



Comparison of Rarely Observed Tumors of the Colorectal Region Clinicopathologically

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Abstract

Background: A majority of colorectal neoplasms are adenocarcinomas; however, there is a small percentage of tumors from other histological cell lines.

Objectives: This study aimed to examine the rare colon and rectum tumors to determine the clinicopathological features of rarely observed histological types and present them to the literature in a comparative way.

Methods: A total of 1100 patients were applied for surgical treatment due to colorectal cancer at a general surgical clinic between 2010 and 2020. The selected patients were divided into four groups of Diffuse large B-cell lymphoma (DLBCL), Malignant melanoma (MM), Medullary carcinoma (MC), and Neuroendocrine tumor (NET). Following that, clinicopathological data of patients and their survival periods have been compared in this study.

Results: A total of 20 patients were included in this study and were divided into the DLBCL (n=5), MM (n=4), MC (n=3), and NET (n=8) groups. The emergency application rate (60%) was the highest in the DLBCL group (P=0.004). The mean age of the patients was above 50 years in all groups, and there was no difference among groups in this regard (P=0.966). The mean tumor diameter values were 8, 6.55, 5.4, and 3.75 cm, respectively (P=0.73) in the groups. Furthermore, the numbers of lymph nodes dissected were 13, 14.5, 19, and 19, respectively (P=0.373), and the numbers of metastatic lymph nodes were determined at 0, 1.5, 0, and 0.5, respectively (P=0.188). The survival rate was significantly the shortest in the MM group, and the longest survival rate was noted in the NET group (15.625, 8.5, 20, 40.857, respectively; P=0.001).

Conclusion: Although clinicopathological features and postoperative follow-up results were similar, there were differences in the survival rates among patients. Malignant melanoma histopathological type had a worse prognosis than the other tumors.

Keywords: Colon, Histopathology, Malignant lesions, Rare subtype, Rectum

1. Background

Colorectal cancer (CRC) is an important public health problem. The anatomical region of the gastrointestinal tract with the most malignancy is the colorectal region. CRC is the third most common cancer diagnosed in both men and women (after prostate cancer in men, as well as breast cancer and lung cancer in women). Approximately, 41% of all CRC occur in the proximal colon; in addition, about 22% and 28% of this malignancy involve the distal colon and rectum, respectively (1,2).

According to the World Health Organization (WHO), although adenocarcinomas make up 95%-97% of all malignant tumors, the remaining 3%-5% belong to rare colon and rectal tumors. It is difficult to determine the incidence of each of these rare tumor. According to the data from the National Cancer Institute Surveillance Epidemiology and Recent Results (2005-2009), CRC cases without lymphomas (n=183,000) included adenocarcinomas (94.3%), other carcinomas (1.7%), carcinoid tumors (3.3%), squamous cell carcinomas (0.5%), sarcomas (0.1%), and other types (0.1%) (3).

The obtained data from the literature regarding

rarely observed tumors in the colorectal region are limited, and they are mostly concerned with patient series of certain institutions. As these tumors are rarely noticed, there is a limited number of randomized studies or meta-analyses with high scientific evidence in the literature (4-6). Since these histotypes are rarely noticed, they present a diagnostic dilemma for the clinician when encountered in clinical practice (7).

2. Objectives

This study aimed to examine the rare colon and rectum tumors to determine the clinicopathological features of rarely observed histological types and present them to the literature in a comparative way.

3. Methods

This study was initiated after obtaining the required permission from the local Ethics Committee of Erciyes University, Kayseri, Turkey (26.05.2021; 2021-385). A total of 1100 patients underwent surgery due to CRC in the general surgery clinic between 2010 and 2020. The patients who were

under the age of 18, and those who had missing medical records and tumors with adenocarcinoma pathology were left outside the scope of the study. After excluding eight patients (with the diagnosis of adenosquamous carcinoma, anaplastic carcinoma, gastrointestinal stromal tumor, marginal zone lymphoma, and mixed adenoendocrine carcinoma), the remaining 20 patients were included in the study and grouped as Diffuse large B-cell lymphoma (DLBCL), Malignant melanoma (MM), Medullary carcinoma (MC), and Neuroendocrine tumor (NET). The data set was prepared with medical records, followed by phone conversations. Afterward, the obtained data were analyzed retrospectively.

This study compared the patients' demographic characteristics, tumor markers, biochemical parameters, variables of the operation performed, pathological results, postoperative follow-up data, presence of recurrence, survival times, and patients' outcomes. The patients who were applied with mechanical bowel obstruction or perforation were considered emergency cases. Pathological examinations were made based on current guidelines valid on operation date.

3.1. Statistical analysis

The data were analyzed in SPSS software (version 23.0). Categorical and continuous measurements were summarized as numbers and percentages, as well as mean±SD and minimum-maximum, respectively. The compatibility of variables to normal distribution was analyzed using the Shapiro-Wilk test as being one of the analytical methods. In the comparison of categorical variables, the Chi-square test and Fischer's Precision Test were applied, and in the analysis of parameters not showing normal distribution, the Kruskal Wallis test has been used. To determine the source of difference between the groups, the Bonferroni method among Post Hoc tests has been applied. In the survival analysis, Kaplan-Meier analysis

and Log Rank tests have been used. A p-value less than 0.05 was considered statistically significant.

4. Results

In total, 20 patients were included in the study and were assigned into four groups of DLBCL (n=5), MM (n=4), MC (n=3), and NT (n=8). The mean age of the patients was above 50 years in all groups, and there was no difference among the groups in this regard (P=0.966). No difference was also observed among the groups in terms of gender (P=0.187) and the American Society of Anesthesiologists classification (P=0.912). Colonoscopy was the main diagnostic tool in all patients, except for two cases with neuroendocrine tumors. The synchronous lesion was present only in the neuroendocrine tumor. Hemoglobin (P=0.225) and albumin (P=0.720) values examined in the preoperative period were similar; however, tumor marker values were low in the DLBCL group. Table 1 tabulates the clinical and demographic characteristics.

Emergency application rate (60%) was the highest in the DLBCL group (P=0.004), and abdominoperineal resection was more common in patients with malignant melanoma (75%, P=0.007). Postoperative complications were observed in three patients (sepsis in the DLBCL group [n=1], pulmonary embolism in the MC group [n=1], and wound site infection in the NET group [n=1]). Among these patients, the cases that developed sepsis and pulmonary embolism resulted in mortality. In the long-term oncological follow-up of the patients, there was no difference among the groups in terms of recurrence (P=0.149) and outcome (P=0.573). Operative and postoperative data are shown in Table 2.

In the groups, tumor diameter was on average (8, 6.55, 5.4, and 3.75 cm, respectively; P=0.073), and the numbers of lymph nodes dissected were 13, 14.5, 19, and 19, respectively (P=0.373). Moreover, the numbers

Table 1. Demographic characteristics and clinical data

		Diffuse large B-cell lymphoma (n=5)	Malignant melanoma (n=4)	Medullary carcinoma (n=3)	Neuroendocrine tumor (n=8)	P-value
Age		50 (39-81)	62 (44-73)	64 (38-68)	56 (30-72)	0.966*
Gender	Male	4 (80%)	2 (50%)	0 (0%)	4 (50%)	0.187**
	Female	1 (20%)	2 (50%)	3 (100%)	4 (50%)	
ASA classification	2	3 (60%)	2 (50%)	1 (33,3%)	4 (50%)	0.912**
	3	2 (40%)	2 (50%)	2 (66,7%)	4 (50%)	
Diagnosis method	CT scan	0 (0%)	0 (0%)	0 (0%)	2 (25%)	0.343**
	Colonoscopy	5 (100%)	4 (100%)	3 (100%)	6 (75%)	
Synchronous lesion in liver		0 (0%)	0 (0%)	0 (0%)	1 (12,5%)	0.664**
Preoperative Hb		11.4 (8.5-12.7)	12.8 (11.4-13.7)	9.8 (8.9-14.5)	13 (10.2-16.7)	0.225*
Preoperative albumin		3.2 (2.7-4.2)	3.8 (3.3-4.6)	4.1 (2.07-4.6)	3.95 (2.8-5.1)	0.720*
CEA ¹		0.84 (0-1.33)	2.06 (2-2.3)	2.35 (2.29-2.35)	2.6 (2.1-3.84)	0.003*
Ca19.9 ²		6 (0.6-8.43)	12.55 (10-15)	10 (0.9-20.73)	18.5 (7.9-35.5)	0.024*

Data presents as frequency (%) or median (min-max).

* Kruskal Wallis, Chi-square test, ** Fischer's Exact Test

1 CEA was significantly lower in the diffuse large B-cell lymphoma group than others (Bonferroni Post Hoc test).

2 Ca19.9 was significantly lower in the diffuse large B-cell lymphoma group than the neuroendocrine tumor group (Bonferroni Post Hoc test).

ASA: The American Society of Anesthesiologists, CEA: carcinoembryonic antigen

Table 2. Operative and postoperative data

		Diffuse large B cell lymphoma (n=5)	Malignant melanoma (n=4)	Medullary carcinoma (n=3)	Neuroendocrine tumor (n=8)	P-value
Emergency elective	Urgent	3 (60%)	0 (0%)	0 (0%)	0 (0%)	0.014*
	Elective	2 (40%)	4 (100%)	3 (100%)	8 (100%)	
Operation	APR	0 (0%)	3 (75%)	0 (0%)	0 (0%)	0.007*
	LAR	0 (0%)	1 (25%)	0 (0%)	1 (12.5%)	
Right Hemicolectomy		5 (100%)	0 (0%)	3 (100%)	7 (87.5%)	
Postoperation complication		1 (20%)	0 (0%)	1 (33.3%)	1 (12.5%)	0.652*
Rehospitalization		0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	0.664*
Postoperative mortality		1 (20%)	0 (0%)	1 (33.3%)	0 (0%)	0.295*
Postoperation stay (days)¹		8 (2-10)	7.5 (7-9)	11 (9-16)	9.5 (9-14)	0.036**
Recurrence		0 (0%)	1 (25%)	0 (0%)	4 (50%)	0.149*
Outcome	Expire	1 (20%)	0 (0%)	1 (33.3%)	1 (12.5%)	0.573*
	Alive with recurrence	0 (0%)	1 (25%)	0 (0%)	3 (37.5%)	
	Alive with no recurrence	4 (80%)	3 (75%)	2 (66.7%)	4 (50%)	

Data presents as frequency (%) or median (min-max).

¹ Postoperation stay in medullary carcinoma group was significantly higher than malignant melanoma group (Bonferroni Post Hoc test).

* Fischer's Exact Test, ** Kruskal Wallis, Chi-square test

APR: Abdominoperineal resection, LAR: Low Anterior Resection

of metastatic lymph nodes were obtained at 0, 1.5, 0, and 0.5, respectively (P=0.188). In one patient in the DLBCL group, the tumor was perforated, and there was no difference among the groups regarding the lymphatic invasion (P=0.676) and venous invasion (P=0.676).

Pathological results are shown in Table 3. The survival rate was significantly the shortest in the MM group, and the longest survival rate was noticed in the NET group (15.625, 8.5, 20, and 40.857, P=0.001). They are shown in Table 4 and Figure 1.

Table 3. Pathological results

	Diffuse large B-cell lymphoma (n=5)	Malignant melanoma (n=4)	Medullary carcinoma (n=3)	Neuroendocrine tumor (n=8)	P-value
Tumor diameter	8 (3-11)	6.55 (2-15)	5.4 (3-5.5)	3.75 (0.68-7)	0.073*
Number of lymph nodes dissected	13 (4-26)	14.5 (1-25)	19 (19-21)	19 (5-28)	0.373*
Number of malignant lymph nodes	0 (0-0)	1.5 (0-3)	0 (0-2)	0.5 (0-16)	0.188*
Tumor perforation	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0.266**
Lymphatic invasion	0 (0%)	1 (33.3%)	2 (66.7%)	3 (60%)	0.676**
Venous invasion	0 (0%)	1 (33.3%)	2 (66.7%)	3 (60%)	0.676**

Data presents as frequency (%) or median (min-max).

* Kruskal Wallis, Chi-square test, ** Fischer's Exact Test

Table 4. Survival rate

Pathological type	Average(months)				P-value*	1-year survival (%)	3-year survival (%)
	Predicted average	Std. deviation	95% confidence interval				
			Lower limit	Top limit			
Diffuse large B-cell lymphoma (n=5)	15.6	5	5.6	25.6	0.001	50.0	-
Malignant melanoma (n=4)	8.5	3.2	2	14.9		25.0	-
Medullary carcinoma (n=3)	20	2	16	23.9		50.0	-
Neuroendocrine tumor (n=8)	40.8	9.9	21.4	60.3		85.7	28.6

* Kaplan-Meier analysis and Log Rank tests

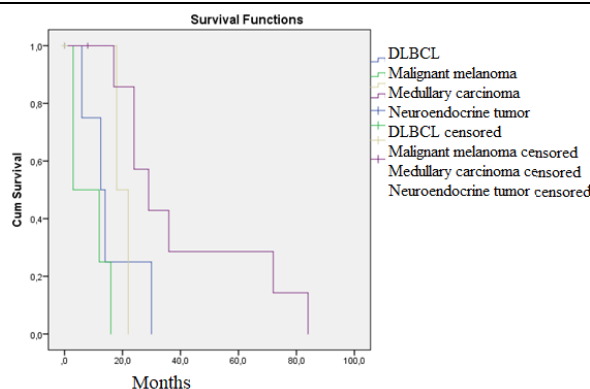


Figure 1. Survival analysis

5. Discussion

It is known that some pathological features have prognostic implications in CRC. The presence of these parameters provides the opportunity to have opinions on the clinical behavior of the disease. Although the histological profiles of colorectal carcinomas generally display adenocarcinoma morphology, the presence of different histopathological features of each tumor is also remarkable (8-10). This study compared rare colorectal tumors, and the results showed that the tumor markers of diffuse large B-cell lymphoma type were low, and emergency admissions were higher in this group; moreover, malignant melanoma was mostly located in the anal canal, and survival situation was worse.

Neuroendocrine tumors (NETs) are well-differentiated neuroendocrine neoplasms consisting of tumor cells expressing neuroendocrine markers that can be located in different locations in the gastrointestinal system. Tumor size determines tumor behavior and the type of treatment required. Resection is recommended in the localized NETs. Curative surgery is recommended in patients with operable liver metastasis as the five-year survival reaches 60% -80%. Adjuvant therapy is not recommended in this regard (5,11,12). In the follow-up of the patients in our series, recurrence developed in half of them, and the most common recurrence site was the liver. In one of our patients, in the beginning, there was a recurrence at the liver. Despite this situation, the mean survival time was 40 months, and the one-year survival rate was estimated at 85%. Wound infection developed in one patient in this group has a prolonged average period of staying at the hospital .

Colon and rectum lymphomas constitute 1.4% of all lymphomas, 10%-20% of gastrointestinal lymphomas, and 0.2%-0.6% of all colon malignant tumors (13,14). The cecum is the most common site for colorectal lymphomas due to the abundance of lymphatic tissue. In the literature, colorectal DLBCL therapy includes chemotherapy, radiation, surgical treatment, or a combination of these approaches (15). In their case series in which they included DLBCL, Haddad I et al. found that the mean age was 68 years. In 18 out of 19 cases, they have stated the place of lymphoma as 44% in the sigmoid, 39% in the cecum, and 17% in the colon.

Among present symptoms, there were abdominal pain, weight loss, diarrhea, constipation, and gastrointestinal bleeding. The most common symptoms were bowel obstruction and abdominal pain that were present in 40% of all 15 cases. In three patients representing nearly 16% of the patient population during the application time, there was perforation (16). In our series, the mean age was estimated at 50 years, which is smaller than that in a

previously conducted study in the literature. In our cases, the applied patients showed findings supporting the literature, and 60% of the patients were operated on under emergency conditions. There was colon perforation in one patient, followed by septic complications and death in the postoperative period. Medullary carcinoma is probably more widespread with respect to what is stated in various studies. According to Knox et al., medullary carcinoma accounts for 2.8% of all resected CRC and 5% of right colon lesions. In addition to being 2 times more common in women, its incidence increases with age, and the mean age at the time of diagnosis is 69.3. This specific type of cancer is generally observed in the right colon (54%) (17,18). In our series, the mean age was 64 years, and all patients were female. The postoperative course of the patients was good, except for pulmonary embolism developed in one postoperative patient. In a way to support the literature, all tumors were located in the right colon.

Melanomas in the digestive system are usually metastatic in origin, and primary melanomas are relatively rare. For primary colon melanomas that have not metastasized to any distant part of the body, wide-edged surgical resection seems to be the treatment being preferred. The prognosis for primary malignant melanoma of the colon appears to be better than other types of primary mucosal melanoma. Until today, there are only 12 reported cases of primary melanoma of the colon. In these patients, the mean age is 60.4 years. Gender distribution was similar, and the right colon (33%) and cecum (33%) were reported as the most common sites of colon melanoma occurrence (19).

However, due to the location of melanocytes, most of these tumors are located in the anorectum. The authors from the MD Anderson Cancer Center, presenting their 20-year experience in the treatment of 54 patients with localized anorectal melanoma, demonstrated that combined surgical wide local excision and adjuvant radiotherapy provided good local disease control with acceptable side effects (20). Five-year survival rates for cutaneous anorectal mucosal melanoma are 20%. Several possible causes of an overall worse prognosis of anorectal melanoma are considered to be delayed diagnosis and earlier spread of the disease as a result of the naturally increased aggression of the tumor biology (21). In their study on 46 patients undergoing surgical resection for anorectal melanoma, Yeh et al. reported a 5-year disease-specific survival rate of 34% with a mean follow-up of 39 months. A total of 34 cases out of 46 patients who relapsed did so in a median 10-month period, and the recurrence rate was 53% at one year (22). Tumors were located in the anorectal region in all patients in our series, and survival was worse than it was stated in the literature .

Totally, 169,073 patients with all histological

subtypes of CRC were evaluated in a large patient population study by Kang H et al. According to the results, malignant carcinoid (n=2,565; 1.5%), malignant lymphoma (n=955; 0.6%), neuroendocrine carcinoma (n=455; 0.3%), squamous cell (n=437; 0.3%), and sarcoma (n=23; <0.1%) were observed in these patients. On the other hand, 164,638 patients (97.4%) had adenocarcinoma .

Furthermore, the results of the aforementioned study showed that malignant carcinoids (91.3%) had a significantly better 5-year survival rate, compared to the other rare tumors (P<0.0002). In other tumors, 5-year survival rates were 53.0% in lymphoma, 21.4% in neuroendocrine carcinoma, 48.9% in squamous cell carcinoma, and 62.1% in adenocarcinoma (7). In this group, the mean survival in malignant melanoma was limited to 8.5 months. Our series is in conformity with the results in the literature, and the best survival rate was determined in relation to neuroendocrine tumors. The mean survival period was estimated at 40 months. In the follow-up, the relapse occurred in one patient. Despite the limitations in this study (retrospective nature and the low number of patients), since these tumors are rarely observed, our study compared clinicopathological characteristics that will contribute to the literature regarding the course of disease and approach to these patients.

6. Conclusion

In our study, demographic characteristics and clinical features of rarely observed colorectal tumors were similar to one another. As is the case in the adenocarcinomas tumors, localization determines the surgery to be made. Postoperative complications could result in mortality similarly. Even though clinicopathological characteristics and postoperative follow-up results are similar, there were differences among patients in terms of survival situation. Malignant melanoma histopathological type had a worse prognosis than other tumors. In a clinical environment, colorectal and anal cancer histotypes rarely come out. As these cancers are observed rarely and as there is no familiarity among the clinicians, generally delay is caused in the diagnosis process. If a rare histotype is found, a multidisciplinary approach will be required to provide the best result to the patient.

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None

Footnotes

Authors' contributions: MA, UT, and MOK conceived the original idea and planned the study. EMS, FD, TT, KD, and HYA supervised the project. MA, UT, and MOK wrote and revised the manuscript. UT and MA

performed the statistical analysis

Ethical Approval: The study protocol was approved by the Ethics Committee of the University of Erciyes, Kayseri, Turkey (26.05.2021; 2021-385).

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