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Clinicopathological and Prognostic Analysis of Neuroendocrine Carcinoma of the Colorectum*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Neuroendocrine carcinoma of the colorectum is a kind of malignant tumor composed of neuroendocrine cells, with a unique hormone synthesis and secretory function. In recent years, more and more attention is being paid to this kind of tumor, with its high malignant potential, poor differentiation, high invasiveness and early metastasis.
Objectives. The aim of this study was to evaluate the clinicopathological characteristics and prognosis of neuroendocrine carcinoma of the colorectum.
Material and Methods. The clinical data on 49 patients treated for neuroendocrine carcinoma of the colorectum from January 1995 to January 2013 were retrospectively analyzed and relevant scientific literature was investigated.
Results. The study subjects included 34 males and 15 females, out of whom 27 patients underwent curative operations, while 18 underwent palliative resections and four others underwent biopsy. All 49 patients underwent adjuvant chemotherapy after operation. Of the 45 resection samples, vascular invasion was found in 33 patients (73.3%) and regional lymph node metastasis was found in 35 patients (77.8%). All the patients were followed up for a period of 3 to 68 months. The 1-year, 3-year and 5-year survival rates were 49.1%, 17.2% and 6.9%, respectively. The patients' survival time was related to the tumor stage, vascular invasion and surgery type (radical or not), but not related to age, gender, tumor size or tumor location.
Conclusions. Neuroendocrine carcinoma of the colon lacked specific clinical manifestations, but showed a high degree of malignancy and a poor prognosis. Tumour stage, vascular invasion and surgery type (radical or not) were important factors influencing the prognosis (**Adv Clin Exp Med 2016, 25, 4, 719–724**).

Key words: colorectal neoplasms, neuroendocrine carcinoma, pathology, clinical, prognosis.

Neuroendocrine cells are found throughout the human body, mainly distributed in the gastrointestinal tract, pancreas, lungs, thyroid, adrenals and many other organs. Neuroendocrine carcinoma of the colorectum is a kind of malignant tumor composed of neuroendocrine cells, with a unique hormone synthesis and secretory function. Increasing attention is being paid to this kind of tumor, with its high malignant potential, poor differentiation, high invasiveness and early metastasis [1–3]. The clinical manifestations of neuroendocrine carcinoma of the colorectum are atypical, with variable biological characteristics, degrees of malignancy, pathological features and prognosis. The pathological diagnostic standard for this tumor is not unified. All of this affects the clinical

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treatment and prognosis for neuroendocrine carcinoma of the colorectum.

This study focusses on the diagnosis and treatment of 49 patients with neuroendocrine carcinoma of the colorectum who were treated at Henan Cancer Hospital, Zhenzhou, China, from January 1995 to January 2013 (colorectal cancer with neuroendocrine differentiation is not included in the study).

Material and Methods

General Material

Among the 49 patients with neuroendocrine carcinoma of the colorectum involved in this study, there were 34 men and 15 women, with a median age of 59 years (ranging from 29 to 83 years). The major clinical manifestations of the 49 patients are as follows: 26 cases with melena or blood in the stool (53.1%), 20 cases with abdominal pain (40.8%), 19 cases with an abdominal mass (38.8%), 16 cases with marasmus (32.7%), eight cases with increased frequency of defecation or diarrhea (16.3%), five cases with fever (10.2%), and three cases with decreased anal exhaust and defecation (6.1%). Endocrine disorder was not found in all the cases. In this study, the experimental protocol and informed consent procedure were in compliance with the Helsinki Convention and were approved by the Institutional Ethics Committee of Henan Cancer Hospital.

Pre-operative Diagnosis

All 49 patients underwent a colonoscopy and biopsy before surgery. Among the patients there were 17 cases (34.7%) diagnosed with neuroendocrine carcinoma in pathology and another 32 cases (65.3%) misdiagnosed as adenocarcinoma or other malignant tumor. The locations of the tumors were: 18 cases in the rectum, 15 cases in the sigmoid colon, two cases in the descending colon, three cases in the splenic flexure of the colon, three cases in the hepatic flexure of the colon, three cases in the ascending colon and five cases in the ileocecus.

Therapeutic Methods

All of the patients in the study underwent surgery according to the principle of malignant tumor treatment without pre-operative chemotherapy or radiotherapy. Twenty-seven cases (55.1%) with tumors confined to the primary positions underwent radical resections. Eighteen cases (36.7%) underwent palliative resections, including 10 cases with distant metastasis, 5 cases with local invasion and 3 cases with extensive retroperitoneal lymph node metastases. Another four cases (8.2%) with extensive implantation metastasis to the peritoneal and pelvic cavity only underwent exploratory laparotomy and biopsy. The 45 cases undergoing radical resections or palliative resections included eight cases of Dixon operations, five cases of Miles operations, three cases of Hartmann operations, 18 left hemicolectomies and 11 right hemicolectomies. There were four cases undergoing combined organ resection, including two cases with combined cauda pancreatis and spleen resection and two cases with combined left ovary resection. All the patients were treated with post-operative adjuvant chemotherapy with a cisplatin plus etoposide regimen.

Follow-up Methods

Post-operative follow-up was accomplished through regular outpatient check-ups, telephone calls and letters. The deadline for completion of the follow-up was January 2014.

Statistical Analysis

This study used the Kaplan-Meier method to conduct the survival analysis and the log-rank test to compare the differences in the survival times. Differences were regarded as statistically significant when $p < 0.05$. SPSS13.0 software (SPSS Inc., Chicago, USA) was used to carry out the data analysis.

Results

Post-operative Pathology Results

Among the samples from the 49 cases, the maximum diameter of the gross tumor specimens was 1.1–12.9 cm (average: 5.2 cm). The 49 cases included 12 cases with protruding tumors, 25 cases with ulcerative tumors and 12 cases with ulcer infiltrative tumors. The tumors were yellowish and their cross sections were homogeneous. The authors referred to a study by Bernick et al. [4] to complete the tumor staging according to American Joint Committee on Cancer (AJCC) standards. The results were 10 stage II cases, 25 stage III cases and 14 stage IV cases. There were 11 cases with tumors infiltrating to the muscular layer (22.4%), 29 cases with tumors invading the serosal layer (59.2%), and 9 cases with tumors infiltrating to adjacent organs (18.4%). The 45 cases that underwent resections included 33 cases with vascular invasion (73.3%) and 35 cases with lymph node

metastasis (77.8%). Among the 49 patients in the study, there were 14 cases with distant metastases (28.6%), which included 9 cases with liver and regional lymph node metastases, 1 case with pulmonary and regional lymph node metastases, and 4 cases with regional lymph node metastases and extensive implantation metastases to the peritoneal and pelvic cavity.

The post-operative specimens were processed for routine hematoxylin-eosin staining. According to the degree of cell differentiation, neuroendocrine carcinoma of the colorectum could be divided into 3 types [5, 6]: Well-differentiated neuroendocrine carcinoma, intermediate neuroendocrine carcinoma, and small-cell neuroendocrine carcinoma. There were 28 cases (57.1%) of well-differentiated neuroendocrine carcinoma whose histological characteristics under a microscope were similar to those of a carcinoid tumor, but with marked cytologic atypia, visible tissue necrosis and vascular invasion. There were 11 cases (22.4%) of intermediate neuroendocrine carcinoma, whose histological characteristics under a microscope included cells that were twice as large as typical small cells with abundant cytoplasm, separations in the periphery and moderate staining. There were 10 cases (20.4%) of small-cell neuroendocrine carcinoma, which was the worst in cell differentiation among the three types. Microscopically, the cells were 12–15 microns in diameter, with a lot of mitotic figures, little cytoplasm, dense cytoplasm staining and obvious abnormalities, all of which was similar to the histological characteristics of small-cell lung cancer.

Immunohistochemical detection showed that there were 36 cases with synaptophysin-positive tumors (73.5%), 23 cases with chromogranin A-positive tumors (46.9%), 43 cases were neuron-specific enolase-positive (87.8%) and 14 cases were CD56--positive (28.6%). Cytoplasms of positive tumor cells were stained claybank and sepia with diffuse granular staining.

Follow-up Results

There were no perioperative deaths and all 49 of the patients in this study were discharged routinely. All the patients received complete follow--up, with a follow-up time of 3–68 months (median: 18 months). The results showed that the 1-year, 3-year and 5-year survival rates of the patients were 49.1%, 17.2% and 6.9% respectively; the average survival time was 18.1 months, and the median survival time was 15 months. A single factor analysis showed that survival time was related to the tumor stage, vascular invasion and the surgery type (radical operations or not) ($p < 0.05$), but not related to age, gender, tumor size or tumor location ($p > 0.05$). Detailed results are presented in Table 1.

Discussion

Neuroendocrine carcinoma can occur in the digestive tract, lungs, pancreas, thyroid, adrenal glands and other organs, but it is most common in the digestive tract [7]. Neuroendocrine carcinoma is a group of tumors ranging from well-differentiated neuroendocrine carcinoma to highly malignant small-cell neuroendocrine carcinoma. However, colorectal cancer with neuroendocrine differentiation should be classified as a form of adenocarcinoma [8]. As a special pathological type, neuroendocrine carcinoma of the colorectum has some clinical and pathological features of its own. The tumors mainly occur in the sigmoid colon and rectum, followed by the cecum, and rarely occur in the transverse colon or descending colon [9]. In this study, the tumor location was mainly in the left colon (20/49) or rectum (18/49), and most patients (79.6%) had regional lymph node metastases and distant metastases at the time of diagnosis. This was basically consistent with the results of other studies [4, 10].

The clinical symptoms of neuroendocrine carcinoma of the colorectum are usually not significantly different from general colorectal tumors [11–13]. In addition to having the same biological characteristics as malignant colorectal tumors, neuroendocrine carcinoma of the colorectum also had the synthesis, storage and secretion function of peptide and/or amine hormones, which could cause symptoms of corresponding endocrine disorders [14, 15]. However, in clinical work obvious symptoms of endocrine disorders could be found in only 1.6% of the patients, most of whom had tumors at an advanced stage [16]. The reasons for that might include: 1) the active substances produced by the tumor were not sufficient to have a significant impact on target organs; 2) the active substances produced by the tumor were quickly degraded in the peripheral blood; 3) the substances secreted by the tumor were probably hormone precursors whose biological activity was lower than that of its end-product; and/or 4) the tumor secreted some substances that could inhibit hormone activity [17]. The signs and symptoms of the 49 patients in this study were similar to those of patients with colorectum adenocarcinoma, but endocrine disorder symptoms were not found in any of the patients in the study.

Although diagnosing colorectal neuroendocrine carcinoma for a surgical decision is often difficult because of a lack of specific clinical symptoms

Table 1. Correlations between clinicopathologic factors and survival time in neuroendocrine carcinoma of the colorectum

Clinicopathologic factors	n	Survival time [($\bar{x}$ ± s) months]	p-value
Age (years)			0.386
≤ 59*	24	17.1 ± 2.8	
> 59	25	20.9 ± 3.7	
Gender			0.237
male	34	16.4 ± 3.5	
female	15	21.5 ± 5.1	
Tumor location			0.271
left hemicolon	20	21.2 ± 4.8	
rectum	18	17.5 ± 3.4	
right hemicolon	11	20.1 ± 3.9	
Tumor size (cm)			0.365
≤ 5.2**	26	21.6 ± 6.1	
> 5.2	23	17.8 ± 3.8	
Tumor stage			0.013
II	10	36.2 ± 11.6	
III	25	18.7 ± 4.6	
IV	14	6.9 ± 1.5	
Surgery type			0.022
radical resection	27	27.5 ± 6.3	
palliative resection	18	12.7 ± 2.2	
biopsy	4	4.6 ± 1.2	
Vascular invasion			0.029
yes	33	13.1 ± 2.7	
no	16	25.3 ± 5.9	

* 59 – the median age; ** 5.2 cm – the average maximum tumor diameter.

[18–20], several approaches have been developed for better diagnostics and/or prognostics. Ultrasound, CT and MRI are the conventional imaging methods for a clinical diagnosis. Serum tumor markers such as CEA, AFP and CA19-9 could be used for an auxiliary diagnosis of neuroendocrine carcinoma of the colorectum. In addition to these conventional serum markers, a serum CgA assay may also be valuable in diagnosing neuroendocrine carcinoma. Research has shown that the level of serum CgA is higher than normal in 81% of patients with neuroendocrine carcinoma, and it has therefore been suggested as a conventional tumor marker [21]. However, caution is required, since the level of serum CgA may also be higher than normal in some cases of benign diseases such as chronic gastritis [22]. For colorectal tumor patients with endocrine symptoms, the hormone corresponding to the patient's symptoms should be monitored, along with its precursors or metabolites; this could play an important role in diagnosis, guiding the treatment and the assessment of tumor growth and recurrence. Furthermore, neuroendocrine carcinoma of the colorectum can be definitively diagnosed by histopathologic examination [23]. The main basis for the diagnosis is a typical pathological morphology and detection of related neuroendocrine markers by the immunohistochemical method [24]. A combinational approach using multiple neuroendocrine markers and detection may help to increase sensitivity and accuracy, and to reduce misdiagnosis.

Surgery is the preferred treatment for neuroendocrine carcinoma of the colorectum [25]. The selection of the operation method depends on the tumor characteristics – its size, location, the depth of invasion, the presence or absence of lymph node and distant metastase, and so on. Comprehensive and detailed exploration is necessary during surgery to exclude metastatic lesions and multicentricity [26]. For tumors whose diameter was less than 1 cm, local endoscopic resection was very suitable [27]. For tumors whose diameter ranged from 1 to 2 cm, local excision or extended local excision could be appropriate, and it is generally necessary to ensure that the length from the incisal margin to the margin of the tumor is more than 3 cm. For tumors larger than 2 cm in diameter, radical resec-

tion is necessary in accordance with adenocarcinoma treatment principles. For tumors smaller than 2 cm in diameter that have invaded the muscular layer radical resection is also necessary. Patients with metastases should undergo radical resection if possible; if radical resection is not possible, cytoreductive surgery should be undertaken [28].

Post-operative adjuvant chemotherapy is an important measure to control and eliminate residual lesions and tiny metastatic lesions [29]. It has been shown that combined cisplatin and etoposide chemotherapy is effective in the treatment of neuroendocrine carcinoma of the colorectum [30–32].

The prognosis for neuroendocrine carcinoma of the colorectum is poor due to its poor differentiation, high invasiveness and early metastases. It is currently considered that the reasons for this are probably associated with the following factors: 1) neuroendocrine cells are derived from immature tumor stem cells; and 2) the cancer cells themselves might secrete some substances promoting the growth, proliferation and metastases of tumor cells. In this study, various degrees of local lymph node metastases and distant metastases were found in 79.6% of patients at the time of their diagnosis. Although all the patients in the study underwent post-operative chemotherapy, the 3-year survival rate was only 17.2%. Even among those undergoing radical resection and post-operative adjuvant chemotherapy, most of the patients died of tumor recurrence or metastases within five years. It has been reported in the literature that the longest survival time in neuroendocrine carcinoma patients was 263.7 months (one patient), and that the average survival time is 10.4 months [33]. The average survival time of patients in this study was 18.1 months; the 1-year, 3-year and 5-year survival rates were 49.1%, 17.2% and 6.9%, respectively. The survival time of patients was related to the tumor stage, vascular invasion and surgery type. Therefore, early diagnosis and treatment are the key to improving patients' survival.

In summary, neuroendocrine carcinoma of the colorectum is a rare, highly malignant tumor with a poor prognosis. Radical surgery plus chemotherapy contribute to improving patients' survival, but the 5-year survival rate is still less than 10%. Therefore, further study is needed to investigate how to achieve early diagnosis and early treatment, and how to choose the best therapeutic regimen.

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