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Clinicopathological Features of Colorectal Neuroendocrine Tumors

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ABSTRACT Objective: As colorectal neuroendocrine tumors (NETs) are very rare, studies on this topic are limited. In this study, we presented the patients who were followed up in our clinic and described their clinicopathological features. **Material and Methods:** We retrospectively evaluated data collected from the patients with colorectal NETs admitted to our hospital from 2005 to 2023. The demographic characteristics of the patients, tumor characteristics, and treatments received were obtained from the files. **Results:** We included 25 patients in this study; 56% of the patients were male, and the median age of the patients was 55 (21-80) years. The most common locations of tumors were the proximal colon (52%) and rectum (44%). Among all tumors, 80% were Grade 1. Among the patients, 60% were T1 and 80% were N0. Moreover, 60% of patients were diagnosed in Stage 1. The median follow-up time was 5.4 years, and the five-year survival rate was 95.7%. Recurrence was observed in two patients. Among the three patients with metastases, one patient had metastasis in the liver, whereas the other two patients had metastasis in the liver, bone, and peritoneum. Additionally, a rectal NET patient had distant metastasis. Progression-free survival with a somatostatin analog was 43 months. The colonic NET patient with liver metastasis was administered a somatostatin analog, capecitabine-temozolomide, and radionuclide therapy, respectively. The colonic NET patient with distant metastasis was administered a somatostatin analog but died after five months. **Conclusion:** Colorectal NETs are rare. Most patients were diagnosed at an early stage, and surgical treatment was mostly sufficient.

Keywords: Colorectal tumors; neuroendocrine tumors

Neuroendocrine tumors (NETs) originate from cells of the endocrine system. They are most commonly observed in the gastrointestinal tract, lungs, bronchi, thymus, and pancreas. According to the 2012 Surveillance, Epidemiology, and End Results data, the incidence of NET was found to be seven cases per 100,000 individuals.[1] The incidence of NET has increased in the last three decades.[1] The incidence of colorectal NETs has increased in recent years and is primarily attributed to an increase in the use of colonoscopies for cancer screening and other indications. The estimated incidence of colorectal NETs is one case in 100,000 people.[2] In the gastrointestinal system, besides the pancreas, the stomach, small intestine, appendix, and rectum are the most common sites of NETs; about 25% of gastrointestinal NETs occur in the rectum and less than 10% in the colon.[3]

The small intestine, proximal colon, and the first third of the transverse colon originate from the midgut, while the last two-thirds of the transverse colon to the rectum originate from the hindgut. Therefore, NETs of the small intestine, appendix, colon, and rectum have very different prognoses. However, information on NETs is quite limited. This is because data on colorectal NETs are based on various retrospective analyses. Previous studies have shown that stage, tumor size, differentiation, and location of tumors affect prognosis.[2]

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Prognostic parameters also differ between these studies. Therefore, findings and recommendations regarding disease characteristics are dissimilar and controversial.

In this study, we retrospectively evaluated the patients diagnosed with colorectal NET in our center, determined their clinicopathological features and survival characteristics, and presented our findings based on 18 years of experience with colorectal NET.

MATERIAL AND METHODS

PATIENT SELECTION

The data of patients diagnosed with colorectal NET and followed up in our clinic between December 2005 and November 2023 were reviewed in this study. Patients who were over 18 years old and diagnosed with colorectal NET were included in the study. These individuals were administered follow-up care at Ankara Numune Training and Research Hospital and Ankara City Hospital Medical Oncology clinics. The clinical characteristics and prognostic outcomes were retrospectively extracted from patient data. Cancer staging was performed according to American Joint Committee on Cancer 2017 (8^{th} edition).

STATISTICAL ANALYSIS

Descriptive data were presented as the mean±standard deviation or median and interquartile range according to the distribution of variables. To determine differences in parameters (continuous data) between groups, Student's t-tests were performed when the data followed a normal distribution, and Mann-Whitney U test was used when the data did not follow a normal distribution. Additionally, chi-square tests were performed to determine the differences between the proportions of categorical variables. Overall survival (OS), disease-free survival, and progression-free survival (PFS) were determined by the Kaplan-Meier test, and the differences in these parameters between groups were determined by the log-rank test. All analyses were performed using SPSS 22.0.(SPSS Inc., Chicago, IL, USA) All differences were considered to be statistically significant at $p<0.05$.

The study followed the principles of the Declaration of Helsinki. The study design was approved by the Ethics Committee of Ankara Bilkent City Hospital No. 1 with approval number E1-23-4465/December 27, 2022.

RESULTS

PATIENT AND TUMOR CHARACTERISTICS

In this study, 25 patients were included. The median follow-up time was 5.4 years. The clinicopathological features of the patients are shown in Table 1.

The median age of the patients was 55 (21-80) years; 14 (56%) patients were male, and 11 (44%) patients had a tumor in their rectum. Only 16% of patients were asymptomatic. Abdominal pain was reported in 52% of patients at diagnosis. Also, at diagnosis, four patients (16%) had constipation, three patients (12%) had diarrhea, and two patients (8%) experienced weight loss. The tumors were most commonly located in the proximal colon (52%), rectum (44%), and distal colon (4%).

Most of the tumors (60%) were at the T1 stage. In colonic NETs, T1, T2, T3, and T4 tumors were observed in 36%, 7%, 57%, and 0% of cases, respectively. Most rectal NETs (91%) were diagnosed at the T1 stage. The tumor of only one patient (9%) was diagnosed at the T4 stage. Lymph node metastasis occurred in 20% of patients. The rate of lymph node metastasis in colonic NETs was 28%. Among these, 21% were N1 and 7% were N2. The rate of lymph node metastasis in rectal NETs was 9% (1/11). The N2 rate was 9%. Three patients (12%) had distant metastases at diagnosis.

All patients without metastases underwent surgery, whereas three metastatic patients (12%) did not undergo surgery. Among all patients, 20 (80%) underwent R0 resection, and two patients (8%) underwent R2 resection. The five-year survival rate of the patients was 95.7%.

Recurrence was observed in two of the 22 operated patients. In the first patient with recurrence, the tumor originated from the proximal colon and was Grade 1. The patient had no symptoms during diagnosis. Local recurrence occurred 10 months after surgery. After undergoing another surgery, the patient was followed up for 70 months. The recurrent tumor did not progress during follow-up.

TABLE 1: Clinical and pathological features of the patients.

		All groups	Colon	Rectum	p value
Age (years)	Median (minimum-maximum)	55 (21-80)	57 (27-80)	51 (21-73)	0.295
Gender	Male	14 (56%)	8 (57%)	6 (56%)	0.821
	Female	11 (44%)	6 (43%)	5 (44%)	
Symptoms and signs	Anemia	2 (8%)	1 (7%)	1 (9%)	
	Fatigue	4 (16%)	2 (14%)	2 (18%)	
	Nausea	1 (4%)	0 (0%)	1 (9%)	
	Abdominal pain	13 (52%)	8 (57%)	5 (45%)	
	Constipation	4 (16%)	2 (14%)	2 (18%)	
	Diarrhea	3 (12%)	1 (7%)	2 (18%)	
	Losing weight	2 (8%)	2 (14%)	0 (0%)	
Surgery procedure	R0 resection	20 (80%)	11 (79%)	9 (82%)	0.055
	R1 resection	0 (0%)	0 (0%)	0 (0%)	
	R2 resection	2 (8%)	1 (7%)	1 (9%)	
	No resection	3 (12%)	2 (21%)	1 (9%)	
pT	pT1	15 (60%)	5 (36%)	10 (91%)	0.008
	pT2	1 (4%)	1 (7%)	0 (0%)	
	pT3	8 (32%)	8 (57%)	0 (0%)	
	pT4	1 (4%)	0 (0%)	1 (9%)	
pN	N0	20 (80%)	10 (72%)	10 (91%)	0.234
	N1	3 (12%)	3 (21%)	0 (0%)	
	N2	2 (8%)	1 (7%)	1 (9%)	
M	M0	22 (88%)	12 (86%)	10 (91%)	0.642
	M1	3 (12%)	2 (14%)	1 (9%)	
Stage	Stage 1	16 (64%)	6 (43%)	10 (91%)	0.089
	Stage 2	3 (12%)	3 (21%)	0 (0%)	
	Stage 3	3 (12%)	3 (21%)	0 (0%)	
	Stage 4	3 (12%)	2 (14%)	1 (9%)	
Grade	Grade 1	20 (80%)	12 (86%)	8 (73%)	0.457
	Grade 2	5 (20%)	2 (14%)	3 (27%)	
Ki67	<3%	19 (76%)	12 (86%)	7 (64%)	0.294
	3-20%	6 (24%)	2 (14%)	4 (36%)	

In the second patient with recurrence, the tumor was located in the rectum and was Grade 2. The patient experienced abdominal pain at diagnosis. Tumor recurrence in the liver was observed 19 months after surgery. After recurrence, surgery was not suitable for the patient. Therefore, they received capecitabine and temozolomide as first-line treatment. Their PFS1 was 11 months. They were administered a somatostatin analog as second-line treatment. No recurrence was observed during the follow-up of 11 months.

Three patients (12%) had metastasis during diagnosis. Two patients with colon tumors (14%) and one patient with rectal tumors (9%) had metastases.

The first patient with metastatic colonic NET had a Grade 1 tumor. The patient with liver metastasis received a somatostatin analog as first-line treatment. Progression was observed after 6 months. Capecitabine and temozolomide were administered as second-line treatment. Their PFS2 was 73 months. After progression, radionuclide treatment was administered as third-line treatment. No progression was observed in the fifth month of follow-up after radionuclide treatment. The second patient with metastatic colonic NET had a Grade 2 tumor. The patient had bone and liver metastases and was administered a somatostatin analog as first-line treatment. Progression was observed after three months, and they died 5 months after diagnosis.

The patient with metastatic rectal tumor had a Grade 2 NET. The patient had liver, bone, and peri-

toneal metastases. A somatostatin analog was administered as first-line treatment. Progression occurred after 43 months, and then, the patient was lost to follow-up. However, when their status was viewed in the national death notification system, the patient was alive.

DISCUSSION

Colorectal NETs are rare. Information on NETs is limited and mostly based on retrospective data. Studies on NETs have differences in prognostic parameters. Therefore, findings and recommendations regarding disease characteristics have discrepancies and are controversial. In this study, we presented the clinicopathological features of colorectal NETs recorded in our clinic from 2005 to 2023.

Gastrointestinal NETs are rare and have highly heterogeneous features. NETs originate from cells of the endocrine epithelium. The pathophysiology of gastrointestinal NETs is not clear. The risk of NETs is higher in patients with high cholesterol and ferritin levels, and those with metabolic syndrome and a family history of NETs.[4,5] NETs are most commonly found in the gastrointestinal system (67%), followed by the respiratory system (25%).[6] In the gastrointestinal system, NETs are most commonly found in the small intestine (38%), followed by the rectum (34%) and the colon (16%).[7] The incidence of colorectal NETs was found to be 1/100,000 in Western studies and 2/100,000 in a Japanese study.[3,8] This rate was 45-70% in colonoscopies performed for cancer screening in Poland and England.[9,10] The frequency of NET detection has increased in the last three decades. Imaging and colonoscopy are the main reasons for this increase in the detection rate. Rectal NETs have the most frequent increase in incidence. The incidence of colonic NETs has increased 10-fold.[11-13] The incidence of low-grade colonic and rectal NETs has increased considerably.

As per the categorization performed by the World Health Organization in 2019, NETs are defined based on histopathological features and biological attributes.[14] The method involves assessing the grade of tumor cells, size and location of the primary tumors, markers indicating tumor cell proliferation, invasion within local tissues and blood vessels, and the secretion of biologically active substances. NETs are well-differentiated tumors. They are graded as low, intermediate, and high according to the Ki-67 index and the mitosis rate (Table 2).[15]

Colonic NETs represent a highly heterogeneous group of tumors. NETs of the proximal colon and ileum originate from the midgut. However, they have different characteristics, behavior, treatment response, and prognosis. The genetic characteristics of colonic NETs are not clear, and none of the abnormalities described in ileal NETs, such as chromosome 18 loss or CDKN1B mutations, have been reported in colonic NETs.[16,17] Colonic NETs do not have CDKN2B alterations, unlike ileal NETs.[2]

Two main biological types of NETs are recognized, although their clinical behaviors are very similar. The enterochromaffin-cell type is the most frequent and typical NET and produces serotonin. In contrast, the L-cell type is characterized by a more prominent trabecular arrangement and produces glukagon like peptid-1 or other proglucagon-derived peptides.[18] Colonic NETs are usually single, unlike ileal NETs. Colonic NETs also have a higher grade and invade more frequently. In our study, 86% of colonic NETs were low-grade NETs. The rate of occurrence of low-grade colonic NETs in this study was higher

TABLE 2: Neuroendocrine tumors classification.

Grade	Differentiated	Mitotic count	Ki67 index (%)
Grade 1 (low)	Well differentiated	2 mitoses/10 HPF	≤2
Grade 2 (intermediate)	Well differentiated	2-20 mitoses/10 HPF	3-20
Grade 3 (high)	Well differentiated	>20 mitoses/10 HPF	>20
Neuroendocrine carcinoma	Poor differentiated	>20 mitoses/10 HPF	>20

HPF: High power fields.

than the rate reported in other studies. This occurred probably because of the small sample size. Lymph node and distant metastasis rates were higher in colonic NETs than in rectal NETs, which was also reported in other studies.[7]

The ratio of female to male colonic NET patients in this study was similar to that reported in other studies.[19,20] This ratio was similar in colonic and rectal NET patients. The median age of patients with colonic and rectal NETs was 57 and 51 years, respectively. No significant difference was observed between ages at diagnosis (56 vs. 51 years, p=0.27).

The most common symptoms are abdominal pain and weight loss in patients.[2] In other studies, abdominal pain and weight loss were recorded in 60% and 40% of patients, respectively. Other symptoms include fatigue, constipation, and jaundice. In our study, most patients presented with abdominal pain similar to that reported in other studies. This was followed by fatigue and constipation.

NETs are more common in the proximal colon than in the transverse and distal colon.[20] In this study, most of the colonic NETs were localized in the proximal colon. Although various studies found different results, the metastasis frequency was generally found to be 30-40% in colonic NETs. In our study, 35% of colonic NETs were Stage 3-4. The most common sites of metastasis are the liver, lymph node, peritoneum, and mesentery.[21] Among our two colonic NET patients who had metastases at diagnosis, one had liver metastasis while the other had liver and bone metastases.

Over the last 20 years, the incidence of rectal NETs has increased the most.[22] They account for 18% of all NETs, and 1-2% of all rectal malignancies are NETs.[11,23,24] While the prevalence in the USA is 1-2/100,000, it is lower in European studies, especially in Austria and Norway, which is probably due to an underreporting of the disease because of a lack of national registries.[12,13] These NETs are mostly located on the anterior wall and lateral wall of the rectum. The age at diagnosis of patients with rectal NETs is slightly lower than that of patients with colonic NETs. Rectal NETs are diagnosed at an average age of 56 years, and they are slightly more common in men (57% vs. 43%).[23] In this study, the age at diagnosis of patients with rectal NETs was 51 years, and 56% of the patients were male. The age at diagnosis of patients with rectal NETs was lower than that of patients with colonic NETs. It was slightly more common in men than in women.

Approximately half of rectal NETs are asymptomatic.[2] The most common symptoms are hematochezia, tenesmus, change in defecation habits, anorectal pain, and weight loss.[18,25,26] In this study, the most common symptoms were abdominal pain, followed by constipation and diarrhea. Most tumors smaller than 1 cm are low-grade tumors. The metastasis rate at diagnosis is 2-8%.[23] In high-grade tumors larger than 2 cm, the metastasis rate is 60-80%.[27] During diagnosis, 91% of patients had tumors that were smaller than 2 cm, and 9% of the tumors were metastatic in this study. The metastasis rate was lower in our study compared to that reported in a large retrospective series.[10,13]

Tumor location, tumor size, and tumor grade are the most important factors determining prognosis. Along with these, wall invasion, lymph node involvement, and the presence of distant metastasis are poor prognostic factors.[23,24,28,29] The rate of Grade 1-2 NETs is higher in the rectum than in the colon. The rate of Grade 3 NETs is higher in the colon than in the rectum. In the colon, the rate of Grade 3 NETs is similar in both stages and Stage 4 (48%).[3] In the rectum, the rate of Grade 3 NETs is higher in patients with metastatic disease compared to the rate in all patients (41% vs. 21%).[30] The metastasis rate is lower in the rectum than in the colon (32% vs. 47%). Our patients had Grade 1 and 2 tumors.

The five-year survival rate of patients with colonic NETs is 40-70%.[21] The five-year survival rates of patients with local, regional, and metastatic disease were found to be 76%, 72%, and 30%, respectively.[31] When patients with cecum and right colon cancer are evaluated together, they survive longer than those with left-sided colon cancer; however, OS is similar for patients with both types of colon cancer.[32] NETs of the right colon also include cecal tumors. Studies have shown that cecal NETs resemble ileal NETs; both are generally low-grade tumors. OS of patients with local, regional, and

metastatic disease was found to be 130 months, 100 months, and 54 months, respectively.[7] When patients with cecal NETs were excluded from the data on colonic NETs, the duration of survival of patients with regional and metastatic colonic NETs was found to be 52 months and 7 months, respectively.[7] In a Canadian study, the OS of patients with colonic and ileal NETs was similar. However, most colonic NETs are localized in the proximal colon and the proportion of cecal NETs among them is not known.[33]

Rectal NETs have the best prognosis among all early-stage NETs. The five-year survival rate of rectal NET patients is 76-88%. The survival duration is 290 months for local disease and 26 months for metastatic disease. In our study, most of the patients were in the early stage and the number of events was low. We found that 76% of the patients were at Stages 1-2. All tumors were Grade 1 or 2. OS did not reach the median value, and the five-year survival rate was 95.7%. The higher survival of patients in this study compared to that recorded in other studies may be associated with these factors. Detection at an early stage was possible probably because colonoscopic imaging was performed for broad indications.

All patients were examined with Ga-DOTATATE positron emission tomography/computed tomography (PET/CT) at diagnosis. Patients who underwent surgery were screened by thorax-abdomen-pelvic CT examinations during follow-up. In case of suspected recurrence, patients underwent magnetic resonance image or Ga-DOTATATE PET/CT examinations. Metastatic patients were followed up with thorax abdominopelvic CT. Metastatic patients with suspected progression also underwent Ga-DOTATATE PET/CT examinations.

CONCLUSION

Colorectal NETs are rare and generally have a good prognosis. Their incidence is increasing due to the widespread screening of colon cancer. The localization of colon tumors may alter tumor biology and tumor behavior, and the prognosis of colonic and rectal NETs may be different. To gain further insights into this subject and develop new treatment strategies, studies need to be conducted with a large number of patients from different populations.

Source of Finance

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

Conflict of Interest

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

Authorship Contributions

Idea/Concept: *Furkan Ceylan, Doğan Uncu;* ***Design:*** *Furkan Ceylan, Selin Aktürk Esen;* ***Control/Supervision:*** *Fahriye Tuğba Köş, Doğan Uncu;* ***Data Collection and/or Processing:*** *İsmet Seven, Furkan Ceylan;* ***Analysis and/or Interpretation:*** *Furkan Ceylan, Selin Aktürk Esen;* ***Literature Review:*** *İsmet Seven, Doğan Uncu;* ***Writing the Article:*** *Furkan Ceylan, Selin Aktürk Esen;* ***Critical Review:*** *İsmet Seven, Fahriye Tuğba Köş;* ***References and Fundings:*** *Doğan Uncu, Fahriye Tuğba Köş;* ***Materials:*** *Doğan Uncu, Fahriye Tuğba Köş.*

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