Original Article

Neuroendocrine Tumor of the Colon and Rectum: Results of 9-year Single-Institute Experience

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Key Words
Neuroendocrine tumors;
Colon;
Rectum;
Retrospective review

Purpose. To review the experience of a single hospital in treating neuroendocrine tumors (NETs) of the colon and rectum.
Methods. This retrospective chart review evaluated the diagnosis, treatment, and survival of patients with colorectal NET treated by Taipei Medical University Hospital, Taiwan from January 2008 to March 2016. Post-treatment follow-up (through January 2017) was accomplished through regular outpatient check-ups and telephone calls.
Results. Sixty-eight patients were characterized in this study; 38 were treated using endoscopic mucosal resection (EMR), 20 received transanal resection, and 10 had laparoscopic anterior resection (LAR). In the EMR group, majority of tumors were low tumor grade (84.21%), and AJCC pathology stage I/II tumors (100%). Compared with the EMR and transanal groups, the LAR group had higher AJCC stage (70% of patients had stage III/IV AJCC pathology stage). In addition, patients treated with LAR had the largest tumor size (22.4 mm) followed by transanal resection (5.7 mm) and EMR (5.39 mm). Survival rates that were ≥ 90% did not significantly differ across surgical procedure groups ($p = 0.198$).
Conclusions. NETs are rare in the colon or rectum. Results of the present retrospective chart review reveal the main factor affecting NET-bearing patients' survival is early tumor detection and treatment of choice.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2018;29:159-167*]

Tumors of submucosa layer tumors are rare, with an incidence ranging from 0.1% to 3.9% of all colorectal malignancies, and can be divided into two subgroups, gastrointestinal stromal tumors and neuroendocrine tumors (NETs), depending on the origin.[1-3] Neuroendocrine tumors can occur in the digestive tract, lungs, pancreas, thyroid, adrenal glands and other organs but most common in the digestive tract.[4] Colorectal NETs are rare, however, the incidence of colorectal NETs have been increasing and make up 29% of all gastroenteropancreatic tumors.[5] NET of the colon and rectum have unique hormone synthesis and secretory function, resulting in unique clinical and pathological features, with different biological characteristics, degrees of malignancy, pathological features and prognoses.[1,2,6] The tumors mainly occur in the sigmoid colon and rectum, followed by the cecum, and rarely in the transverse colon or descending colon.[1-3]

Compared with adenocarcinomas, patients with neuroendocrine carcinoma have poorer prognosis with a median survival of < 1 year.[7-9] At the time of diagnosis, most tumors have metastasized to other areas of

Received: January 2, 2018. Accepted: August 28, 2018.
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the body. Hence correct early diagnosis is important, it will influence the start of treatment.[10] Treatment of colorectal NET depends upon tumor characteristics and disease severity. Surgery is the preferred approach for patients carrying colorectal NET.[11] The selection of the operation relies on the tumor characteristics. Colorectal NET of low-grade differentiation, lower tumor stage, and tumor size less than 2 cm can be excised using colonoscopy procedures.[12] For high-grade, late tumor stage, and significant differentiated tumors, more aggressive surgical approach are essential.[12]

The aim of this study was to retrospectively review our experience of diagnosing and treating colorectal NET over a nine-year period with emphasis on the pathology and clinical characteristics.

Material and Methods

This retrospective chart review included patients from Taipei Medical University, Taipei, Taiwan who were treated for colorectal NETs from January 2008 to March 2016. Post-treatment follow-up (through January 2017) was accomplished through regular outpatient check-ups and telephone calls. The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the institutional review board of the hospital.

Surgical procedures

Patients with non-metastatic small tumors (< 1 cm) were treated with local excision by endoscopy (EMR: endoscopic mucosal resection). As the study was performed prior to the publication of the NCCN Guidelines (2016), the workup used in the study and described below are the methods used at the hospital prior to these guidelines.

For tumors > 1 cm, imaging study (e.g., magnetic resonance imaging [MRI], computed tomography [CT], or ultra sound) was performed followed by complete colonoscopy examination to clinically stage the tumor. During colonoscopy the examining physician decided if the lesion needed resection, based on experience and clinical tumor morphology and size. If the examining physician judged that the tumor exceeded 1 cm in size or had a morphology indicating malignancy, the physician would send tumor sections (biopsy) for pathological examination, and then select an appropriate type of surgery for resection of the lesion on the basis of laboratory examination and imaging results. The preoperative imaging assessments and postoperative tissue pathology results were presented and discussed with other surgeons at regular tumor discussion conferences within Division of Colorectal Surgery, Taipei Medical University Hospital. Subsequently, either laparoscopic resection (LAR) or transanal resection was used to remove the tumor (see below).

Laparoscopic resection

Laparoscopic resection (i.e., low anterior resection with total mesorectal excision) was used to treat patients with larger tumors (> 2 cm) and those with intermediate tumors (1 to 2 cm) that invaded the muscularispropia. With a 5-trocar approach, the inferior mesenteric vessels were ligated after left ureter identification, followed by retromesenteric dissection using a medial to lateral route. The splenic flexure was then mobilized, followed by laparoscopic total mesorectal excision dissection with preservation of the hypogastric plexus and nerves. For tumors located in the distal rectum, a complete total mesorectal excision was performed laparoscopically after splenic flexure mobilization. The rectum was transected with an endoscopic or conventional stapler through a low abdominal transverse incision at the level of the pelvic floor. A colo-rectal anastomosis was performed. Transanal anastomoses were performed at least 1 cm from the dentate line with an adequate oncological distal margin of 2 cm, using a double-stapling technique and end-to-end anastomosis.

Transanal resection

Tumors that were < 10 cm from the anal verge were resected with a transanal excision. In preparation for surgery, full bowel prep was performed, systemic antibiotics administered, and all anticoagulant use discontinued. The patient was placed in lithotomy posi-

tion for posterior tumors and in prone jackknife position for anterior and lateral tumors. Regional or general anesthesia were utilized to remove the tumor. To aid in visualization, the anus was gently dilated and retracted. The goal of transanal excision is a full-thickness excision of the tumor down to the mesorectal fat with at least 1 cm radial/circumferential margin. Good hemostasis was obtained and the defect in the bowel wall was closed in a transverse manner to avoid narrowing the lumen using interrupted absorbable sutures. For all surgical procedures, tumor specimens underwent pathological assessment of the margins.

Statistical analysis

Continuous variables were presented as mean and standard deviations (SDs); categorical variables were presented as counts and percentages. Patients were grouped into three categories according to the initial treatment (i.e., endoscopic mucosal resection, transanal resection, and laparoscopic resection). Wilcoxon test and Fisher's exact test were used to compare the differences among the three groups. Kaplan-Meier curves and log-rank testing were used to compare the survival rates between the groups. All statistical analyses were performed by SAS version 9.4 (Windows NT version, SAS Institute, Inc., Cary, NC, USA). Two-tailed $p < 0.05$ indicated statistical significance.

Results

A total of 1631 patients were found to have tumor formation at the colorectal region from January 2008 to March 2016 at Taipei Medical University Hospital. The flow chart of inclusion and exclusion is shown in Fig. 1. Of these, 98 patients were diagnosed with NET. Seventy-three patients who underwent colonoscopy and had complete information on clinicopathologic and demographic characteristics, including neuroendocrine type, tumor location, tumor stage, responses to treatment, and survival status were included in the study. Among these 73 patients, 38 had undergone endoscopic mucosal resection (EMR) and 35 had the tumor biopsied with colonoscopy due to the tumor size, location, and formation. Among those 38 patients who received EMR, 28 had pathological report showing clean tumor resection margin, while the other 10 had unclean tumor resection margin. These ten patients' demographic and clinical characteristics are summarized in Supplementary Table 1. Three of them underwent transanal tumor resection operation according to tumor size or location and other seven were lost to follow-up. With regard to the 35 patients receiving biopsies, 20 had underwent transanal resection, 10 had received laparoscopic anterior resection (LAR), four were lost to follow-up, and one did not receive any surgical treatment due to chronic inflammation (Fig. 1). As a result, 68 patients (38 EMR, 20 transanal resection, and 10 LAR) were included in the comparison of patient characteristics.

The average duration from first diagnosis of colorectal cancer with neuroendocrine differentiation to operation was 16.1 days (range, 0-79 days). The follow-up duration was 21.08, 16.40 and 17.30 months for EMR, transanal resection and LAR groups, respectively (Table 1). The age significantly differed across the three groups (46.6 years in EMR group, 48.8 years in transanal resection group, and 55.1 years

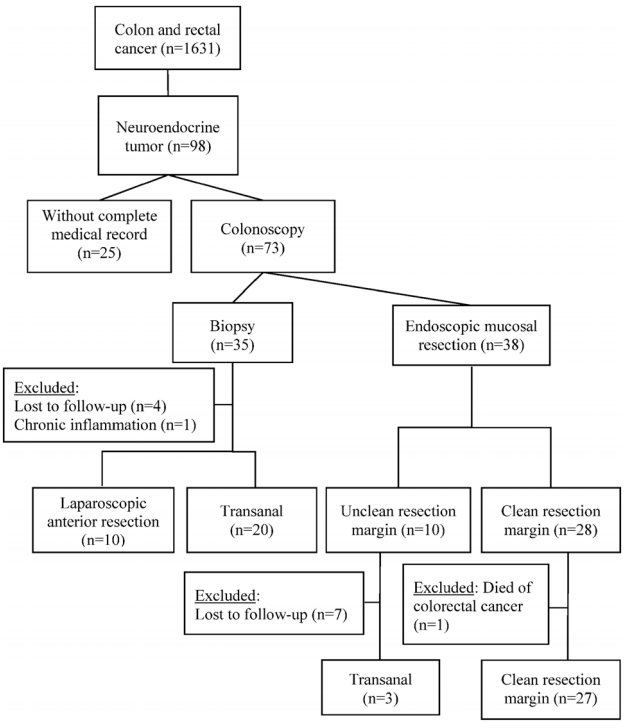

Fig. 1. The flow chart of inclusion and exclusion.

in LAR group; $p = 0.04$). The tumor location was more commonly found in the rectum (n = 58) followed by sigmoid colon (n = 2) and colon (n = 1). The tumor AJCC (American Joint Committee on Cancer) stage differed across groups, AJCC stage III/IV patients were more prevalent in the LAR resection group than in the EMR and Transanal groups (70% and 0%, respectively). Across the groups, the most common tumor grade was G1 (range, 80% to 90%). Patients in the LAR group had larger tumor size than the other two groups (5.39 mm in EMR group, 5.66 mm in transanal resection group, and 22.44 mm in LAR group; $p = 0.004$).

The surgical outcomes of three surgical treatments were summarized in Table 2. Among the 38 patients who received EMR, 10 patients had unclean resection margin and 28 patients had clean resection margin. In contrast, all patients who underwent either transanal resection or LAR had clear resection margin. The average volumes of blood loss for EMR, transanal resec-

Table 1. Baseline characteristic of study population according to initial surgery

	EMR (N = 38)	Transanal resection (N = 20)	LAR (N = 10)	*p*-value
Age (years)	46.66 ± 14.02	48.85 ± 13.68	55.10 ± 6.14	0.04[a]*
Sex				
Male	20 (52.63%)	9 (45%)	4 (40%)	0.80[b]
Female	18 (47.37%)	11 (55%)	6 (60%)	
Tumor size (mm)	5.39 ± 2.38	5.66 ± 2.77	22.44 ± 13.40	0.004[a]*
Tumor location				
Splenic flexure	0 (0%)	0 (0%)	1 (10%)	0.13[b]
Sigmoid colon	1 (2.63%)	0 (0%)	1 (10%)	
Rectosigmoid junction	1 (2.63%)	0 (0%)	0 (0%)	
Rectum	36 (94.74%)	20 (100%)	8 (80%)	
Histology				
Carcinoid tumor	18 (47.36%)	14 (70%)	3 (30%)	0.006[b]*
Neuroendocrine tumor	20 (52.63%)	6 (30%)	7 (70%)	
Tumor grade				
G1	32 (84.21%)	18 (90%)	8 (80%)	0.55[b]
G2	6 (15.79%)	2 (10%)	1 (10%)	
G3	0 (0%)	0 (0%)	1 (10%)	
AJCC stage (pathology)				
I/II	38 (100%)	20 (100%)	3 (30%)	< .0001[b]*
III/IV	0 (0%)	0 (0%)	7 (70%)	
AJCC stage (clinical)				
I/II	38 (100%)	20 (100%)	4 (40%)	0.0002[b]*
III/IV	0 (0%)	0 (0%)	6 (60%)	
Follow-up (month)	21.08 ± 22.12	16.40 ± 18.14	17.30 ± 17.84	0.86[a]

EMR: endoscopic mucosal resection; LAR: laparoscopic anterior resection; AJCC: American Joint Committee on Cancer; Continuous variables were presented as mean and SDs; categorical variables were presented as counts and percentages.
[a] Kruskal-Wallis Test. [b] Fisher's Exact Test; * $p < 0.05$.

Table 2. The surgical outcomes of three surgical treatments

	EMR (n = 38)	Transanal resection (n = 20)	LAR (n = 10)
Resection margin	28 clean/10 unclean	All clean	All clean
Average blood loss	7 ml	5 ml	83.7 ml
Complication	Bleeding (n = 2)	Bleeding (n = 1)	Pneumonia (n = 2)
			Urinary tract infection (n = 1)
Recurrence	Yes (n = 5; 4 clean/1 unclean)	No	No

tion, and LRA were 7 ml (range, 0-50 ml), 5 ml (0-100 ml), and 83.7 ml (5-1500 ml), respectively. Two patients who underwent EMR and one patient who underwent transanal resection had postoperative bleeding. Among the patients who received LRA, two patients had pneumonia and one got urinary tract infection after surgery. Five patients who received EMR (4 with clean margin and 1 with unclear margin) had recurrence. No recurrence was observed in patients who underwent transanal resection or LAR.

Among the ten patients who received EMR and had unclean resection margin, sever patients were lost to follow-up and three underwent a second surgical resection, namely, transanal resection (Fig. 1). Before the end of the study period, these three patients survived and did not have recurrence and complication.

Survival probabilities for each treatment were determined. Ten patients who received EMR and had unclean resection margin were excluded from the survival analysis (Fig. 1). In addition, one patient who received EMR with clean resection margin died of stage IV colorectal cancer with hepatic metastases. Since the cause of death of this patient was not relevant to the surgical outcome of EMR, this patient was excluded from the survival analysis (Fig. 1). Accordingly, a total of 57 patients (27 EMR, 20 transanal resection, and 10 LAR) were included in the survival analysis. The five-year survival rates in EMR, transanal, and LAR groups were 100%, 100% and 90%, respectively; no significant difference was observed ($p = 0.198$; Fig. 2).

Discussion

Over the nine-year period of the current study, 98 patients, out of 1631 with tumor formation at the colorectal region, were identified with colorectal NET. Among them, 73 patients received either EMR, transanal resection, or LAR were included in this study. In this study, the tumors located mainly in the rectum (n = 58) followed by sigmoid colon (n = 2) and colon (n = 1). The majority of tumor grade and AJCC pathology stage in EMR/Transanal groups was low (84.21/90% in G1) and all were I/II stage tumors. Compared with the EMR/transanal groups, the LAR group had not only larger tumor in size but also advanced in AJCC stage (70% in stage III/IV). The complete resection rate of EMR in the present study was 73.6% (28/38), which is comparable to that reported in other studies.[13,14] The five-year survival rate was ≥ 90% across the three groups, which may reflect the fact that most patients are at early stage in disease progression.

Prior publications have reported a 5-year survival rate for colorectal NET of 90.6, 83.9, 64.8, and 24.9% for stage I, II, III, and IV, respectively.[15,16] The 5-year survival rate observed in our study is consistent with these earlier findings as most of the tumors in the current study were stage I/II. Due to the higher mortality associated with stage III and IV tumors, the choice of surgery to treat the disease and the management of tumors 10 to 20 mm in size are still under debate.[17]

Sung and colleagues reported that they successfully resected the NET even when size up to 16 mm via endoscopically.[13] However, one patient in the present study had tumor size 17 mm who was treated with LAR, and later pathological examination indicated lymph node positive. Notably, EMR cannot detect lymph node involvement. For the above particular patient, lymph node involvement was likely to be missed if EMR, but not LAR, was performed according to the NCCN Guidelines (2016). This patient was initially classified as stage I after preoperational tumor survey, but postoperative pathological examination revealed positive lymph node, which changed tumor staging

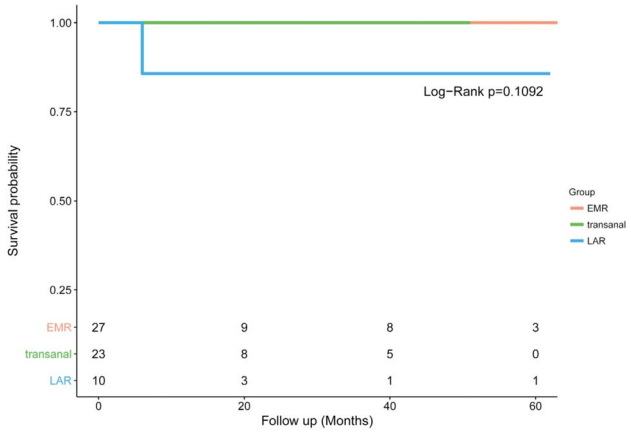

Fig. 2. Survival curve between EMR, LAR and transanal groups. EMR: endoscopic mucosal resection; LAR: laparoscopic anterior resection.

from I to III. Radical surgery was adequate with R0 resection margin to this patient. Based on this case, the EMR might not be enough for larger size tumors especially when the possibility of lymphatic involvement had not been sufficiently ruled out yet. This is agreed with the prior study's propose that endoscopic surgery can be appropriate in well differentiated colorectal NETs with size less than 15 mm only if there is no evidence of lymphovascular involvement or distant metastasis.[13] Regarding this issue, we did have a concern that colonoscopy cannot ensure there is no lymphovascular involvement or distant metastasis, and additional examinations and/or criteria should be specifically illustrated for tumor with size ranging from 10 to 20 mm.

In the beginning, all patients underwent colonoscopy to visualize the size of tumor prior to any surgical treatment. According to the NCCN Guidelines (2012), tumors less than 10 mm could be resected by EMR and tumors larger than 20 mm should be resected by either LAR or transanal resection; however, there was no specific illustration for tumor with size ranging from 1 to 2 cm. Notably, the NCCN Guidelines (2016) recommended that tumors < 2 cm can be also resected by EMR. From 2012 to 2016, for safety concern, tumors with size larger than 1 cm were resected by either LRA or transanal resection at our hospital. Therefore, six stage III/IV patients (with tumor sizes greater than 2 cm or near to 2 cm, eg. 1.7 or 1.8 cm) underwent LAR. Nevertheless, we have followed with the NCCN 2016 Guidelines since it was released. In the present study, three stage I/II patients also underwent LAR because their tumor sizes were greater than 2 cm or exhibited malignancy. We suggested that the NCCN Guidelines should be updated by specifying the treatment recommendation on tumor with size ranging from 1 to 2 cm.

In our study, four patients with stage III tumors who were treated with LAR had no perioperative complication and all survived through the 5-year follow-up. Although the number of patient was small, the survival rate of these three stage III patients is better than that of a prior study which found a 5-year survival rate of 42.9% for NET patients with stage III disease.[19] Two patients in the present study with stage IV tumors also underwent LAR, and one of them died of distal liver metastasis. Prior studies had found that the utilization of more aggressive curative surgery could impact the survival rate.[18] The present findings suggest that aggressive curative surgery like LAR did not substantially affect better survival rate of stage III/IV patients (90%, shown in Fig. 2), although the findings are limited by the small number of patients.

A prior single hospital study examined the treatment and outcomes of eleven patients with stage II to IV NET.[3] All their patients with stage II to III received surgery plus chemotherapy and/or radiation. The patients with stage IV tumor (n = 5) underwent palliative chemotherapy or radiation, which did not appear to offer significant survival improvement, with an overall survival of 11 months.[3] Their study suggested that aggressive adjuvant chemotherapy with cistplatin and etoposide may offer long-term survival benefit for patients with stage II and III NET; patients receiving these treatments were alive 10 years after treatment.[3] These findings and those from our study suggest that in patients with stage III NET may benefit from both aggressive surgical and specific chemotherapy approaches.

Our retrospective study indicates that there was no difference in complete removal rate and tumor recurrence rate between LAR and transanal resection for stage I/II patients, and these patients tend to have outstanding prognosis. On the other hand, if the margin of these tumors was completely removed by EMR, the 5-year survival rate is 100%. Hence, patients who underwent EMR may only be needed to have out-patient follow-up on the regular basis. However, if complete removal was not achieved, additional surgery may be necessary. For example, three patients in the present study who did not have complete removal subsequently underwent transanal excision surgery. In our experience, after colonoscopy the patients with NET greater than 2 cm or having malignant morphology shall be subject to either LAR or transanal excision. Otherwise, the patients will be subject to EMR. In Taipei Medical University Hospital, both LAR and transanal excision achieved similar complete removal rate and tumor recurrence rate.

Although NET is potentially malignant, early detection and suitable resection can lead to good overall survival. In our study, routine colonoscopy provided

good results, as EMR or biopsy can be carried out during a colonoscopy examination depending on the tumor size or appearance. Moreover, if the clean margin after the initial endoscopic mucosal resection is reported, no further treatment is required and only routine outpatient follow up can be sufficient. For patients who initially cannot receive EMR due to tumor overall appearance and size, the colonoscopy is still useful for obtaining a biopsy for next surgical treatment options (transanal resection or LAR).

The study has several limitations, including the patients sample size is not as big as exception, the findings are from a single institution, and this was not a prospective comparative study.

Conclusion

Neuroendocrine tumors are rare but have malignant potential in the colon or rectum. Factors identified that impact survival are tumor stage, vascular invasion, and surgery type.[18] In this study, the main factors affecting survival are early tumor detection, accurate staging, and appropriate treatment. Our findings in conjunction with prior works suggest that the surgical treatment shifting from EMR to LAR give a good survival when tumor size and stage became more advanced. More large-scale studies were warranted to evaluate the best treatments for different stages of NET. Routine and early colonoscopy examination is critical for early tumor detection, thereby initiating early and proper treatment for better overall survival.

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Supplement

Supplementary Table 1. Demographic and clinical characteristics of patients with unclean resection margin

#	Age (age)	Sex	Tumor size (mm)	Tumor location	Histology	Tumor grade	AJCC stage (pathology)	AJCC stage (clinical)	Results
1	37	Male	6	Rectosigmoid junction	Carcinoid tumor	G1	I	I	Lost-to-follow-up
2	32	Female	3	Rectum	Carcinoid tumor	G1	I	I	Lost-to-follow-up
3	26	Male	6	Rectum	Carcinoid tumor	G1	I	I	Lost-to-follow-up
4	55	Female	6	Rectum	Carcinoid tumor	G1	I	I	Transanal resection
5	48	Male	6	Rectum	Carcinoid tumor	G1	I	I	Lost-to-follow-up
6	39	Female	3	Rectum	Neuroendocrine tumor	G1	I	I	Lost-to-follow-up
7	45	Male	4	Rectum	Neuroendocrine tumor	G1	I	I	Lost-to-follow-up
8	55	Female	5	Rectum	Neuroendocrine tumor	G1	I	I	Lost-to-follow-up
9	35	Male	5	Rectum	Neuroendocrine tumor	G1	I	I	Transanal resection
10	31	Female	7	Rectum	Carcinoid tumor	G2	I	I	Transanal resection

原　著

結腸及直腸神經內分泌腫瘤：單一醫療機構九年經驗

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目的　回顧及研究單一醫療機構治療結腸及直腸神經內分泌腫瘤的經驗。

方法　這是一篇回顧性的研究，針對結腸及直腸神經內分泌腫瘤的病人在台北醫學大學附設醫院從西元 2008 年一月到西元 2016 年三月，診斷、治療及預後的病歷分析。治療後的追蹤則是藉由門診及電話訪視，一直持續到西元 2017 年一月。

成果　研究總共納入 68 位病人：其中 38 位接受內視鏡黏膜切除術、20 位接受經肛門腫瘤切除手術、10 位接受腹腔鏡前位切除手術。在內視鏡黏膜切除術組，大部分的腫瘤 (84.21%) 屬於低分化度，美國癌症協會 (AJCC) 癌症分期第一期及第二期 (100%)。比較內視鏡黏膜切除術及經肛門腫瘤切除手術的病人，接受腹腔鏡前位切除手術的病人有較高的美國癌症協會 (AJCC) 癌症分期 (70% 的病人屬於第三期或第四期)。除此之外，接受腹腔鏡前位切除手術的病人，比起其它兩組病人有較大的腫瘤大小 (腹腔鏡前位切除手術腫瘤大小 22.4 mm、經肛門腫瘤切除手術腫瘤大小 5.7 mm、內視鏡黏膜切除術腫瘤大小 5.39 mm)。關於存活率大於 90% 的病人，分析起來跟手術的方式並沒有顯著意義。

結論　神經內分泌腫瘤在結腸和直腸中很少見，這篇回顧性研究的結果顯示，主要影響結腸及直腸神經內分泌腫瘤病人的預後因子為早期發現及治療的選擇。

關鍵詞　神經內分泌腫瘤、內視鏡黏膜切除術、經肛門腫瘤切除手術、腹腔鏡前位切除手術。