Case Analysis

Neuroendocrine Carcinomas of the Colon and Rectum: Result of a 15-year Experience

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Key Words
Neuroendocrine carcinoma;
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Large cell;
Adjuvant chemotherapy;
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Purpose. The experience of the uncommon malignancy, neuroendocrine carcinomas of the colon and rectum with emphasis on the pathology and clinical characteristics at a single hospital was reviewed.
Methods. Of more than 11,000 colon or rectal cancers removed from July 1992 to June 2007 at Chang Gung Medical Center in Taipei, 11 cases diagnosed as colon or rectal neuroendocrine carcinoma were evaluated. Pathology was reviewed by a single pathologist. Medical records were retrospectively reviewed and patients were analyzed in terms of clinicopathologic and demographic characteristics including neuroendocrine type, tumor location, tumor stage, responses to treatment (operative procedure, chemotherapy or radiotherapy), metastases, and survival.
Results. Five patients had distant metastasis at the time of diagnosis. Palliative chemotherapy or radiotherapy did not seem to offer a modest improvement in survival for these patients, with an overall survival of less than 11 months after diagnosis. Lymph node metastasis was found in 75%, and the distant metastasis in 45% of the 11 patients at the time of diagnosis. Overall survival rates for six-month, one-year, and three-year survival were 73 percent, 45 percent, 20 percent, respectively. These findings are in accordance with other publications, which demonstrate that the neuroendocrine carcinomas behave aggressively and are associated with worse prognosis than that of conventional adenocarcinomas of the same stage. Unexpectedly, improved results were found for two stage IIA and IIIB rectal small cell neuroendocrine carcinoma patients administered with adjuvant chemotherapy treatment with cisplatin and etoposide at our hospital. They were alive without evidence of disease at more than 10 years after treatment.
Conclusions. Neuroendocrine malignancies are rare but behave aggressively in the colon or rectum, accounting for less than 0.1 percent of all colorectal cancers at our institution. Aggressive adjuvant chemotherapy with cisplatin and etoposide might offer a better chance of long-term survival for patients with stage II and III neuroendocrine carcinomas in the colon and rectum, which deserves further investigation.
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Neuroendocrine cells are diffusely distributed throughout the body and are found in the gastrointestinal tract, pancreas, lung, thyroid, adrenal gland, and many other organs. The gastrointestinal tract has the largest component of neuroendocrine cells. In spite of this, neuroendocrine carcinomas of the colon

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and rectum are rare entities. Previous publications demonstrated an incidence of this tumor ranging from 0.1 percent to 3.9 percent of all colorectal malignancies.[1] Either the introduction of more sensitive diagnostic tools (e.g. immunohistochemical stains) or an overall increased awareness among physicians contributes largely to the rising incidence of neuroendocrine carcinomas.[2]

Neuroendocrine tumors of the colon and rectum are divided into two groups: carcinoid tumors with low-grade atypia and malignancy; and endocrine cell carcinomas with high-grade atypia and malignancy.[3] High grade neuroendocrine carcinoma includes both small cell (SCNC) and large cell neuroendocrine carcinoma (LCNC). The neuroendocrine tumor cells are characterized by the presence of neurosecretory granules that can be detected by electron microscopy and by the presence of neurosecretory markers within the cytoplasm. These markers such as neuron-specific enolase (NSE), chromogranin, synaptophysin, and CD56 can be detected with immunohistochemical stains.[4] Carcinoid tumors generally exhibit a more indolent behavior and do not response to cisplatin-based chemotherapy, whereas high-grade neuroendocrine carcinomas behave aggressive but often do response transiently to cisplatin-based chemotherapy.[1]

Compared with adenocarcinomas, patients with neuroendocrine carcinomas have a particularly poorer prognosis with a median survival of less than 1 year as previously reported.[2,5,6] At the time of diagnosis, the majority of tumors have metastasized to the lymph nodes, liver, lung, or other sites. Correct diagnosis is important because it will affect treatment and may better predict the clinical course.[1,4]

The purpose of this study was to review experience with neuroendocrine carcinomas of the colon and rectum at a single institution over a 15-year period, with emphasis on the pathologic and clinical characteristics.

Materials and Methods

Included in this study were a total of more than 11,000 patients diagnosed as colorectal cancer at the Chang Gung Medical Center (CGMC) in Taipei, Taiwan from July 1992 to June 2007. Of these, 8 patients with neuroendocrine carcinomas of the colon and rectum were identified from a prospective colorectal service database at CGMC, while 3 patients with neuroendocrine carcinomas were recovered from the pathology service database at identical institution. A single expert pathologist reviewed the histopathology for all cases.

Hematoxylin and eosin-stained slides were available for review in each case. Carcinoid tumors, atypical carcinoids, adenocarcinomas with carcinoid features (so-called adenocarcinomas tumors), and adenocarcinomas with focal scattered chromogranin-positive or synaptophysin-positive cells were not included in this study.

High-grade neuroendocrine carcinomas were classified into SCNC and LCNC on the basis of histologic and immunohistochemical findings. Such tumor classification of the colon and rectum was introduced by the World Health Organization (WHO) in 2000.[7-9] The SCNC is morphologically identical to small cell carcinoma of lung, characterized by minimal cytoplasm, fusiform cell shape, finely granular chromatin, small or absent nucleoli, and nuclear molding, and corresponds to grade 3 tumors according to Rindi et al.[10] (Fig. 1). Small cell carcinomas typically express neuroendocrine markers (e.g. chromogranin, synaptophysin, NSE, CD56) by immunohistochemistry. LCNC is a malignant neoplasm composed of large cells having organoid, nesting, trabecular, rosette-like and palisading patterns that suggested endocrine differentiation, which can be confirmed by immunohistochemistry and electron microscopy. In contrast to small cell carcinoma, cytoplasm is more abundant, cell shape is round or polygonal, chromatin pattern is coarser, nuclei are more vesicular and nucleoli are prominent[1] (Fig. 2).

The diagnosis of SCNC of the colon and rectum still remained a morphologic diagnosis, not an immunohistochemical one. The diagnosis of LCNC was typically based on a combination of characteristic morphology and NE phenotype as demonstrated by immunohistochemical staining, which showed positive results for one of the four neuroendocrine markers (chromogranin, synaptophysin, NSE, and CD56).

Clinical information and follow-up, where avail-

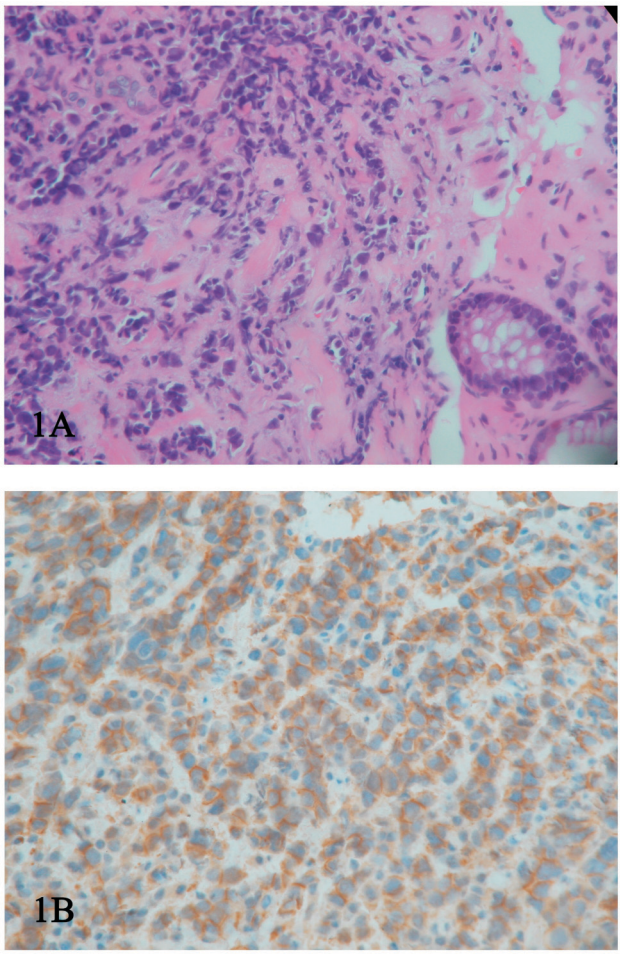

Fig. 1. SCNC of colon. A. Morphology observed by routine H&E staining (original magnification × 200). Scanty cytoplasm, fusiform nuclei with granular chromatin, and no nucleoli are characteristics of the tumor cells. Extensive necrosis indicates the high-grade nature of the tumor. B. Immunohistochemical staining for CD56 (original magnification × 400). The tumor cells reveal a strong positive and diffuse reaction. Demonstration of neuroendocrine differentiation by immunochemistry is not definitely required for the SCNC diagnosis because of its unique morphology.

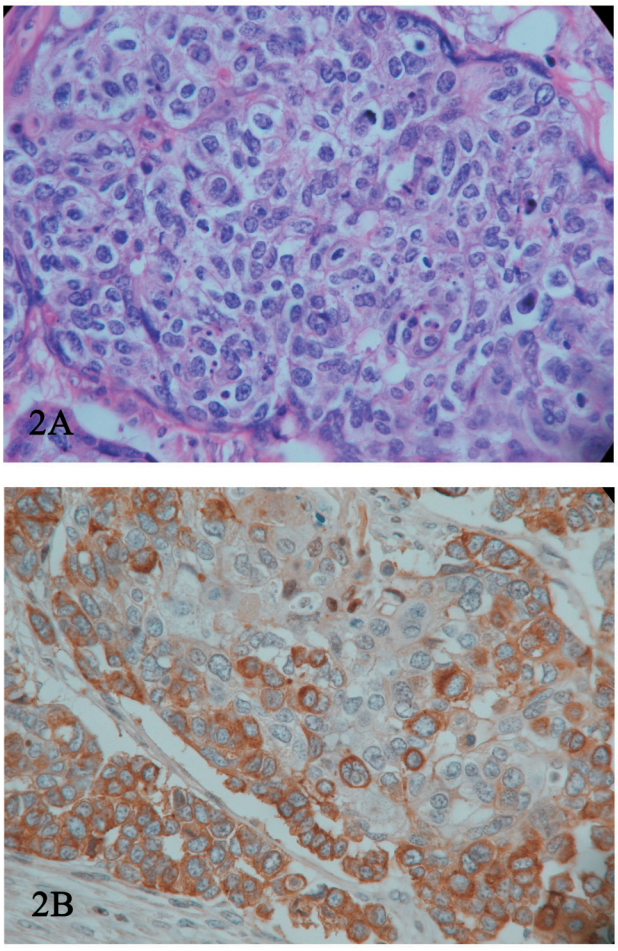

Fig. 2. LCNC of colon. A. Morphology observed by routine H&E staining (original magnification × 400). The nested arrangement of the tumor cells is observed. The tumor cells have more abundant cytoplasm, large and round nuclei, and prominent nucleoli as well. B. Immunohistochemical staining for synaptophysin (original magnification × 400). The tumor cells reveal a strong positive and diffuse reaction, confirming the neuroendocrine differentiation of the tumor. A high mitotic rate reflects the high-grade nature of this tumor.

able, were obtained from review retrospectively of the corresponding hospital records and the referring pathologist. The records of these patients were analyzed for clinical presentation, location and stage of tumor, surgical procedure performed, site of metastases, adjunctive therapy, and clinical outcome. Tumors were staged according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system.[12] Survival time was defined as the time elapsed from the date of the neuroendocrine carcinoma diagnosis until death from all causes, or until April 30, 2008, the date of analysis for the study.

Results

Clinicopathologic features including patient age at diagnosis, gender, histologic subtype, tumor location, tumor stage, treatment (surgery, chemotherapy

and radiotherapy), the distant metastatic site and survival are outlined in Table 1. Patient demographics are shown in Table 2. Two tumors were located in the ascending colon, two in the sigmoid colon, one in the descending colon, five in the rectum, and one case of synchronous lesion in the cecum and sigmoid colon.

The SCNC were diagnosed on the basis of routine hematoxylin and eosin (H&E) staining due to its unique morphology. Immunohistochemical techniques for tumor markers synaptophysin, chromogranin, neuron-specific enolase (NSE), or CD56 were performed to confirm the diagnosis of all LCNC. All cases exhibited the typical histological characteristics of high-grade neuroendocrine carcinoma within at least 50 percent of the tumor, including a densely cellular, solid growth pattern, with cells arranged in nests having minimal intercellular stroma. The nuclear features also suggested neuroendocrine differentiation, with a "stippled or salt-and-pepper" chromatin pattern.

Stages of the tumors at the time of diagnosis were as follows: two AJCC stage II, four stage III, and five stage IV. Distant metastases were noted at the time of diagnosis in nearly half patients (5/11, or 45 percent),

Table 2. Distribution of demographic and clinicopathologic characteristics

Factor	Mean	Range
Age (yr)	54.5	38-73
Male	60.2	41-73
Female	47.8	38-60
	N	%
Gender		
Male	6	55
Female	5	45
Location		
Right colon	2	18
Left colon	3	27
Right and left colon	1	9
Rectum	5	46
Pathology		
SCNC	5	45
LCNC	6	55
Tumor stage at diagnosis		
Stage I	0	0
Stage II	2	18
Stage III	4	36
Stage IV	5	46
Survival		
6 months	8	73
1 year	5	45
3 years	2	20

Table 1. Clinicopathologic features of colorectal neuroendocrine carcinoma

Case	Age (yr) /Gender	NE Type	Location	Stage[a]	Surgery	Chemotherapy	Radiotherapy	Metastases	Survival (mo)
1	60/F	SCNC	Rectum	IIA	APR	CDDP,VP-16[b]	60 Gy, pelvis	None	186, A/NED
2	73/M	SCNC	Rectum	IIIC→IV	LAR	5-FU, LV[b]	30 Gy, brain	None→Brain	14, DOD
3	41/F	SCNC	Rectum	IIIB	LAR, BSO	CDDP,VP-16[b]	None	None	139, A/NED
4	38/F	LCNC	Rectum	IV	S-loop colostomy, Biopsy	None	None	Carcinomatosis	2, DOD
5	44/F	LCNC	Ascend	IV	RH, hepatectomy	Folfox[c]	None	Liver	7, DOD
6	41/M	LCNC	Sigmoid	IIIC→IV	HAR	5-FU, LV[b]	None	None→Liver	7, DOD
7	63/M	SCNC	Ascend	IV	Biopsy	CDDP,VP-16[c]	25 Gy, bone	Lung, Bone	5, DOD
8	65/M	LCNC	Rectum	IV	HAR	Folfiri[c]	None	Liver	3, DOD
9	55/M	LCNC	Descend	IIA→IV	LH	CDDP,VP-16[c]	None	None→Lung	26, DOD
10	56/F	SCNC	Cecum, Sigmoid	IV	Biopsy	CDDP,VP-16[c]	30 Gy, brain	Brain	11, DOD
11	64/M	LCNC	Sigmoid	IIIB	HAR	None[d]	None	None	14, A/NED

SCNC: small cell neuroendocrine carcinoma; LCNC: Large cell neuroendocrine carcinoma; APR: combine abdominoperineal resection; LAR: low anterior resection; HAR: high anterior resection; RH: right hemicolectomy; LH: left hemicolectomy; BSO: bilateral salpingo-oophrectomy; A/NED: alive with no evidence of disease; DOD: dead of disease.

a. Stage groupings according to the AJCC and UICC system for cancer of the colon and rectum., 6th edition.

b. Adjuvant chemotherapy.

c. Palliative chemotherapy.

d. Post operative persist perianal infection, hold adjuvant chemotherapy.

such as liver (cases 5 and 8), brain (case 10), bone and lung metastasis (case 7), and peritoneal carcinomatosis as well (case 4).

The chemotherapeutic regimens included the following: two postoperative adjuvant chemotherapy with the combination of cisplatin (CDDP) and etoposide (VP-16) (cases 1 and 3), and two of 5-FU (5-fluorouracil) and LV (leucovorin) (cases 2 and 6). In addition, three patients underwent palliative chemotherapy with cisplatin and etoposide (cases 7, 9, and 10), one with Folfox (case 5), and one with Folfiri (case 8). Two patients did not receive chemotherapy. One with stage IV rectal cancer with peritoneal carcinomatosis received sigmoid-loop colostomy alone because of the colonic obstruction, and refused further combined chemotherapy/radiotherapy. She was dead of disease two months after operation (case 4). And the other with stage IIIB sigmoid colon cancer with regional lymph node metastasis received no chemotherapy because of persistently postoperative perianal infection and the history of Fournier's gangrene three years ago (case 11).

In addition, four patients received radiation therapy. The dose of adjuvant radiotherapy for case 1 patient submitted to postoperative pelvic irradiation was 60 Gy. However, the side effects from radiotherapy led her to incomplete treatment. Another two patients underwent palliative radiation therapy for brain metastases (30 Gy, cases 2 and 10), and the last received 25 Gy for painful bone metastasis (case 7). All conducted treatment of 11 patients was listed in Table 1.

Most patients with neuroendocrine carcinoma have poor prognosis, thus in this study only 6-month, 1-year, and 3-year survival were taken into consideration. Overall survival rates for six-month, one-year, and three-year survival were 73 percent, 45 percent, 20 percent, respectively (Table 2). Improved results was found for two stage IIA and IIIB rectal small cell neuroendocrine carcinoma patients administered with adjuvant chemotherapy treatment with cisplatin and etoposide at our hospital. They were alive without evidence of disease at more than 10 years after treatment.

Discussion

During the past 15-year period between July 1992 and June 2007, only 11 patients with neuroendocrine carcinomas of the colon and rectum were identified at our institution. In this study, neuroendocrine carcinomas comprise approximately 0.1% of colorectal malignancies that have been treated at CGMC. The possible reasons for the lower incidence than previously reported 0.1-3.9% might be the selection bias of a single hospital as well as the term "large cell neuroendocrine carcinoma (LCNC)" of the colon and rectum appeared to be well-recognized at our institution since 2000 when the WHO Classification of Tumours[7-9] was introduced. This classification is based upon size, proliferative rate, and differentiation, and comprises three subtypes of tumors: well-differentiated endocrine neoplasm (both classified as carcinoid), and two poorly differentiated neuroendocrine neoplasm, SCNC and LCNC. Before this tumor classification system was in place, only carcinoid tumors and SCNC were extensively discussed in the literature.

In 2006, Kobayashi et al.[15] conducted a literature review on neuroendocrine carcinoma of the colon and rectum. The incidence of neuroendocrine carcinoma, rate of lymph node metastasis, rate of distant metastasis at diagnosis, and survival documented in our study and in the literature are summarized in Table 3. The aggressive behavior of SCNC and LCNC has been described in the literature. At the time of diagnosis, clinically, surgically or pathologically detectable metastases were present in most patients. Based on the available literature, the rate of distant metastasis appears to be between 38% and 73%, and the rate of lymph node metastasis ranges from 60% to 87%.[1,2,6,13,14] Moreover, the reported one-year survival rate was between 15% and 46%.[1,2,6,14,16] In this study, we found the distant metastasis rate of 45% and lymph node metastasis rate of 75%. Overall survival rates for six-month, one-year, and three-year survival were 73 percent, 45 percent, 20 percent, respectively. Our findings are in accordance with other publications, which demonstrate that the neuroendocrine carcinomas behave aggressively and are associated with worse prognosis than that of conventional adenocarcinomas of the same stage.[1,2,6,14] Bernick et al.[1] described a highest level of one-year survival rate (46%) relatively similar to our result (45%). A plausible explanation for this favorable prognosis is that

Table 3. Neuroendocrine carcinoma of the colon and rectum in the literature and this study

Author	Year	Frequency in colorectal cancer (%)	No. of cases	Distribution (right colon, left colon, rectum, other)	Rate of lymph node metastasis (%)	Rate of distant metastasis at diagnosis (%)	Survival
Wick et al.[13]	1987	N/A	10	N/A	60	N/A	MS: 5M
Staren et al.[14]	1988	1.9	13	6, 3, 4, 0	62	38	6M SR: 58%, 1Y SR: 33%, 3Y SR: 25%
Gaffey et al.[6]	1990	N/A	24	10, 6, 8, 0	87	73	6M SR: 33%, 1Y SR: 21%, 3Y SR: 8%
Saclarides et al.[2]	1994	3.9	39	19, 11, 9, 0	79	39	6M SR: 58%, 1Y SR: N/A, 3Y SR: 15%
Bernick et al.[1]	2004	0.6	38	N/A	N/A	66	6M SR: N/A, 1Y SR: 46%, 3Y SR: 13%
This study	2008	0.1	11	2, 3, 5, 1	75	45	6M SR: 73%, 1Y SR: 45%, 3Y SR: 20%

N/A: not available; MS: median survival; M: month; Y: year; SR: survival rate.
Modification of Table 1 from *Jpn J Clin Oncol* 2006;36(5):325-328.

chemotherapy treatment contributes to the improvement in survival of patients with colorectal neuroendocrine carcinoma to some extent.

Clinicopathologic features of the stage II and III patients were outlined in Table 4. In our study, several chemotherapeutic regimens such as 5-FU/LV, Folfox, Folfiri, and cisplatin/etoposide have been used as adjuvant or palliative treatment. Postoperative adjuvant chemotherapy was given to 4 of 6 stage II or III patients. One stage IIA patient receiving adjuvant chemotherapy with cisplatin and etoposide remains alive for more than 10 years with no evidence of disease recurrence and distant metastases (case 1). Another stage IIA patient who did not undergo postoperative adjuvant chemotherapy was found to have brain metastasis in around 24 months after the initial diagnosis. Although treated with palliative radiotherapy and cisplatin/etoposide chemotherapy, he died 2 months after beginning therapy (case 9). These two cases emphasize the importance of adjuvant chemotherapy

Table 4. Postoperative adjuvant chemotherapy for stage II and stage III patients

Case	Age (yr) /Gender	NE Type	Location	Stage[a]	Surgery	Chemotherapy	Metastases	Survival (mo), Status
1	60/F	SCNC	Rectum	IIA	APR	CDDP, VP-16	None	186, A/NED
2	73/M	SCNC	Rectum	IIIC→D	LAR	5-FU, LV	None→Brain	14, DOD
3	41/F	SCNC	Rectum	IIIB	LAR, BSO	CDDP, VP-16	None	139, A/NED
6	41/M	LCNC	Sigmoid	IIIC→D	HAR	5-FU, LV	None→Liver	7, DOD
9	55/M	LCNC	Descend	IIA→D	LH	None[b]	None→Lung	26, DOD
11	64/M	LCNC	Sigmoid	IIIB	HAR	None[c]	None	14, A/NED

SCNC: small cell neuroendocrine carcinoma; LCNC: Large cell neuroendocrine carcinoma; APR: combine abdominoperineal resection; LAR: low anterior resection; HAR: high anterior resection; RH: right hemicolectomy; LH: left hemicolectomy; BSO: bilateral salpingo-oophrectomy; A/NED: alive with no evidence of disease; DOD: dead of disease.

a. Stage groupings according to the AJCC and UICC system for cancer of the colon and rectum., 6th edition.

b. Without receiving postoperative adjuvant chemotherapy.

c. Without receiving postoperative adjuvant chemotherapy due to his Fournier's gangrene history and persistently postoperative perianal infection.

treatment on patients with stage II neuroendocrine carcinoma of the colon and rectum. The American Society of Clinical Oncology (ASCO) panel did not recommend the routine administration of adjuvant chemotherapy for stage II colon cancer patients but suggested that it should be considered, particularly for certain high-risk patients.[17] Several considering factors such as tumor differentiation, tumor perforation, number of lymph nodes examined, and T stage are advocated when assessing the likely benefit:risk ratio. There is growing evidence that the prognosis of certain stage II patients with unfavorable prognostic factors can be improved by adjuvant chemotherapy, and increasingly refined tools are now available to define those most likely to benefit.[18] Thus, routine postoperative adjuvant chemotherapy similar to that used in high-risk stage II colon cancer is recommended for patients with stage II neuroendocirne carcinoma of the colon and rectum. Referral of stage II patients for individual assessment is strongly recommended.

Of four stage III patients, three received adjuvant chemotherapy. The two treated with adjuvant 5-FU/LV had distant metastasis (cases 2 and 6), and the one with adjuvant cisplatin/etoposide remains alive for more than 10 years with no evidence of disease recurrence and distant metastases (case 3). This finding suggests, in accord with published results[19] that systemic chemotherapy regimens for colorectal neuroendocrine carcinoma should be similar to those for small cell lung cancer. On the basis of objective responses demonstrated in our patients, the combination of two chemotherapeutic regimens, cisplatin and etoposide, are recommended for stage II and III tumors. However, the role of adjuvant chemotherapy requires further evaluation so that we might better understand the overall treatment effect for patients with neuroendocrine carcinomas of the colon and rectum.

The combination of cisplatin and etoposide has been considered as the reference treatment for poorly-differentiated neuroendocrine tumors.[20] Moertel et al.[21] reported that of 18 patients received palliative chemotherapy with cisplatin and etoposide for metastatic neuroendocrine carcinoma, 9 exhibited partial response and 3 exhibited complete regression. An overall regression rate of 67% was obtained with a median duration of regression of 8 months. In our study, there were two patients underwent palliative chemotherapy with cisplatin and etoposide. One patient achieved a partial response and died within 11 months while the remaining one showed no response and died within 5 months after diagnosis. Thus, palliative chemotherapy with cisplatin and etoposide can be considered as treatment preference for colorectal neuroendocrine carcinoma, particularly if the patient has no other available options.

Previous reports suggest that there are geographic differences in the incidence rates of colorectal neuroendocrine carcinoma, with the predominance of right-sided colon (41.6-48.7%) and rectum (23.7-36.8%).[2,6,14] Moreover, Yasui et al.[22] reviewed the predominant distribution of small cell carcinoma as well, with the disease affecting especially the right-sided colon (47.2%) and rectum (44%). As a result of the small sample size and the selection bias at single institution, our study showed a distinctively predominant distribution (18% in right-sided colon and 46% in rectum) from the publications.

Liver is the commonest site of distant metastasis. In this report, we demonstrated a lower incidence of liver metastasis (37.5%) than that reported in previous studies (53.3-87.5%),[2,6,14,22] possibly due to our limited sample size.

Conclusion

Neuroendocrine malignancies are rare but behave aggressively in the colon or rectum, accounting for less than 0.1 percent of all colorectal cancers at our institution. Limited sample size and inconsistency of treatment in our study make it difficult to generate an exact recommendation regarding the optimal choice of chemotherapeutic regimen. However, aggressive adjuvant chemotherapy with cisplatin and etoposide is still recommended on the basis of objective responses demonstrated in our patients, which might offer a better chance of long-term survival for patients with stage II and III neuroendocrine carcinomas in the colon and rectum.

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病例分析

結直腸神經內分泌癌 — 單一醫學中心之 15 年經驗

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目的 結直腸神經內分泌癌為少見之惡性腫瘤。本研究回顧林口長庚紀念醫院過去治療結直腸神經內分泌癌之經驗，並就其臨床與病理特徵進行綜述。

方法 本研究回顧並收集林口長庚紀念醫院之結直腸癌及病理學資料庫於 1992 至 2007 年間，經診斷罹患結直腸癌之 11,000 餘名病患中，病理診斷結果為結直腸神經內分泌癌者共 11 例。11 例病患之病理檢查結果皆由同一位病理科醫師加以重新檢閱。另回顧分析上述病患之個別醫療紀錄，並就其臨床病理及人口統計學特徵，如神經內分泌之病理分類、腫瘤位置、腫瘤期別、治療 (手術方式、化學治療或放射線治療) 成效、轉移情形，以及存活率等進行分析。

結果 5 例病患於初次診斷時即發現有遠處轉移的情形，緩和性放射線治療或化學治療對於上述病患之存活率似無法提供適當之改善，整體存活率自診斷日起算不到 11 個月。11 名病患之初次診斷結果顯示其中 75% 有淋巴結轉移，45% 有遠處轉移，整體之六個月、一年與三年之存活率依序約為 73%、45% 以及 20%。上述結果與前人文獻相符，即相較於常見之同期腺癌，結直腸神經內分泌癌之侵襲性更強，預後亦較差。然而，兩名 IIA 與 IIIB 期直腸小細胞神經內分泌癌病患在接受 cisplatin 合併 etoposide 之輔助性化學治療後，其存活率有正面且具積極意義的初步結果，治療後存活期達 10 年以上，且期間無疾病再發或轉移的情形。

結論 結直腸神經內分泌癌為一罕見但具侵襲性之疾病，占本院收治所有結直腸癌病例的 0.1% 以下。積極給予 II 期與 III 期結直腸神經內分泌癌患者進行 cisplatin 合併 etoposide 之輔助性化學治療，可能有助提高病患之存活率，此值得未來進一步研究。

關鍵詞 神經內分泌癌、小細胞、大細胞、輔助性化學治療、結腸與直腸。