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Surgical treatment of extra-appendiceal colorectal neuroendocrine tumors

Authors' Contribution:
A–Study Design
B–Data Collection
C–Statistical Analysis
D–Data Interpretation
E–Manuscript Preparation
F–Literature Search
G–Funds Collection

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ABSTRACT:

Background: Extra-appendiceal colorectal neuroendocrine tumors are rare neoplasms with variable biological behavior.

Materials and Methods: The study group consisted of 15 patients with an extra-appendiceal colorectal neuroendocrine tumor who underwent surgical resection (M/F=3:12, mean age=62.9 years). Lower-grade neuroendocrine tumors (NET G1-G2) and neuroendocrine carcinomas were recognized in 5 and 10 patients, respectively. Data were evaluated retrospectively with regard to clinical and pathologic characteristics and outcomes.

Results: The median age of the patients with lower-grade NETs was significantly lower than that in patients with NECs (53 yrs vs. 68 yrs, p=0.03). NETs G1-G2 were significantly smaller than neuroendocrine carcinomas (4.0 cm vs. 6.4 cm, p=0.02). There were no differences between lower-grade NETs and NECs with regard to tumor location, local infiltration, rate of nodal involvement, and distant metastases. All the patients underwent open segmental resection of the colon or rectum. Complete resection was achieved in 3 of 5 patients from the lower-grade NET group, and in 5 of 10 patients in the NEC group (p=1.0). The overall survival was significantly better for lower-grade NETs tumors (p=0.005). The median survival was 4.8 months in the NEC group. The median survival in the lower-grade NET group was not achieved after a median follow-up of 69 months. Three-year overall survival was at a level of 100% for lower-grade NETs, and only 27% for NECs.

Conclusion: Lower-grade neuroendocrine tumors seem to exhibit comparable potential for dissemination as neuroendocrine carcinomas, however, prognostic implications of metastases are distinct.

KEYWORDS: colorectal neuroendocrine tumor, gastrointestinal neoplasm, colorectal surgery

Recommendation: *Prognosis in patients with neuroendocrine carcinoma is significantly poorer than in patients with low-grade neuroendocrine tumors, despite comparable clinical staging.*

INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms of the gastrointestinal tract. These tumors most often affect the small intestine or appendix(1). NETs involving the large intestine are uncommon and account for less than 2% of all colorectal malignant tumors(2). Kang et al.(2) estimated the incidence of colorectal neuroendocrine carcinomas as 0.2 per 100,000 people, whereas the incidence rate for low-grade NETs was approximately 5 times higher. Importantly, the incidence of intestinal neuroendocrine tumors increased 2.9-fold over a 20-year period(3). The majority of neuroendocrine tumors of the large bowel originates from the appendix(4). Appendiceal neuroendocrine tumors exhibit uniformly a favorable long-term prognosis, and usually are incidental findings in the specimens after appendectomy for acute appendicitis. Steffen et al.(5) found that the 10-year relative survival rates in patients after resection of an appendiceal neuroendocrine tumor were comparable to those observed in the general population of the same age. In contrast, extra-appendiceal colorectal neuroendocrine tumors are generally regarded as more aggressive neoplasms, which show the poorest prognosis among all gastroenteropancreatic neuroendocrine tumors. At the time of presentation, most colorectal NETs have already disseminated to regional lymph nodes or there are distant metastases(6-9). However, this subgroup of neuroendocrine tumors seems to exhibit a variable biological behavior. The purpose of this study was to evaluate the clinical characteristics and outcomes of surgical management of extra-appendiceal colorectal neuroendocrine tumors.

MATERIALS AND METHODS

Data from the hospital database including patients treated in our department between January 2000 and December 2014 were searched to identify patients with neuroendocrine tumors involving the colon or rectum. Excluded from the study were patients with appendiceal neuroendocrine tumors, mixed neuroendocrine tumors (MANEC), and colorectal NETs which had been removed endoscopically. The pathologic specimens were re-evaluated to conform the WHO2010 (World Health Organization) classification for neuroendocrine tumors. Medical records were reviewed retrospectively for each patient. Clinical and pathological data were extracted from hospital charts, pathology reports, and operative protocols. The group was evaluated in terms of clinical and demographic variables, perioperative data, morbidity and overall survival. The study was approved by the Institutional Ethics Committee Board of The Medical University of Warsaw.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistica 12 softwa-

Tab. I. Clinicopathologic characteristics and outcomes in patients with extra-appendiceal colorectal neuroendocrine tumors. NET – neuroendocrine tumor, NEC – neuroendocrine carcinoma, *1 patient with NX, n/r – not reached, IQR – interquartile range, F – female, M – male.

	NET G1-G2 (N = 5)	NEC (N = 10)	P VALUE
Age, median (IQR); years	53 (51–55)	68 (62–73)	0,03
Gender: F:M	5:0	7:3	0,50
Symptoms:			
Abdominal pain	3	7	
Loss of weight	1	3	
GI bleeding	0	2	
Change in defecation habits	0	4	
Incidental finding	2	0	
Tumor size, (IQR), cm	4,0 (1,5–4,2)	6,4 (5,5–9,0)	0,02
Tumor location (n):			0,58
Cecum/ascending colon	4	5	
Rectum	1	5	
Local infiltration (n):			
T1	1	0	
T2	1	0	
T3	3	8	0,16
T4	0	2	
Lymph node metastases, n	4	9*	0,36
Distant metastases, n	2	3	1,00
Completeness of resection: R0/R2	3:2	5:5	1,00
Overall survival (median), months	n/r	4,8	0,005

re (StatSoft Poland). Continuous data were presented as medians and interquartile ranges. The Mann-Whitney U test was used for continuous data, and the Fisher exact test or Pearson's Chi-square test were used for categorical data analysis. Survival analysis was estimated using the Kaplan-Meier method. Overall survivals (OS) were compared using the log-rank test. Two-sided p-value of < 0.05 was regarded statistically significant.

RESULTS

A total of 15 patients with extra-appendiceal colorectal neuroendocrine tumors who underwent surgical resection was identified. Of 15 neuroendocrine tumors, five were lower-grade NETs, including three grade 1 NETs and two grade 2 NETS. Ten tumors were neuroendocrine carcinomas, i.e., grade 3 NETs or NECs. Half of neuroendocrine carcinomas were of small-cell type. The median age of the patients with lower-grade NETs was significantly lower than those with NECs (53 yrs vs. 68 yrs, p=0.03). Colorectal neuroendocrine tumors were more common in females than in males (80%). G1-G2 NETs were significantly smaller than neuroendocrine carcinomas (median size: 4.0 cm vs. 6.4 cm, p=0.02). There were no differences between lower-grade NETs and NECs with regard to tumor location, local infiltration, rate of nodal involvement or distant metastases. All the patients with NECs were symptomatic, whereas 2 of 5 lower-grade NETs were incidental findings at colonoscopy. The most common presenting symptom in both groups was abdominal pain. None of the tumors was hormonally active. Neuroendocrine tumors tended to localize in the ascending colon, cecum and rectum (Fig. 1), and none involved the transverse or left colon. Table I summarizes the clinical and pathologic characteristics of patients with extra-appendiceal colorectal NETs.

All the operations were elective, although 4 of 15 patients were admitted acutely because of abdominal pain. In 4 cases, including 2 patients with incidental tumors, a preoperative confirmation of neuroendocrine tumor was established in the pathological examination of specimen collected at colonoscopy. In the remaining patients, the indications to surgical treatment were symptomatic tumors of the large intestine recognized in computed tomography and/or colonoscopy. All the patients underwent open segmental resection of the colon or rectum. In the lower-grade NET group, patients additionally required the following procedures: partial resection of the small intestine, right adenexectomy, and gastrojejunostomy in one case each. One patient from the NEC group underwent also gastrojejunostomy. Gastrojejunostomy was performed in order to relieve duodenal obstruction due to extensive local tumor infiltration. Complete resection was achieved in 3 of 5 patients (60%) from the lower-grade NET group, and in 5 of 10 patients (50%) in the NEC group. Curative resection was not possible because of locally advanced tumors and distant metastases in 2 and 5 patients, respectively. One patient with NEC died of liver failure due to massive hepatic metastases soon after the operation.

Overall survival was significantly better for lower-grade NETs (p=0.005). The median survival was 4.8 months in the NEC group, whereas the median survival in the lower-grade NET group was not achieved after a median follow-up of 69 months. Three-year overall survival was at a level of 100% for lower-grade NETs, and only 27% for NECs (Fig. 2).

DISCUSSION

In 2010, the World Health Organization divided pure neuroendocrine tumors into three grades based on mitotic counts or Ki-67 proliferation index(10). This classification remains arbitrary, and differences in clinical behavior between lower-grade NETs (G1-G2) and neuroendocrine carcinomas (NEC, G3) are unclear. Neuroendocrine tumors which exhibit a mitotic count above 20 per HPF or Ki-67 higher than 20% are classified as G3 NETs or neuroen-

docrine carcinomas. Although the threshold for the diagnosis of NEC is only 20%, all but one neuroendocrine carcinomas in this series showed proliferative indices higher than 70% which reflected highly aggressive biology of this subset of tumors.

The clinical picture of neuroendocrine tumors is non-specific and variable. In our series, some low-grade NETs were asymptomatic and found incidentally, whereas all neuroendocrine carcinomas caused symptoms. In a series reported by Lin et al.(11), 77.8% of patients with lower-grade colorectal neuroendocrine tumors were asymptomatic. In comparison, colorectal neuroendocrine carcinomas usually cause symptoms. Aytac et al.(8) found, that only 16% of patients with NEC were asymptomatic at the time of diagnosis, while the remaining patients complained about rectal bleeding (36%) and abdominal pain (32%). In our series, abdominal pain was the most common complaint. Hormonal activity is rare among colorectal neuroendocrine tumors with only single cases of functioning colorectal NETs reported in the literature(6, 9). Likewise, there were not any hormonally active tumors in this series. All neuroendocrine tumors in our series were located in the rectum, cecum or ascending colon. Similarly, in a study by Conte et al.(12), 40% and 31% of NECs originated from the rectum or the right half of the colon, respectively.

Although colonoscopy is highly effective for prevention and early diagnosis of colorectal adenocarcinoma, the value of colonoscopic surveillance in neuroendocrine carcinomas is disputable. One of the patients in this series developed a large cecal NEC, although routine colonoscopy performed one year earlier was unremarkable. Two similar cases were reported by Grassia et al.(13). In contrast to our case, both these patients had underlying ulcerative colitis. Compared with colorectal adenocarcinoma, precancerous lesions are unknown for neuroendocrine carcinomas but the latency time for their development might be relatively short. On the other hand, endoscopy still constitutes a useful tool for diagnosis and local management of lower-grade colorectal NETs(11).

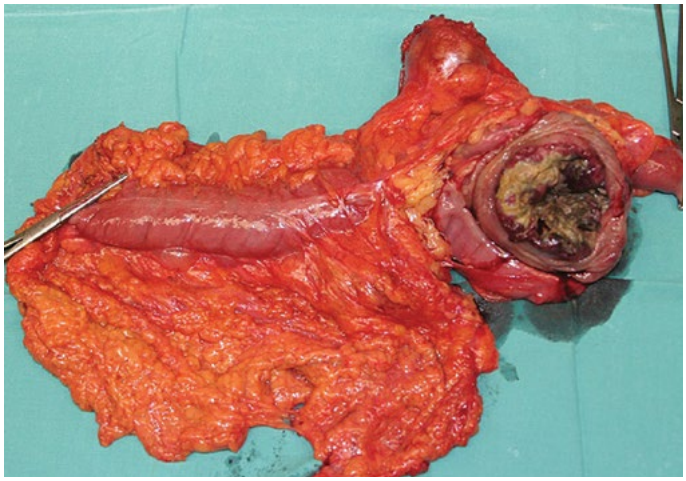

Fig. 1. Advanced ulcerated neuroendocrine carcinoma involving the cecum.

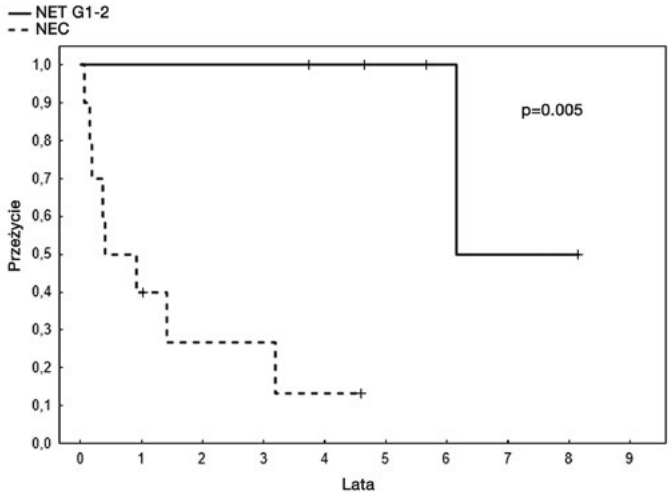

Fig. 2. Comparison of overall survival between patients with lower-grade NETs and neuroendocrine carcinomas (+ censored).

Extra-appendiceal colorectal neuroendocrine tumors are generally considered to have the worst prognosis among all gastroenteropancreatic NETs. In our series, the prognosis was favorable for patients with G1 and G2 NETs. In contrast, the prognosis for G3 NETs was dismal, and only 2 patients were still alive 3 years following the diagnosis. Low proliferative activity in G1-2 NETs implies much lower potential for dissemination or local infiltration than that of neuroendocrine carcinomas, which show extremely high proliferation indices. Nevertheless, grade 1 and 2 NETs in this series had a similar proclivity for nodal and distant metastases as NECs. The rate of nodal and liver metastases at presentation was comparable in both groups. Furthermore, a rectal G2 NET as small as 7 mm metastasized to the liver. Similarly, local infiltration of the tumors was also comparable, and most patients had locally advanced tumors, i.e., T3 or T4. Due to frequent nodal involvement, a segmental colectomy with resection of the lymphatic drainage is recommended in most colorectal NETs. Endoscopic resection might be acceptable in small (< 1 cm) and superficial well-differentiated neuroendocrine tumors (limited to the mucosa and submucosa) (14). However, even these tumors carry the risk of nodal metastases of 4-25% (6, 14). Prior to endoscopic treatment, endosonographic examination should be performed in order to assess the depth of intestinal wall infiltration by the tumor and detection of regional lymph node metastases(15). Resection of colorectal neuroendocrine tumors with endoscopic submucosal dissection (ESD) or transrectal surgical resection, including TEM – transanal endoscopic microsurgery, were superior to endoscopic mucosal resection (EMR) in terms of locally complete resection. In a study by Son et al(16), the rates of pathologic complete resection were 30.9%, 72.0% and 81.8% for EMR, ESD and transrectal surgical resection, respectively. Despite an apparent comparable metastatic potential, the clinical and prognostic consequences were distinct for low-grade NETs and neuroendocrine carcinomas. G1 and G2 neuroendocrine tumors had an indolent course with a 100% survival at 3 years following presentation, also in patients with lymph node or hepatic involvement. In line with our observations, Strosberg et al.(17) found a significant correlation between the tumor grade and overall survival in metastatic gastroenteropancreatic neuroendocrine tumors, although only 18.1% were primarily colorectal. In their study, 2-and 5-year OS for grade 1-2 NETs was 100% and 85%, whereas the overall survival for neuroendocrine carcinomas was 23% and 0%, respectively. Recently, Kim et al.(18) reported a case of a small-grade 1 NET which was managed endoscopically. At the time of initial resection, a 7-mm perirectal lymph node was noticeable on CT scans. Subsequently, this lymph node increased to 10 mm over the next 7 years. This case shows, that the natural course of metastatic lymph nodes in low-grade neuroendocrine tumors might be benign with an extremely slow growth rate. In

our series, 2 of 5 patients with lower-grade NETs underwent incomplete oncological resection. Both these patients had multiple hepatic metastases from G1 NETs. One patient survived 6 years, and the other is alive 4 years after primary treatment. In contrast to lower-grade neuroendocrine tumors, NECs are almost invariably connected with a poor prognosis. Shafqat et al.(19) reported 5-year overall survival in neuroendocrine carcinomas of 16.3%. In a series published by Smith et al.(9) ,3-year overall survival was 5% in metastatic NECs and 8% for patients without metastases. Similarly, Saclarides et al.(20) found a 5-year overall survival of 6% for neuroendocrine carcinomas. The median survival for NECs ranged from 6 to 21 months(9, 19, 21). The median survival in this study was only 4.8 months. The worse prognosis in this series might be partly accounted for by an advanced stage at the time of diagnosis and a low proportion of localized tumors. In line with this observations, Conte et al.(12) found a median OS of 8.7 months for metastatic neuroendocrine carcinomas and 20.6 months for localized NECs ($p<0.001$). In addition, colorectal neuroendocrine carcinomas exhibit a poorer prognosis for the same clinical stage compared with adenocarcinomas(19).

Recently, the role of surgical resection in neuroendocrine carcinomas has been questioned. Interestingly, Smith et al.(9) found that the resection of primary tumor was not associated with improved survival in either a metastatic or localized disease upon multivariate analysis. The only predictive factor for better survival in this study was a collision tumor with a component of adenocarcinoma (MANEC). Likewise, Shafqat et al.(19) found better overall survival after resection only in non-small cell neuroendocrine carcinomas compared with non-resectional treatment (median survival 21 months vs. 6 months, $p<0.0001$), whereas there was no difference in OS for small-cell NECs, whether resected or not (median survival 18 months after resection vs. 14 months without resection, $p=0.95$).

This study has some limitations. First, the study is retrospective and the patient groups are relatively small, and thus, statistical analysis was underpowered providing only a rough estimation for general insight. Second, the influence of adjuvant chemotherapy for NECs on the overall survival was not accounted for.

CONCLUSIONS

Extra-appendiceal colorectal lower-grade neuroendocrine tumors exhibit comparable metastatic potential as neuroendocrine carcinomas, however, prognostic implications of metastases are distinct. Neuroendocrine carcinomas are highly aggressive neoplasms with poor prognosis even despite potentially curative resection.

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