Original Article

Prognosis of the Neuroendocrine Tumors of the Colon and Rectum with Lymph Node Metastasis after Surgical Treatment with or without Adjuvant Therapy

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Key Words
Neuroendocrine tumors of the colon and rectum;
Lymph node metastasis;
Adjuvant therapy

Purpose. Neuroendocrine tumor (NET) of the colon and rectumis rare and is different from the way of treatment of the so-called colorectal cancer. The treatment of the NET of the colon and rectum is mainly based on the endoscopic or surgical resection. However, the adjuvant therapy beyond the resection to the advanced disease is still not standardizedand there is little evidence discussion about it. Theaim of the study is to review the outcome of the advanced neuroendocrine tumor of the colon and rectum with or without adjuvant therapy in two medical centers in Taiwan.
Methods. From 1995 to 2015, a totalof seventeen patients with NET of the colon and rectum with lymph node metastasis without distant metastasis were enrolled in this case serie. The clinical symptoms, lab data, pathology result and treatment were reviewed and disease survival was obtained for further evaluation.
Results. In 2010, WHO divided the NET into three categories according to the cell proliferation by the pathology. In our case series (NET of the colon and rectum with lymph node metastasis, TMN stage IIIb), the disease survival is correlated with the WHO 2010 classification ($p < 0.001$). Others factors including T stage, adjuvant therapy, location of the NET have no significance difference between the disease survivals.
Conclusion. NET of the colon and rectum is rare and the prognosis of tumor with lymph node metastasis after surgical treatment depends on the 2010 WHO classification according to the tumor cell differentiation. There is no apparent benefit from adjuvant therapy after surgical treatment with curative intent in our case series. Further case collection and a prospective study are needed to confirm the treatment options of NET of the colon and rectum.
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Neuroendocrine tumors are heterogeneous tumors derived from the cells of the neuroendocrine system. These tumors share the capacity of producing some vasoactive peptides and hormones, which can

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induce the carcinoid syndrome. In the colon and rectum, neuroendocrine tumors can arise from the L cells and are a rare disease in comparison with other colorectal tumors.[1] The prevalence of neuroendocrine tumors in the colon and rectum is 0.9% according to the US Surveillance Epidemiology and End Research program from 1973 to 2007.[2] These tumors share the same symptoms as other colorectal tumors, including abdominal pain, rectal pain, tenesmus, and bleeding or palpable abdominal mass lesions. However, the disease prognosis and staging are different. There are two main staging systems describing the neuroendocrine tumors of the colon and rectum; one is the 2010 WHO guidelines dividing these tumors into three groups based on cell proliferation and the other is the TMN system.[3] The treatment of the neuroendocrine tumorsofthe colon and rectum is mainly based on endoscopy or surgical resection.[4] However, adjuvant therapy beyond the resection to the advanced disease is still not standardized. The aim of the study was to review the outcome of advanced neuroendocrine tumors of the colon and rectum with or without adjuvant therapy at two medical centers in Taiwan.

Materials and Methods

Information on neuroendocrine tumors of the colon and rectum diagnosed at the Linkou Chang Gung Memorial Hospital and Taipei-Veterans General Hospital was prospectively collected since 1995 at CGMH and since 2000 at VGH. Until 2015, a total of one hundred and seventy six patients were recorded in these databases.

We selected patients who were diagnosed with neuroendocrine tumors of the colon and rectum combined with lymph node metastasis. Patients with distant metastasis were excluded from this case series. Seventeen patients were included in this case series and their medical records were retrospectively obtained. All patients were followed up for three to six months after surgery during the first three years and annually thereafter. Digital examination, chest X-ray, abdominopelvic ultrasound, or computed tomography (CT) scan was used. Survival time was defined as the time elapsed from the date of diagnosis of the neuroendocrine tumor until death from all causes or until 3rd February 2015, which was the final date of analysis in this case series.

Statistical analysis

The statistical endpoint of the analysis was overall survival from the date of the diagnosis. The group distributions for each clinicopathologic trait were compared using the chi-square test. Data are expressed as mean ± standard deviation. Kaplan-Meier survival curves were plotted and compared using the log-rank test. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 16.0 software.

Results

A total of seventeen patients were enrolled in this study. Table 1 shows the characteristics of our study population. The study population comprised twelve men (71%) and five women (29%). The mean age at diagnosis was 56 ± 16.7 years (range: 29-82 years; median: 50 years). There were eleven patients with lesion of the rectum (65%), one patient with lesion of the hepatic flexure (6%), two patients with lesion of the ascending colon (12%), two patients with lesion of the sigmoid colon (12%), and one patient with lesion of the descending colon (6%). Six of these patients suffered from changing bowel habits (35%), five suffered from abdominal or anal pain (29.4%), and four suffered from bloody stool passage (23.5%).

According to the 2010 WHO guidelines, our study population of neuroendocrine tumors with lymph node metastasis in the colon and rectum was composed of eight grade 1 (G1) tumors (47%), four grade 2 (G2) tumor (23.5%), and five grade 3 (G3) tumors (29.5%). The mean overall survival was 70.9 months in the G1 group and 59.7 months in the G2 group, which were statistically significant compared with overall survival in the G3 group (22.5 months, Fig. 1, $p < 0.001$). The mean overall survival was 59.8 months (95% confi-

dence interval: 42.2-77.4 months) in our study population.

All patients included in this case series showeda tumor size larger than 2 cm. There were eight patients (47.1%) who presented with a T2 lesion, five patients (29.4%) with a T3 lesion, and four patients (23.5%) with a T4 lesion. The mean overall survival in the T2 group was 66.8 months, which was better than that in the T3 (52.7 months) and T4 (40.3 months) groups. However, there was no statistically significant difference between each group ($p = 0.6$).

Among these seventeen patients, sixteen received surgical treatment with curative intent. Only one of the patients received exploratory laparotomy for tumor resection and an unresectable tumor was found during the operation. Palliative colostomy was then performed during the operation. Seven of these patients received adjuvant chemotherapy or hormone therapy. Chemotherapy regimens were mostly based on the drugs of etoposide and cisplatin. For patients who received the adjuvant chemotherapy or hormone therapy, the mean overall survival was 67.6 months. Compared with the patients who did not receive further adjuvant therapy, the mean overall survival was 45.3 months and showed no statistically significant difference ($p = 0.21$, Fig. 2).

As shown in Table 1, neuroendocrine tumors were more likely to be found at the rectum (n = 11, 64.7%) than at the colon (n = 6, 35.3%). The mean overall sur-

Table 1. The clinical data, pathology, treatment, staging and survival in this case series

Case No.	Age	Gender	Tumor location	Pathology	Surgical treatment	Stage	Chemotherapy/ hormone therapy	Survival status	Survival (months)
1	48	Female	Rectum	Carcinoid, G1	LAR	pT3N1M0		Alive	17
2	40	Male	Rectum	Carcinoid, G1	LAR	pT3N1M0	5FU	Dead	68
3	77	Male	Rectum	Carcinoid, G1	LAR	pT4N1M0		Dead	97
4	79	Female	Ascending colon	Large cell neuroendocrine carcinoma, G3	RH	pT3N1M0	Etoposide+ cisplatin	Dead	22
5	65	Male	Rectum	Large cell neuroendocrine carcinoma, G3	APR	pT2N1M0	Etoposide+ FOLFOX	Dead	10
6	55	Male	Sigmoid colon	Neuroendocrine carcinoma, G3	AR	pT4N1M0	5FU	Dead	7
7	65	Male	Sigmoid colon	Large cell neuroendocrine carcinoma, G3	AR	pT3N1M0		Dead	27
8	46	Male	Rectum	Neuroendocrine tumor, G2	LAR	pT2N1M0		Alive	34
9	49	Female	Ascending colon	Carcinoid tumor, G1	RH	pT3N1M0		Alive	42
10	50	Male	Descending colon	Large cell neuroendocrine carcinoma, G3	AR	pT4N1M0	FOLFIRI+ Etoposide+ Cisplatin	Alive	9
11	76	Male	Rectum	Carcinoid, G2	LAR	pT2N1M0		Dead	85
12	51	Male	Hepatic flexure	Carcinoid, G1	RH	pT2N1M0		Dead	72
13	82	Male	Rectum	Carcinoid, G2	Colostomy	cT4N1M0		Dead	30
14	32	Female	Rectum	Carcinoid, G1	LAR	pT2N1M0		Alive	78
15	29	Female	Rectum	Carcinoid, G1	LAR	pT2N1M0	Etoposide+ Cisplatin	Alive	83
16	76	Male	Rectum	Carcinoid, G1	LAR	pT2N1M0		Dead	34
17	48	Male	Rectum	Carcinoid, G2	LAR	pT2N1M0	Octreotide LAR	alive	60

LAR: low anterior resection; RH: right hemicolectomy; APR: abdominoperineal resection; AR: anterior resection.

vival of those with neuroendocrine tumor arising from the rectum was 68.5 months, which was higher than those with neuroendocrine tumor arising from the colon having a mean overall survival of 41.4 months. However, there was no statistically significant difference between these two groups ($p = 0.083$, Fig. 3).

Discussion

Neuroendocrine tumors (NET) of the colon and rectum are rare and comprise less than 1% of malignancies of the colon and rectum.[5,6] Gould and Chejfec first described the disease in 1978. Several small case series were reported and people are now more familiar with this disease.[7] Evidence has shown the benefit of treatment of NET of the colon and rectum with etoposide and cisplatin. However, a small number of patients were encountered because of the rarity of NET.[8,9] Because colon and rectal cancer benefit from adjuvant chemotherapy, it is interesting to show the result of advanced NET of the colon and rectum after surgical treatment with or without adjuvant therapy.[10]

In our case series, males were predominant than females, which corroborates previous case series.[11] None of our patients showed symptoms of carcinoid syndrome, and the most prevalent symptoms noted were bowel habit changes and abdominal or anal pain. Previous observations have shown similar results, wherein non-specific symptoms were noted in NET of the colon and rectum without the carcinoid syndrome. Reports have shown that carcinoid syndrome was rarely seen in NET of the colon and rectum (less than 5%).[12]

According to the 2010 WHO guidelines, NET was classified into three categories based on tumor cell proliferation: G1, mitotic count < 2 per 10 high-power fields (HPF) and/or Ki67 < 2%; G2, mitotic count 2-20 per 10 HPF and/or Ki67 3%-20%; G3, mitotic

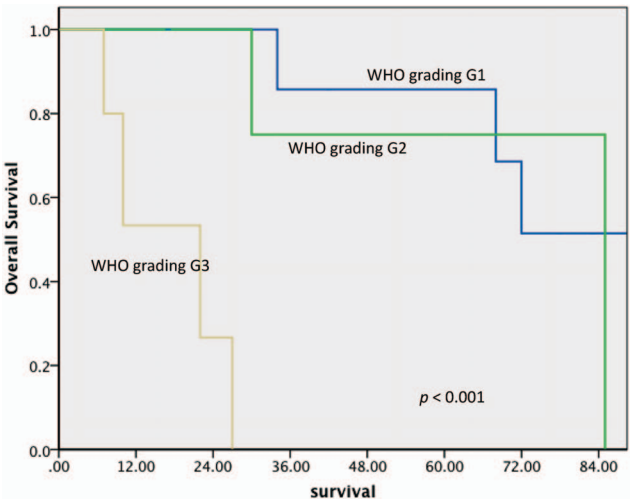

Fig. 1. The overall survival curve between different WHO grading.

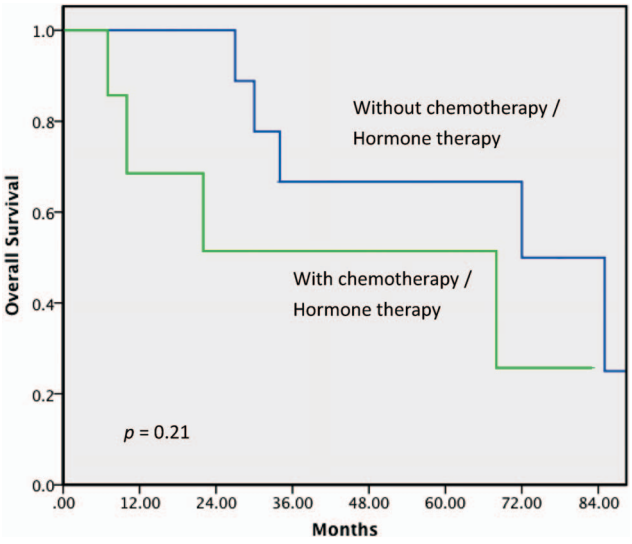

Fig. 2. The overall survival curve between groups with or without chemotherapy or hormone therapy.

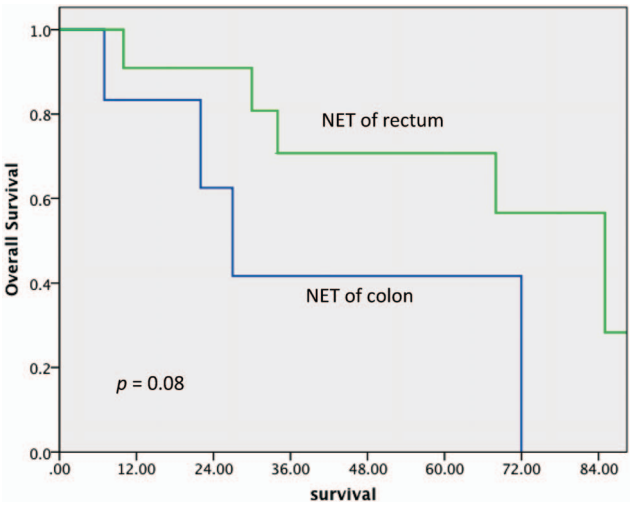

Fig. 3. The overall survival curve between neuroendocrine tumor of the colon and rectum. NET: neuroendocrine tumor.

count > 20 per 10 HPF and/or Ki67 > 20%.[4] In this case series, we included neuroendocrine tumors of the colon and rectum with the presentation of lymph node metastasis without distant metastasis. According to TMN staging, they all belong to stage IIIb. However, different WHO grading was obtained. It is interesting to show that different grading independently indicated different prognosis, even under the same TMN stage (Fig. 1).

Previous studies have shown that the size of the NET of the colon and rectum is related with the risk of lymph node or distant metastasis and further with disease survival. Tumor size larger than 2 cm has a higher rate of lymph node metastasis or more advanced disease in presentation; thus, the European Society of the neuroendocrine tumor suggests that extensive surgical treatment should be performed in such patients.[4,11] In our study, all included patients presented with lymph node metastasis and the tumors were all larger than 2 cm in size. Comparing the different T stages in our series, there was no statistical difference between each of the groups. This revealed that lymph node metastatic status has a superior prognostic effect on tumor invasion or size and they all belong to the same disease stage on the TMN system.

Chemotherapy for NET of the colon and rectum is less effective and there is a lack of robust evidence. In advanced NET of the colon and rectum, chemotherapy is the last choice of treatment.[6,13,14] Reports had showed the treatment regimens of streptozocin, 5-fluorouracil, doxorubicin, capecitabine, temozolomid, cisplain and etoposidein NET, and better response of combined therapy with cisplatin and etoposide was obtained. Reports have shown the response rate of combined cisplatin and etoposide in the treatment of NET of the colon and rectum is between 42%-67%.[14-17] In addition to chemotherapy, recent literature has shown some benefit from the treatment of NET with octerotide.[18] The benefit from octerotide is not only improves the symptoms caused by NET but also improves the disease survival and quality of life.[19] In our case series, data showed better disease survival of the patients who had received the adjuvant therapy. However, this was not statistically significant (Fig. 1). Further case collection for augmented statistical power would clarify the benefits of the treatment.

In our study, we also compared the prognosis of the tumor site over the colon or rectum. The data showed a higher percentage of tumor at the rectum than at the colon, which is compatible with the previous studies.[13,20] It is believed that the tumor of the rectum has an earlier disease stage than that of the colon because the earlier disease symptoms present at the rectum. However, many previous studies have shown that there is no difference in disease prognosis between the sites of the tumor.[13,21] Our study corroborated this finding with respect to disease survival (Fig. 3).

Interestingly, our case series showed a case of NET at the rectum with unresectable tumor, for which palliative colostomy was performed during the operation. Because of old age and poor clinical status of this patient, further adjuvant therapy was not conducted. The disease stage was the same as that for other patients belonging to stage IIIb and the 2010 WHO grading was G2. This patient died 30 months after the diagnosis of the NET, and this indicates that even without treatment, the patient still had a period of time after diagnosis of the advanced NET tumor, wherein the 2010 WHO grading was not G3.

The limitations of the present study are that the number of patients was small because of the rarity of NET of the colon and rectum. Retrospective data review also showed some selective bias within the case series. The indication in the adjuvant therapy group was not clear because of retrospective data collection. Adjuvant therapy regimens were different in the study, and different treatment effects would cause bias in the group with adjuvant therapy. However, this study shows the current treatment results and experience of recent years in Taiwan. Further case collection or a prospective study could enrichinformation about this disease.

Conclusion

NET of the colon and rectum is rare and the prognosis of tumor with lymph node metastasis after surgical treatment depends on the 2010 WHO classifica-

tion according to the tumor cell differentiation. The disease prognosis showed no difference between colon and rectum in our case series. There is no apparent benefit from adjuvant therapy after surgical treatment with curative intent in our case series. Further case collection and a prospective study are needed to confirm the treatment options of NET of the colon and rectum.

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原　著

大腸直腸神經內分泌瘤合併淋巴轉移術後接受輔助性治療的預後

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目的　大腸直腸神經內分泌瘤是很罕見的大腸直腸疾病，而且和傳統上所認知的大腸直腸癌有著不一樣的特性。這種神經內分泌瘤的治療主要都是靠外科手術切除，但若是術後發現有淋巴轉移時，該不該採取輔助性的治療目前還未定論，臨床上的證據也不多。這個研究主要探究大腸直腸神經內分泌瘤合併淋巴轉移在台灣的治療現狀，比較手術後是否有輔助性治療的預後。

方法　從林口長庚和台北榮總兩家醫學中心 1995 年到 2015 年間，大腸直腸神經內分泌瘤合併淋巴轉移接受手術治療的案例一共是 17 人。回朔性地回顧這些病人的臨床症狀，病理切片，治療方針和癒後，將資料統計分析並比較其中的差異並加以呈現。

結果　世界衛生組織 (WHO) 在 2010 年將大腸直腸的神經內分泌瘤依據病理的細胞分化區分成三種程度。統計發現這 17 人的預後 (大腸直腸神經內分泌瘤合併淋巴轉移經手術治療後) 和 WHO 的分類是有相關性的 ($p < 0.001$)。而其他的因素像是這些病人腫瘤的大小和侵犯程度，術後是否接受輔助性治療，來自大腸或是直腸的內分泌瘤，都不會影響這些病人疾病的預後。

結論　大腸直腸的內分泌瘤是很少見的大腸直腸腫瘤，在這個研究案例中，這些腫瘤如果合併有淋巴轉移，在接受手術切除後其預後和 WHO 的腫瘤分類是有統計上的相關性的。而手術後儘管發現有淋巴的轉移，術後有沒有接受輔助性治療並不會影響疾病的預後。然而這個結論仍需更進一步的案例收集和前瞻性的研究來加以確認。

關鍵詞　大腸直腸的內分泌瘤、淋巴轉移、輔助性治療。