the prognosis can vary for different tumor types [42-44].

In some studies investigating the effect of MSI in poorly differentiated CRCs, it was found that MSI-H CRCs had better survival rates but this finding was not statistically significant [45,46]. Several authors have described two different subsgroups of MAC based on their microsatellite phenotype [47,48]. It was found that the MSI type of MAC was more likely to be located in the proximal colon, had better survival rates, and was associated with less advanced stage [47]. In our study, the rate of MSI-H was significantly higher in the MC group.

There are several limitations in our study. Although the data was collected prospectively, the retrospective design of this study is the main limitation because of possible biases. Although our present study is limited by the small number of patients with MC and MAC, it is difficult to collect large numbers at a single institution because of the low overall incidence of these subtypes. Furthermore, this study did not include information regarding specific genetic mutations and molecular profiling that may influence outcomes.

In conclusion, medullary carcinoma is diagnosed at larger sizes and more advanced stages and therefore entails reduced rate of minimally invasive procedures. In our series, the absence of distant metastasis in mucinous adenocancarcinoma patients also had a positive effect on OS. We think that clinical manifestation of pathological differences and their impact on prognosis should be assessed in large-scale studies.

Authors' contributions

Study concept and design: Zenger; Acquisition of data: Zenger, Gurbuz, Can; Analysis and interpretation: Zenger; Drafting the manuscript: Zenger, Gurbuz; Critical review of the manuscript: Balik, Bugra; Statistical analysis: Zenger, Can; Administrative, technical, and material support: Zenger; Study supervision: Balik, Bugra. All authors have read and approved the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

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