Original Article

Treatment Outcome of Colorectal Neuroendocrine Tumor

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Key Words
Colon;
Rectum;
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Surgery

Background. Neuroendocrine tumors, previously known as carcinoid tumors, are the second most common malignancy in the colon and rectum. Their incidence is gradually increasing due to progressively advanced screening tools and spreading awareness of the detection of adenocarcinomas. Neuroendocrine tumors are classified according to their behavior as low (well-differentiated) and high (poorly-differentiated) grade. We analyzed the treatment outcome of colorectal neuroendocrine tumor.

Methods. We retrospectively reviewed 60 patients who were diagnosed with colorectal neuroendocrine tumor between May 2005 and December 2014. The distribution of the tumor location was evaluated. For smaller tumors (< 2 cm), we compared the complete resection rate, complication rate, and oncologic outcome between transanal tumor resection and endoscopic submucosal dissection. For larger tumors (> 2 cm) or advanced disease, we analyzed the surgical morbidity, mortality, and overall survival rates as compared to nonsurgery patients.

Results. Out of 60 colorectal neuroendocrine tumor patients, 10 were excluded due to incomplete information or loss of follow-up. A total of 19 patients underwent endoscopic resection and 11 underwent transanal excision of the tumor. There was no significant difference in the complete resection rate between the endoscopic and transanal groups. None of those patients had recurrent tumor during follow-up. Among 11 patients who underwent radical colectomy and lymph node dissection, 4 had distant metastasis initially and 2 (50%) died within 1 year. Of the other 7 patients without distant metastasis initially, 4 (57%) eventually had distant metastasis but only 1 (14%) died within 1 year. Of 9 patients who didnot undergo surgical treatment (all 9 had initial liver metastasis), 5 (56%) died within 1 year. There was no significant difference in overall survival between the surgery and nonsurgery groups among patients with distant metastasis.

Conclusion. Small colorectal neuroendocrine tumors have a good prognosis, with no significant difference in outcome when treated by colonoscopic removal or transanal resection. For larger or high grade neuroendocrine tumors, radical surgery provided acceptable survival despite having a high risk of distant metastasis. For patients with initial stage IV disease, the 1-year survival rate was relatively low and there was no difference in outcome between the surgery and nonsurgery groups.

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Colorectal neuroendocrine tumors (NETs) are a subgroup of gastroenteropancreatic neuroendocrine tumors. They are a fairly rare disease and are derived from the diffuse neuroendocrine system of the gastrointestinal tract.[1] In 1907, Siegfried Oberndorfer reported a series of 6 cases with benign tumorlets in the small intestine and proposed the term "carcinoid."[2] After decades of research and modification, those carcinoids were renamed as NETs. According to cell differentiation, NETs are divided into three groups (low, intermediate, and high grade), which are synonymous to the classification of the European Neuroendocrine Tumor Society (ENETS) and World Health Organization (WHO) of neuroendocrine tumor grades 1 (G1) and 2 (G2), and neuroendocrine carcinoma (NEC) grade 3 (G3). In 2010, the American Joint Cancer Commission published a tumor, nodes, and metastasis (TNM) classification system for colorectal NETs.[3] The incidence of colorectal NETs is increasing and many of them are discovered incidentally by screening colonoscopy. However, the prognosis of colorectal NETs varies with different location, grade, and stage. Small NETs can be treated by endoscopy and usually have good prognoses.[4] Large or high grade NECs appear to have relatively poor prognoses, requiring more aggressive treatment, including intestinal resection and lymph node dissection. The role of surgery remained controversial because some studies declared that surgery may not offer a survival benefit for the majority of patients.[5] The aim of this study was to analyze the treatment outcome of low grade colorectal NETs and high grade NECs in our institution and provide information to adjust surgical strategy.

Methods

From May 2005 to December 2014, patients who were diagnosed with colorectal NETs were collected retrospectively through the medical record database of National Taiwan University Hospital. The inclusion criteria were pathologically proven neuroendocrine tumor, primary tumor located in the colon and rectum, and regular clinical follow-up. The exclusion criteria were suspicious disease without tissue proof, simultaneous diagnosis of NET and any other cancer, and loss to follow-up. Medical information, including age, sex, past history, initial presentation, pretreatment diagnosis, and pretreatment biopsy results, was collected. Endoscopic treatment included endoscopic biopsy and endoscopic submucosal dissection (ESD). Surgical treatment included transanal tumor excision, transanal minimally invasive surgery (TAMIS), and radical colorectal resection with lymph node dissection. For locally advanced NETs, debulking surgery was performed to achieve R0–1 resection. Tumors spreading to the liver were treated with radiofrequency ablation or transarterial chemoembolization. Other nonsurgical treatments included chemotherapy and target therapy. ESD of NETs was performed by specialists in gastroenterology. Transanal tumor excision, TAMIS, and radical surgery were performed by colorectal surgeons. Chemotherapy and target therapy were arranged by oncologists. The tumor location, operation time, hospitalization days, complications, and follow-up period were also recorded. All tumors obtained through biopsy or resection were sent for pathologic analysis. The tumor size, TNM stage [American Joint Committee on Cancer (AJCC)], and resection margin status were recorded. The grading of NET was assessed by WHO classification according to the tumor mitotic count and Ki-67 ratio. For small tumors (< 2 cm), we compared the complete resection rate, complication rate, and oncologic outcome between transanal tumor resection and endoscopic submucosal dissection. Patients with metastatic NETs underwent colonoscopy to identifythe primary tumor. For relatively larger tumors (> 2 cm) or advanced disease, we analyzed and compared the surgical morbidity, mortality, and overall survival between the surgery and nonsurgery groups. The overall survival was compared using the log rank test and describedusing the Kaplan-Meier curves.

Results

From May 2005 to December 2014, 60 patients were diagnosed with colorectal NET in National Taiwan University Hospital. In total, 10 patients were

excluded according to the inclusion and exclusion criteria. The diagnosis was proven by a pathologist from either a tumor biopsy or resection. The mean age at the time of diagnosis was 54.1. There were 33 men and 17 women. The mean follow-up period was 22.2 months. Ten patients presented with tarry stool or positive stool occult blood tests, and colorectal NETs were found by colonoscopy. A total of 21 patients had colorectal NET during health exams and 19 underwent colonoscopy or surgery due to various symptoms (Table 1). Of the primary tumors, 38 (76%) were located in the rectum. Among all tumors, 36 (72%) were Grade 1, 3 (6%) were Grade 2, and 11 (22%) were Grade 3. For AJCC stage, stages I (56%) and IV (30%) constituted the majority of the disease. All patients were divided into four groups: endoscopic resection, transanal resection, radical surgery, and non-surgery (Fig. 1).

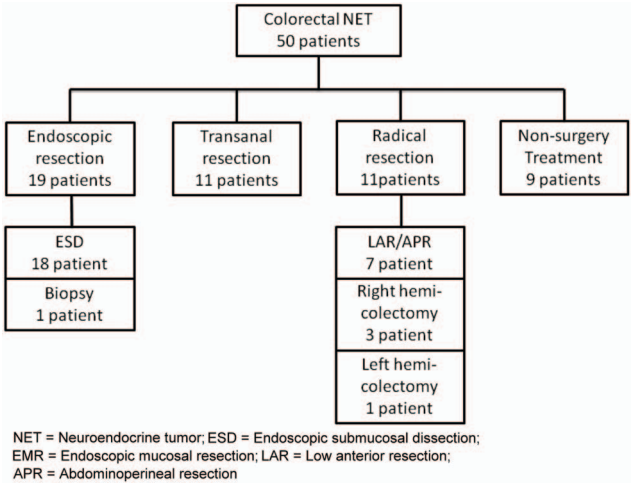

Fig. 1. Algorithm for the treatment of colorectal neuroendocrine tumor (NET).

Table1. Patient's demographic information

	Endoscopic resection (n = 19)	Transanal resection (n = 11)	Radical surgery (n = 11)	Non-surgery (n = 9)	Total (n = 50)
Age (years)	48.6	53.5	56	64.3	54.1
Sex					
Male	14	7	7	5	33
Female	5	4	4	4	17
Symptom					
Health exam	12	7	2	0	21
Bloody stool	7	2	1	0	10
Habit change	0	2	4	1	7
Abdominal pain	0	0	4	4	8
Liver mass	0	0	0	4	4
Tumor size (mm)	7.61	10.45	38.10	N/A	16.33
Tumor location					
Rectum	16	11	6	5	38
Sigmoid	3	0	2	2	7
Descending	0	0	0	0	0
Transverse	0	0	2	0	2
Ascending	0	0	1	1	2
Unknown	0	0	0	1	1
Tumor grade					
G1	19	11	4	2	36
G2	0	0	2	1	3
G3	0	0	5	6	11
AJCC stage					
I	18	10	0	0	28
II	1	1	2	0	4
III	0	0	5	0	3
IV	0	0	4	9	15
Follow-up (months)	18.8	20.2	35.7	18.8	22.2

Endoscopic resection versus transanal resection groups

A total of 19 patients underwent endoscopic treatment by enterologists: 18 (94.7%) underwent ESD and 1 (5.3%) underwent endoscopic excision biopsy (Table 2). There were no complications in 18 (94%) patients, and only one had bleeding and perforation during the procedure, which was resolved by endoscopic hemoclip deployment. The mean procedure time was 31.1 min. The mean hospital stay was 3.4 days. A total of 13 (68.4%) patients underwent complete resection according to the pathology report. Six (31.6%) patients had positive margins: 5 with focal tumor cell involvement and 1 with deep margin involvement.

Transanal resection was performed by colorectal surgeons in 11 patients. The mean procedure time was 24.3 min. The mean hospital stay was 3.5 days. No patient had postoperative complications. Seven (63.6%) patients had complete resection according to the pathology report. Four (36.4%) patients had positive margins: 2 with focal tumor cell involvement and 2 with deep margin involvement.

There was no significant difference between the endoscopic and transanal treatment groups regarding the length of hospital stay, complication rate, and complete resection rate. The operation time was longer in the endoscopic resection group, but did not reach statistical difference. No local recurrence was found in both groups during follow-up.

Table 2. Endoscopic versus transanal

	Endoscopic resection (n = 19)	Transanal resection (n = 11)	p value
Operative time (min)	31.1	24.3	NS
Hospitalization (day)	3.4	3.5	NS
Complication			
Nil	18 (94%)	11 (100%)	NS
Bleeding	0	0	
Perforation	1	0	
Resection margin			
Complete	13 (68.4%)	7 (63.6%)	NS
Focally involved	5	2	
Deep margin involved	1	2	
Follow-up (months)	18.8	20.2	NS
Local recurrence	0	0	NS

Radical surgery group

Radical colectomy and lymph node dissection were performed in 11 patients, all of whom had undergone colonoscopy preoperatively confirming that endoscopic resection was not feasible. The average tumor size was 38.1 mm, which is significantly larger than those resected endoscopically or transanally. Low anterior resection (LAR) and abdominoperineal resection (APR) constituted the majority of the surgical procedures (Table 3). Seven (63.6%) patients underwent LAR/APR, 3 (27.3%) underwent right hemicolectomy, and 1 (14.3%) underwent left hemicolectomy. The average operation time was 299.2 min, and the average hospital stay was 20.1 days. Two patients had anastomotic leakage after LAR surgery and 1 of them died of sepsis. Urine retention occurred in 1 patient after robotic APR and resolved after conservative treatment. The overall complication rate was 27.3% and the surgical mortality rate was 9.1%.

Radical surgery group versus nonsurgery group

Among 11 patients who underwent radical colectomy, 7 had no evidence of distant metastasis initially. Postoperatively, 4 (57.1%) of 7 patients had distant metastasis but only 1 (14%) died within 1 year. The liver, bone, and lung were the major sites of metastasis. Of 4 patients who had liver metastasis preoperatively, 2 (50%) died within 1 year. Two (18.2%) of the 11 patients had local recurrence postoperatively.

All patients in the nonsurgery group had liver tumors initially, followed by pathologic confirmation of neuroendocrine carcinoma via colonoscopy or liver biopsy. Thus, they did not undergo surgical treatment. Among them, 5 (56%) patients died within 1 year.

The mean follow-up time in the surgery group was 35.7 months, which is longer than that in the nonsurgery group (18.8 months). For analysis, the surgery group was further divided into two subgroups: local-

ized and metastatic disease. The overall survival of the two subgroups and the nonsurgery group are illustrated in Fig. 2. There was no significant difference in the surgical outcome between patients with localized and metastatic disease ($p = 0.299$). Meanwhile, among the patients with initial stage IV disease,the overall survival showed no statistically significant difference between the surgery and nonsurgery groups ($p = 0.394$).

Table 3. Radical surgery versus nonsurgery

	Radical surgery ($n = 11$)	Nonsurgery ($n = 9$)
Operation method		
LAR/APR	7	0
Left hemicolectomy	1	0
Right hemicolectomy	3	0
Endoscopic biopsy	0	6
Endoscopic EMR	0	2
Nil	0	1
Operative time (min)	299.2	N/A
Hospitalization (day)	20.1	N/A
Complication		
Anastomosis leakage	2	N/A
Urine retention	1	N/A
Nil	8	N/A
Initial disease		
Localized	7	0
Metastatic (liver)	4	9
Late metastasis		
Liver	1	N/A
Bone	1	N/A
Liver + Bone	1	N/A
Liver + Bone + Lung	1	N/A
Local recurrence		
Yes	2	N/A
No	9	N/A
Treatment of liver metastasis		
TAE	1	2
RFA	3	1
R/T	0	1
None	3	5
Chemotherapy		
Yes	5	5
No	6	4
Follow-up (months)	35.7	18.8
Localized	36.9	N/A
Metastatic	33.8	18.8

Discussion

The incidence of colorectal NETs has increased in recent years because of the popularization of colonoscopy. In the 2004 Surveillance, Epidemiology, and End Results (SEER) database, the incidence of rectal carcinoid tumors was approximately 0.2 per 100,000 in 1973, compared to 0.86 per 100,000 in 2004.[6] There also was a higher rate of NETs in blacks and Asians compared to Caucasians according to the SEER database.[7] However, few reports collected such data from Asian countries. In the 2012 Taiwan Cancer Registry Annual Report (TCRAR), the incidence of colorectal NETs was 1.48 per 100,000 in Taiwan; rectal NETs (1.16 per 100,000) were more common than colonic NETs (0.32 per 100,000). The male-to-female ratio was approximately 1.5:1, consistent with other reportsand our study. Although NETs are the second most common colorectal malignancy, they are far rarer than adenocarcinomas, accounting for only 2.31% of all colorectal malignancies according to the 2012 TCRAR.

Tumor size was related to the potential of distant metastasis and the feasibility of local excision. Soga[8] reported that metastatic rates of rectal NETs were 3.7% in tumors smaller than 5 mm and 13.2% in tumors 5.1 to 10 mm. Among the nonsurgery group in our study, 5 of 9 patients had relatively small lesions

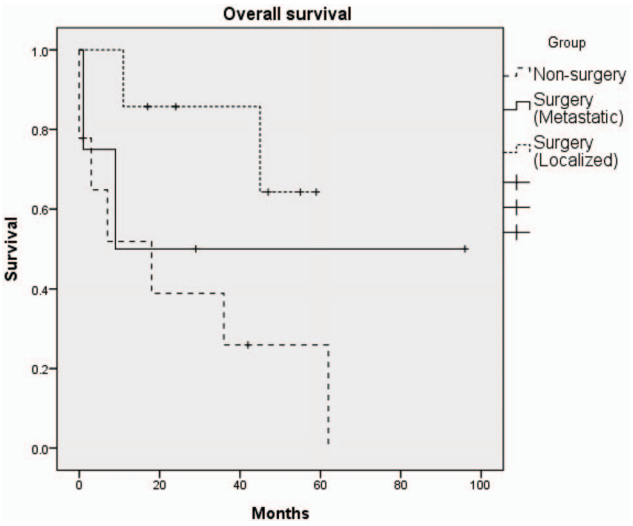

Fig. 2. Kaplan-Meier survival curves for patient with localized/metastatic NET with/without surgery.

during colonoscopy. Notably, one patient had liver metastasis more than 15 years after polypectomy of the primary tumor; furthermore, he survived at least 3 more years after development of liver metastasis. Nevertheless, the North American Neuroendocrine Tumor Society (NANETS) 2010 Consensus Guideline[9] suggested that small tumors (< 1-2 cm) confined to the mucosa or submucosa can be treated with endoscopic resection or transanal excision alone. Other reports claim that minimally invasive techniques are safe treatments for small to medium-sized T1/T2 rectal carcinoids.[10] In our study, the mean tumor size was approximately 7.6 mm in the endoscopic resection group and 10.5 mm in the transanal resection group. Notably, transanal resection sometimes could have a role in rescue treatment in the case of incomplete endoscopic resection. In our record, 3 patients underwent transanal resection during 2009 to 2010 due to positive margins after endoscopic polypectomy or mucosal resection (EMR). Nowadays, the endoscopic technique and tools have advanced and resection areas can be wider, deeper, and safer. Some reports state that ESD is a feasible treatment technique with higher endoscopic complete resection rates and similar safety compared to EMR.[11,12] In the present study, more than 90% of patients underwent ESD in the endoscopic resection group. The management of positive marginsstill is controversial. Although the complete resection rate was only approximately 65.5% to 83% in various studies, the overall recurrence rate was still relatively low, ranging from 0% to 14%.[4,13-15] The complete resection rates of the endoscopic and transanal resection groupsin our study were 68.4% and 63.6%, respectively. However, none of these patients had local recurrence during follow-up. This finding suggested that regular follow-up may be an alternative to further wide excision. Interestingly, among the three patients who underwent transanal wide excision due to positive margins after endoscopic treatment, all specimens showed no residual tumor cell deposit. This might be attributed to electrocoagulation effects, which may compromise the accuracy of histopathologic determination. Many research studies have discussed whether ESD or transanal resection was superior; in our study, the two groups shared similar results. Both methods had their limitations; endoscopic resection had longer operation times and higher technical requirement, whereas transanal resection was not suitable for tumors located far away from the anus.

For tumors larger than 2 cm, it is necessary to perform radical colectomy and lymph node dissection due to the higher risk of muscular invasion and lymph node involvement. Multivariate analysis revealed that lymphatic invasion and tumor sizes over 1 cm were related to lymph node metastasis, whereas venous invasion and tumors larger than 2 cm were related to distant metastasis.[16] According to the AJCC staging system, advanced disease represented poor prognosis. Ryaz Chagpar et al.[17] reported the 5-year overall survival rates for stages I, II, III, and IV to be 90.6%, 83.9%, 64.8%, and 24.9%, respectively. In our study, stages I and IV occurred in 86% of all patients, indicating that most patients either had early or late stage disease. For those with stage III disease who underwent radical colectomy, the outcome was suboptimal and the effect of chemotherapy was questionable. In our study, more than half of the patients with stage III disease had distant metastasis during follow-up. For patients with distant metastasis, the benefits of surgery are yet to be debated because of limited data in the literature. Some studies have reported survival rates as high as 52% to 82%, suggesting that aggressive surgical resection should be considered.[18,19] However, these studies included patients with all gastrointestinal neuroendocrine tumors (including pancreatic endocrine tumor), rather than colorectal NETs alone. Conversely, multivariable analysis from another report showed that metastasis was the only strong factor associated with overall survival, and that resection of the primary tumor may have no benefit for patients with colorectal NETs.[5] Currently, there are few data on the surgical outcome of metastatic colorectal NETs. The overall survival of patients undergoing surgery for local and metastatic disease, and in the nonsurgery group is illustrated in our study. The presence of metastasis did not seem to affect the surgical outcome ($p = 0.299$; Fig. 2). Furthermore, patients who underwent surgery for metastatic disease in the present study may not have a better prognosis comparing to those in the nonsurgery group ($p = 0.394$).

It also should be noted that the tumor progression rates appeared to be inconsistent. The 1-year survival rates for initial metastatic disease were 50% in the surgery group and 56% in the nonsurgery group. According to this study, patients who survived for more than 1 year could live mostly for at least 3 more years. The reason is unclear, probably due to various cell differentiations and activities, and may warrant further investigation.

There were a few limitations in our study. First, this was a retrospective study which may be susceptible to some bias when comparing endoscopic, transanal, radical surgical, and nonsurgery groups. Second, the number of cases in this study was not large due to the relatively low incidence of the disease, requiring further accumulative data. Furthermore, the mean follow-up time was only 22 months, and further follow-up may be required to achieve more accurate recurrence rates.

Conclusion

Small colorectal neuroendocrine tumors have a good prognosis and there was no difference in outcome either by colonoscopic removal or transanal resection. The recurrence rate was low, and close follow-up may be an alternative to further wide excisionfor tumors with positive margins. For larger or high grade neuroendocrine tumors, as well as for adenocarcinomas, radical surgery provided acceptable surgical safety, despite a high risk of distant metastasis. For patients with initial stage IV disease, surgery did not seem to affect overall survival and may not offer benefit for these patients. Patients who survived for more than 1 year could live mostly for at least 3 more years, suggesting that the first year after diagnosis could be the key point for predicting prognosis.

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原　著

大腸直腸神經內分泌瘤之治療與預後

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背景　神經內分泌腫瘤，或稱類癌，為第二常見之大腸直腸惡性腫瘤。由於大腸鏡篩檢之普及，此腫瘤的發生率也隨之提高。根據腫瘤表現可分為低惡性 (低分化) 及高惡性(高分化)。本篇研究之目的為大腸直腸神經內分泌瘤之治療成果及預後分析。

方法　本篇研究收集 2005 年至 2014 年六十位大腸直腸神經內分泌瘤患者進行回溯性研究分析。針對腫瘤直徑較小者 (< 2 公分)，本研究比較由內視鏡切除及經肛門手術切除之完全切除率、併發症發生率及存活率。針對腫瘤直徑較大 (> 2 公分) 或侵犯範圍較大者，本研究比較手術與非手術治療之併發症發生率、死亡率及整體存活率。

結果　六十位大腸直腸神經內分泌瘤患者中，有十位病患因資訊不足或未回診追蹤而排除。十九位病患接受內視鏡切除、十一位病患接受及經肛門手術切除。兩者之完全切除率無明顯差異，且在追蹤過程中並未發現腫瘤復發。十一位病患接受部分大腸切除及廣泛性淋巴廓清手術。四位病患手術前已發現遠端轉移而其中兩位在一年內死亡。七位手術前未發現遠端轉移之病患中有四位在術後追蹤過程中發現遠端轉移，然而僅一位病患在一年內死亡。九位病患接受非手術治療，皆因一開始即發現遠端轉移，其中五位在一年內死亡。在一開始即發現遠端轉移之病患中，手術與非手術在整體存活率無顯著差異。

結論　直徑較小之大腸直腸神經內分泌瘤預後良好，以內視鏡切除及經肛門手術切除知預後無明顯差異。直徑較大或高惡性腫瘤者，手術治療成果佳但仍有相對高風險發生遠端轉移。在一開始即發現遠端轉移之病患中，手術與非手術在整體存活率無顯著差異。

關鍵詞　大腸、直腸、神經內分泌瘤、手術。