Long term outcomes of neuroendocrine carcinomas (high-grade neuroendocrine tumors) of the colon, rectum, and anal canal

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Summary

Introduction and aim: Neuroendocrine carcinomas (NEC) of the large intestine are rare and aggressive neoplasms. This study was designed to review the experience at a single institution and analyze the outcomes to improve our understanding of these tumors.

Methods: The patients with NEC (high-grade neuroendocrine tumor) of the colon, rectum, and anal canal were identified from June 1993 to April 2011. Clinical features studied were patient demographics, presenting symptoms, tumor location, tumor stage, treatment status and length of follow-up.

Results: Twenty-five patients were identified. Stages of the diseases were I (n=5), II (n=1), III (n=10) and IV (n=9). Locations of the tumors were: colon (36%); rectum (28%) and anal canal (36%). Rectal bleeding (36%) and pain (32%) were the most common symptoms but 16% of patients were asymptomatic. Among the patients with local or locally advanced disease, only five patients had surgery alone. The remainder of the patients underwent chemotherapy with/without radiation. Mean follow-up was 33.7 ± 8.4 months after diagnosis. NEC of the large bowel and anal canal has very distinctive pathologic features and a very poor prognosis. More than one third of the patients with NEC had metastatic disease at the time of diagnosis. When these tumors are in an advanced stage none of the treatment modalities impact on survival.

Conclusion: The present study showed the poor prognosis of these rare tumors.

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Introduction

Neuroendocrine carcinomas (NEC) of the colon and rectum are rare, extremely aggressive neoplasms with a high mortality rate [1]. The term, neuroendocrine carcinoma or high-grade neuroendocrine tumor describes malignant epithelial tumors with evidence of neuroendocrine differentiation based on light microscopic, ultrastructural,
or immunohistochemical evaluation [1–12]. These tumors are morphologically and biologically similar to bronchogenic small cell carcinoma [3,11]. The reported incidence of NEC represents between 0.1% and 3.9% of all colorectal malignancies [2,3]. It is important to recognize clinical characteristics and outcomes of NEC, as the optimal treatment for these tumors is still unclear. The aim of this study is to analyze the outcomes and improve our understanding about NEC of the colon, rectum and anal canal by reviewing the experience at a single institution.

Patients and methods

We used the institutional review board approved, prospectively maintained colorectal cancer database of the Department of Colorectal Surgery, Digestive Disease Institute in Cleveland, Ohio, and reviewed all patients from June 1993 to April 2011 with diagnosis of NEC. We aimed to create a reliable and inclusive definition for colorectal NEC. Since we evaluated the patients who were diagnosed during a long period of time, re-evaluation of every specimen according to most recent diagnosis criteria was not possible. Various definitions were made to classify neuroendocrine tumors within the study period [11,13–16]. Histopathology reports of all cases were reviewed. Based on the definition of Capella et al. [13], malignant colorectal neuroendocrine tumors were identified. Well-differentiated neuroendocrine tumors (low-grade, intermediate grade), carcinoid and atypical carcinoid tumors were not included in this study. The pathologic evaluation in patients that we reported is consistent with World Health Organization (WHO) 2010 classification of high-grade (Grade 3) neuroendocrine tumors [11,17]. All the NEC in our patient population had more than 20 mitosis/10 hpf. TNM classification was performed based on WHO 2000 classification [15].

Clinical information and follow-up was obtained from hospital charts and electronic records. Clinical features studied were patient demographics, presenting symptoms, tumor location, tumor stage, treatment status and length of follow-up. In non-operated patients, stage of the disease was determined by clinical imaging studies. All survival data were calculated from the date of diagnosis. The comparison with respect to overall survival between the patients with no distant metastasis (stage I, II, III) and with distant metastasis (stage IV) was performed using log-rank test with the Kaplan–Meier method.

Results

Patients’ characteristics

A total of 25 patients with NEC were identified. The mean age of diagnosis was 56.4 ± 2.7 years. There were 8 (32%) males and 17 (68%) females. Tumors were located as follows: 4 in the right colon, 3 in the transverse colon, 2 in the sigmoid colon, 7 in the rectum and 9 in the anal canal. Six cases had a component of adenocarcinoma (‘combined’ type of tumor) in the colon (n = 2), rectum (n = 3) and anal canal (n = 1). One case had an adenosquamous component with neuroendocrine carcinoma in the colon. Computed tomography, colonoscopy and biopsy were performed in all patients. Endorectal ultrasonography (n = 7), magnetic resonance imaging (n = 6), positron emission tomography scan (n = 3) were other diagnostic studies that were utilized in conjunction with endoscopy. Stages of the disease were: I (n = 5, 20%), II (n = 1, 4%), III (n = 10, 40%) and IV (n = 9, 36%). Four patients were asymptomatic at the time of diagnosis. In these four patients, the NEC was endoscopically visualized during a screening colonoscopy. In two, the tumor was located in the ascending colon and in the two others in the rectum. One patient had symptoms of diarrhea and the NEC was located in the cecum. The most common presenting symptom was rectal bleeding (n = 9, 36%) and pain (n = 8, 32%). Three patients presented with abdominal pain and the tumor location was the ascending and transverse colon in these patients. Initial treatment strategies are summarized in the Table 1.

Management of the patients with distant metastasis at the time of diagnosis

Nine patients had distant metastasis at the time of diagnosis. Liver was the organ, which was most commonly involved in metastatic disease. Among these group of patients, 1 had 2 organ metastasis and 1 patient had 3 organ metastasis at the time of diagnosis. The locations of metastasis were liver (n = 5); lung (n = 2); liver, lung and brain (n = 1) and liver and brain (n = 1). One had no oncological treatment because of poor health and died ten months after diagnosis. All other patients with metastatic disease had some sort of surgical or oncological treatment for palliation. Five patients with stage IV disease underwent a total colectomy (n = 2), an abdominoperineal resection (n = 1), a left colectomy (n = 1) and a diverting colostomy (n = 1) because of the obstructive symptoms of the tumors for palliative purposes. No surgical intervention was performed to metastatic organs. None of the stage IV patients underwent a curative treatment.

Management of the patients with no distant metastasis at the time of diagnosis

Seven patients with rectal (n = 3) and anal canal (n = 4) NEC underwent neoadjuvant chemoradiotherapy (NCRT). These patients received standard five weeks NCRT (5-fluorouracil ± cisplatin and 4500–5040 cGy). Four of the patients undergoing NCRT had concurrent adenocarcinoma,
Colorectal carcinoma

Table 2  Operations performed for curative intent.

<table>
<thead>
<tr>
<th>Procedure</th>
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<tr>
<td>right hemicolecotomy</td>
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<tr>
<td>Low anterior resection</td>
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<td>Local excision</td>
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“combined type” of tumor. One patient with a stage III disease located 1 cm proximal to the dentate line received NCRT, did not want to be operated after completion of NCRT and was lost to follow-up. A complete response to chemoradiation was achieved in another patient with low rectal stage III disease. This patient developed right inguinal lymph node recurrence six months later and she underwent a right inguinal lymph node dissection. She has been disease free for 24 months after surgery. Operation was performed within 6–8 weeks after completing NCRT.

Fourteen of sixteen patients with local and locally advanced disease underwent surgery with curative intent (Table 2). Local excision was performed in three patients with T1 rectal (n = 2) and T1 anal canal (n = 1) NEC. The reminder of patients with local or locally advanced disease underwent a radical resection. Four patients underwent surgery alone. Five patients were treated with surgery and adjuvant chemotherapy and five patients were treated with surgery and combination postoperative chemoradiotherapy. There was no death within the perioperative period. In resected specimens, mean tumor size and lymph node number examined was 3.5 ± 3.6 cm and 14.4 ± 15.9, respectively. Radial margin was positive in three cases that were operated with curative intent.

Adjuvant therapy

Cisplatin with etoposide (n = 9) or topotecan (n = 2) based regimens were used as first line primary chemotherapy. FOLFOX (n = 3) and adriamycin with vincristine (n = 2) were administered to two patients who could not tolerate first line chemotherapeutic regimens. Carboplatine and etoposide was preferred for recurrent and stage IV cases. Mean and median follow-up was 33.7 ± 8.4 and 17.2 (range 4.2–153.3) months after diagnosis, respectively.

Follow-up after a curative resection

Six patients had recurrent disease after curative surgery in the following organs: brain (n = 2), lung (n = 1), liver (n = 1), local recurrence (n = 1) and sacrum with liver (n = 1). Only one patient was operated for recurrent disease after primary surgery. The patient with local recurrence underwent surgery and the recurrent lesion was excised. After this operation, a vertebral metastasis developed. The secondary recurrence was also removed. Two patients were lost after surgery. Seven patients were disease free at the time of the last follow-up.

Overall survival according to the stage of the disease was 75% stage I, 100% stage II, 43% stage III and 17% stage IV at most recent follow-up. Patients with metastatic disease (stage IV) had poorer overall survival after diagnosis compared to patients with no distant metastasis in long term (Fig. 1).

Discussion

NEC of the colon and rectum are rare [3]. The first documented series of colonic small cell undifferentiated carcinomas with neuroendocrine features was reported by Gould and Chejfec in 1978 and sporadic reports have appeared since, primarily in the form of small series and case reports [3–12]. In our study, NEC comprised 0.33% of all colorectal malignancies from our prospective database. Within the large bowel, the most frequent site is the rectum, followed by the cecum and sigmoid [8–10]. NEC has rarely been reported in the anal canal and most of the rectal tumors described were located in the mid or upper rectum [1–12,18–21]. In our study, 16 (64%) of the tumors were located in the rectum and anal canal. In previous studies, anal canal originating NEC were considered as part of the rectum. We separately evaluated the anal canal, since it is a different portion of the alimentary tract anatomically and embryologically.

The nomenclature and classification of NEC by pathologists are controversial. Colorectal neuroendocrine tumors are classified as either low-grade carcinoid tumors or high-grade neuroendocrine carcinomas [3,9,11]. The neuroendocrine differentiation of these tumors is based on ultrastructural and/or immunohistochemical studies [22,23]. The light microscopy features of colorectal NEC are essentially indistinguishable from those of pulmonary NEC [9–11]. The tumor is composed of sheets and nests of round to fusiform cells with minimal amounts of cytoplasm, granular nuclear chromatin, and inconspicuous nucleoli. The typical organoid architectural patterns of low-grade neuroendocrine neoplasms (e.g., carcinoid) are generally absent. Abundant necrosis, either confluent or punctuate within nests of tumor cells is present in high-grade tumors [23]. Approximately half of the tumors may contain non-NEC elements, varying in type depending on location. Colorectal NEC may contain adenosquamous carcinoma components or foci of squamous differentiation as well [9–12,23]. In this study, six of our patients had associated adenocarcinoma and one case had accompanying adenosquamous cancer component. No specific risk factors were identified with reasonable confidence for NEC. Colorectal NEC can be
associated with overlying adenomas and ulcerative colitis, and was described in an immune deficient patient [5,23,24]. The pathogenesis of these tumors is unknown but a pluripotent stem cell origin has been hypothesized [6]. A colonoscopy should be done if a colorectal NEC is detected. When a NEC is histologically diagnosed, a primary lung tumor should be excluded. Staging evaluation should include a chest and abdominal/pelvic computed tomography [9,25]. Currently, there is no data supporting the role of magnetic resonance imaging and positron emission tomography in the primary workup of a colorectal NEC. However, preoperative magnetic resonance imaging and endorectal ultrasonography can be used to evaluate local involvement of the tumor in the rectal/anal canal wall.

The clinical presentation is not specific for NEC and may be dominated by the advanced stage at diagnosis. Incidental diagnosis at early stages is uncommon and was present in four of our patients. The most common presenting symptom was rectal bleeding and pain. These symptoms could be seen in any type of colorectal cancer. Thirty-six percent of our patients had metastatic disease when they were diagnosed as NEC. Liver was the most common metastatic organ involved. These tumors are poorly differentiated and are characterized by early dissemination and rapid clinical deterioration. Large bowel NEC has a very poor prognosis [2,3,21]. When they are diagnosed at an early stage and if a curative resection is possible survival may increase. Better outcomes were observed in patients with stage 1 and 2 in our series.

Currently, no standard oncological treatment strategy has been defined for colorectal NEC. Surgery with or without adjuvant treatment is the preferred therapy for localized disease, while primary chemotherapy with or without radiotherapy is used for stage IV patients [14]. Surgery and radiotherapy have a place for palliative purposes in patients with disseminated metastasis. Data regarding the effectiveness of various therapies derive from case reports and small retrospective studies [2—7,14,21]. Poor prognosis and metastatic nature of NEC force physicians to administer multi-drug regimens with or without radiotherapy. We plan adjuvant treatment strategy with a multidisciplinary team, including pathologists, radiologists, geneticists and surgeons. Patients with positive resection margin and stage III patients who had no NCRT underwent adjuvant radiotherapy in our study. Similar therapeutic approach was carried out by other centers [2,12,14,23].

While the neuroendocrine features of gastrointestinal small cell neuroendocrine carcinomas may theoretically allow treatment with radioderbeinated somatostatin analogues, this approach has not been reported in this disease as of yet. More information regarding expression of the appropriate somatostatin receptors, using radio labeled somatostatin analogues, may be helpful in this regard [23]. However, there is lack of evidence-based data showing the benefits of octreotide therapy for extra-pulmonary high-grade NEC [14]. We did not have any patients who underwent somatostatin therapy in this series. Chemotherapy for colorectal NEC usually follows the ones used in pulmonary NEC because of the genetic, pathological and clinical similarities of poorly differentiated extra-pulmonary neuroendocrine tumor with small cell lung cancer [11,21]. Cisplatin, etopside, cyclophosphamide, and doxorubicin represent the backbone of most combination regimens [2,9,12,23]. However, some NEC harbor non-NEC components. In such instances, different systemic agents depending on the predominant cell type of the tumor may be used or alternatively a regimen effective in both types may be utilized.

Currently benefit of NCRT before resection is unknown [14]. The general approach of our group is to use NCRT in patients with extraperitoneal rectal tumors staged as cT3—T4 or any cN1 for rectal adenocarcinoma. However the decision for NCRT is usually made at the discretion of the individual surgeon according to stage and localization of tumors [26]. Majority of the patients who underwent NCRT had an adenocarcinoma component. Treatment strategy was similar in patients with rectal and anal canal NEC. Our patient number was not enough to make an analysis to evaluate the impact of NCRT on survival. Considering poor outcomes of NEC, NCRT may have a role to control local advanced NEC in the rectum and anal canal. Further studies are needed to evaluate the role of NCRT for the treatment of NEC.

The drawback of our study is its retrospective nature. Low patient number was another factor preventing any subset analysis with statistical methods to evaluate the associated factors with survival, such as treatment strategy, location of the tumor or NCRT.

In conclusion, prognosis of patients with colorectal NEC is generally dismal. Most tumors are at an advanced stage at the time of diagnosis. Curative resection if it can be achieved may be effective in survival. Recognition of this uncommon and aggressive type of cancer may lead to the development of new therapeutic strategies.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References

Colorectal neuroendocrine carcinoma


