

# Early diagnosis and treatment of gastrointestinal neuroendocrine tumors

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**Abstract.** The aim of the present retrospective analysis on the macroscopic appearance and pathological characteristics of gastrointestinal neuroendocrine tumors (NETs) was to investigate methods for their early diagnosis and treatment. A total of 78 patients were divided into submucosal NET and deeper invasion NET groups, according to the depth of tumor invasion exhibited by the patients. The clinicopathological characteristics and survival time of the NET patients were analyzed and compared. The pathological characteristics of the submucosal NETs group were investigated according to the diameter of the tumor ( $\leq 5.0$  mm, 5.1-10.0 mm or  $>10.0$  mm). The depth of invasion at diagnosis was observed to significantly correlate with histopathological classification, diameter of the tumor, macroscopic appearance, growth pattern, lymphatic-vascular involvement, lymph node (LN) metastasis and distant metastasis. In the submucosal NETs group, high-grade tumors with lymphatic or venule invasion and distant metastasis were associated with an increased risk of nodal metastases. In patients with minute tumors ( $\leq 5.0$  mm), no lymphatic-vascular involvement, LN or distant metastasis was observed. By contrast, patients with tumors measuring 5.1-10.0 mm in diameter exhibited high lymphatic-vascular involvement and LN metastasis rates (46.2 and 30.8%, respectively). Survival time was significantly longer in patients with submucosal NETs compared with deeper invasion NETs and in patients with NET G1 and NET G2 compared with NEC. The results of the present study indicate that gastrointestinal submucosal NETs are closely associated with a slightly elevated macroscopic type, low-grade tumors and a small diameter. These features may contribute to early diagnosis of gastrointestinal NETs. Therefore, a tumor diameter of

$<5.0$  mm, with slightly elevated macroscopic appearance may indicate an absolute requirement for endoscopic resection, while tumors measuring 5.1-10.0 mm in diameter must be considered carefully.

## Introduction

Neuroendocrine tumors (NETs) were previously considered extremely rare lesions, which most commonly occur in the gastroenteropancreatic system (1,2). However, over the last 30 years, the incidence and prevalence of gastrointestinal NETs have increased significantly due to increased awareness and widespread use of gastrointestinal endoscopy (3,4). Gastroenteropancreatic NETs, which derive from the neuroendocrine cell system and have widely divergent clinical presentations, are relatively infrequent, constituting  $\sim 2\%$  of all neoplasms, and are typically indolent, slow-growing tumors (5,6). Gastrointestinal NETs are increasing (7); in the USA, the prevalence and the incidence of gastrointestinal NETs have been calculated to be 35/100,000 and 5/100,000, respectively (4), revealing a 7-fold increase in the last 35 years. This phenomenon may partly reflect the increased number of diagnoses of benign and incidentally-identified lesions due to the increased availability of advanced endoscopic and radiological imaging (8-10). The overall 5-year survival rate for patients with gastrointestinal NETs has improved by almost 20% in the past 35 years (1,11,12). Diagnosis of early-stage NETs remains difficult, and the majority of patients exhibit locally advanced disease or distant metastasis at diagnosis (4).

At present, an increasing number of gastrointestinal NETs are diagnosed at an early stage, and thus may be treated with local excision (13). According to the National Comprehensive Cancer Network guidelines and American Joint Committee on Cancer staging of gastrointestinal NETs (14), T1 tumors that are limited to the lamina propria or submucosa and present a diameter of  $<1$  cm (the diameter of colorectal and appendix  $\leq 2$  cm), are considered appropriate for endoscopic resection (15,16). However, previous studies have reported that patients with such tumors have experienced lymphatic-vascular involvement and exhibit the risk of recurrence and metastasis following endoscopic resection (13). In the present study, the clinical and pathological features of 78 gastrointestinal NET patients were analyzed to identify appropriate methods for early diagnosis and treatment of this type of tumors.

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**Key words:** neuroendocrine tumors, gastrointestinal tract, early diagnosis, treatment, endoscopy

## Materials and methods

**Patients.** The medical records of 78 patients with histopathologically diagnosed gastrointestinal NETs that were treated at The Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) between January 2007 and March 2013 were retrospectively analyzed. The patient cohort included 42 (53.8%) male patients and 36 (46.2%) female patients with a mean age at diagnosis of 58 years (range, 15-82 years) (Table I).

Patients were divided into two groups, namely, a submucosal NETs group and a deeper invasion NETs group, according to the depth of tumor invasion. The present study defined submucosal NETs as tumors that were restricted to the lamina propria or submucosal layers, with or without lymph node (LN) and distant organ metastasis. Deeper invasion NETs were defined as tumors that had infiltrated into the muscularis propria or deeper structures, with or without LN and distant organ metastasis. The pathological characteristics of the submucosal NETs group were investigated according to the tumor diameter ( $\leq 5.0$ , 5.1-10.0 or  $> 10.0$  mm). A minute tumor was defined as a tumor of  $\leq 5.0$  mm in diameter.

The submucosal NETs group consisted of 24 patients (11 males and 13 females) with a mean age of 57 years (range, 29-70 years). The tumors in this group penetrated the mucosa and were restricted to the submucosa. The deeper invasion NETs group consisted of 54 patients (31 males and 23 females) with a mean age of 62 years (range, 15-82 years).

**Macroscopic appearance of tumors.** According to the Paris classification of superficial neoplastic lesions (17,18), early-stage gastric cancer is classified into three types: Slightly elevated type (type 0-I), flat type (type 0-II) and concaved type (type 0-III). Endoscopy was performed using the GIF-XQ240, GIF-H260, GIF-H260Z, CF-240I/L, CF-H260AI and PCF-Q260AZI endoscopes (Olympus Corporation, Tokyo, Japan) Based on the endoscopic characteristics of the NETs, submucosal NETs were classified into two types: Elevated type (type 0-Is), which consists of elevating lesions such as submucosal tumors, and elevated depressed type (type 0-Is+IIc), which consists of an elevating lesion with a depressed lesion. Deeper invasion NETs were endoscopically classified into four types: Borrmann's type I, Borrmann's type II, Borrmann's type III type and Borrmann's type IV (19).

**NET growth pattern.** Based on the tumor growth pattern, gastrointestinal NETs were classified as exhibiting an expansive or infiltrative pattern. Certain NETs with an infiltrative growth pattern exhibited various invasion directions, including infiltration towards the anterior and lateral sides of the tumors.

**Histopathological classification.** All specimens were dissected at a maximal section. Hematoxylin (catalog no., 130608; Shanghai Boao Biotechnology Co., Ltd., Shanghai, China) and eosin (catalog no., 20130729; Shanghai SSS Reagent Co., Ltd., Shanghai, China) staining and immunohistochemical staining for synuclein- $\alpha$  (rabbit anti-human polyclonal antibody; cat. no. ZM-0506; dilution,

1:300), chromogranin A (EP38; rabbit anti-human polyclonal antibody; cat. no. ZA-0507; dilution, 1:200), neuron-specific enolase (E27; mouse anti-human polyclonal antibody; cat. no. ZM-0203; dilution, 1:200) and Ki-67 (MIB1; mouse anti-human polyclonal antibody; cat. no. ZM-0167; dilution, 1:300) (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China) were subsequently performed using the One-Step Universal kit (containing endogenous peroxidase blocking solution, HRP-Polymer and DAB Diluent; catalog no., PV-8000; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.). Antibodies were incubated for 32 min at 37°C. Stained sections were examined using a Nikon ECLIPSE 50I microscope (Nikon Corporation, Tokyo, Japan). According to the 2010 World Health Organization International Classifications of Tumors (20), NETs were classified into four subtypes: NET G1, NET G2, neuroendocrine carcinoma (large or small cell carcinoma) and mixed adeno-neuroendocrine carcinoma.

**Statistical analysis.** All statistical analyses were performed with SPSS version 20.0 statistical software (IBM SPSS, Armonk, NY, USA). The  $\chi^2$  test was used to evaluate the associations between the depth of invasion and clinicopathological variables of the patients and the association between LN metastasis and clinicopathological variables. Survival was estimated according to the Kaplan-Meier product limit estimator, and differences observed among patient subgroups were assessed by the log-rank test.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Characteristics of gastrointestinal NET patients.** A total of 78 patients with gastrointestinal NETs were included in the present study. The baseline characteristics of the patients are presented in detail in Table I. The median age of the patients was 58 years old. Out of 78 patients, 42 (53.8%) were men and 36 (46.2%) were women. The primary tumor sites were the esophagus (11/78; 14.1%), the duodenum (6/78; 7.7%), the stomach (30/78; 38.5%), the colon (6/78; 7.7%), the rectum (23/78; 29.5%) and the appendix (2/78; 2.6%). In total, 24 patients (30.8%) possessed distant metastasis, while the remaining 54 (69.2%) had no distant metastasis.

**Association between patients' clinicopathological characteristics and depth of tumor invasion.** The association between the clinicopathological characteristics of the patients and the depth of tumor invasion is summarized in Table II.

No significant differences were identified between age ( $P = 0.409$ ) and gender groups ( $P = 0.350$ ) in terms of depth of tumor invasion. However, a significant correlation was identified between depth of tumor invasion at diagnosis and histopathological classification ( $P < 0.001$ ), diameter of the tumor ( $P < 0.001$ ), macroscopic appearance ( $P < 0.001$ ), growth pattern ( $P < 0.001$ ), lymphatic-vascular involvement ( $P < 0.001$ ), LN metastasis ( $P < 0.001$ ) and distant metastasis ( $P = 0.001$ ).

In the submucosal NETs group, 9 (37.5%) patients exhibited an expansive growth pattern and 15 (62.5%) exhibited an infiltrative growth pattern, of which 10 cases infiltrated towards the anterior side of the tumor, 2 cases infiltrated towards the lateral

Table I. Characteristics of 78 patients with gastrointestinal neuroendocrine tumors.

Parameter	Patients, n (%)
Gender	
Male	42 (53.8)
Female	36 (46.2)
Mean age, years (range)	58 (15-82)
Primary tumor site	
Esophagus	11 (14.1)
Duodenum	6 (7.7)
Stomach	30 (38.5)
Colon	6 (7.7)
Rectum	23 (29.5)
Appendix	2 (2.6)
Distant metastasis	
pM0	54 (69.2)
pM1	24 (30.8)

side of the tumor and 3 cases infiltrated towards the anterior and lateral sides of the tumor. In the deeper invasion NETs group, 54 (100.0%) cases exhibited an infiltrative growth pattern.

*Association between patients' clinicopathological factors and LN metastasis in submucosal gastrointestinal NETs.* The association between different clinical and pathological factors of submucosal NETs and the risk of LN metastasis is presented in Table III.

A significant correlation was identified between high-grade tumors with lymphatic or venule invasion or distant metastasis and an increased risk of nodal metastases ( $P < 0.001$ ,  $P = 0.027$  and  $P = 0.049$ , respectively).

In the submucosal NETs group, 7 minute tumors ( $\leq 5.0$  mm) exhibited an expansive growth pattern (0-Is type), with no evidence of lymphatic-vascular involvement, LN or distant metastasis. Tumors measuring 5.1-10.0 mm in diameter exhibited a high rate of infiltrative growth (84.6%; 11/13) (Figs. 1 and 2), lymphatic-vascular involvement (46.2%; 6/13), LN metastasis (30.8%; 4/13) and distant metastasis (7.7%; 1/13). Tumors measuring  $> 10.0$  mm in diameter also exhibited a high rate of lymphatic-vascular involvement (75.0%; 3/4) and LN metastasis (25.0%; 1/4). No significant difference in LN metastasis was identified between the three tumor diameter categories ( $P = 0.238$ ).

*Therapy.* Of the 24 submucosal NETs, 1 case (4.2%) of liver metastasis was identified in a patient who had undergone resection of a primary tumor. In the other 23 cases, 14 cases (60.9%) underwent endoscopic resection of the primary tumor and 5 cases (21.7%) received surgery following endoscopic resection for suspected positive margin or lymphatic-vascular involvement. The other 9 cases (39.1%) underwent surgery.

In the deeper invasion NETs group, 23 (42.6%) patients with distant metastasis and 31 (57.4%) patients without distant metastasis underwent surgical resection of the primary tumor. Among the 23 patients exhibiting distant

metastasis, 14 underwent surgical resection of the primary tumor: 4 cases (17.4%) underwent resection of the metastatic disease and 10 cases (43.5%) received systemic therapy, which included somatostatin analogues (Sandostatin LAR; 30 mg on day 1, every 28 days; Novartis International AG, Basel, Switzerland) and chemotherapy (100 mg/m<sup>2</sup> etoposide on days 1-3 and 25 mg/m<sup>2</sup> cisplatin on days 1-3; every 21 days, for 4-6 cycles).

*Follow-up.* The mean follow-up period, post-surgery or treatment, was 40 months. In total, 12 (15.4%) of the 78 patients succumbed to the disease during the follow-up period. All patients in the submucosal NETs group survived (follow-up time, 33 months). No evidence of recurrence or metastasis was identified in 23 (95.8%) cases, whereas rectal NETs with liver metastasis was diagnosed in 1 (4.2%) patient. This patient was a 29-year-old male, with an 8-mm primary tumor (type 0-Is; NET G2), which exhibited infiltrative growth, lymphatic-vascular involvement and was LN-positive. The patient had undergone resection of the primary tumor and no evidence of recurrence or disease progression was identified during the follow-up period. In the submucosal NETs group, the 3-year survival and disease-free survival rates were 100.0 and 95.8%, respectively. In the deeper invasion NETs group, 12 (22.2%) patients succumbed to the disease, and the 3-year survival rate was 83.3%.

A significant correlation was identified between submucosal NETs or lower grade tumors and prolonged overall survival ( $P < 0.001$  and  $P = 0.009$ , respectively; Table IV). No significant differences were identified between age or gender and overall survival ( $P = 0.276$  and  $P = 0.089$ , respectively).

## Discussion

As the incidence of gastrointestinal NETs has increased, endoscopic therapy has become more common for the treatment of this type of tumors (3,4). Therefore, studies investigating the safety, potential risks and indications of endoscopic therapy have become particularly important.

Several studies have demonstrated that the histological classification, grading, LN metastasis, lymphatic-vascular involvement and perineural invasion of gastrointestinal NETs are associated with the infiltrative growth of the tumor, staging and prognosis (4,21-23). For early-stage gastric cancer, tumors exhibiting an expansive growth pattern and elevated macroscopic type are less invasive, whereas poorly differentiated tumors are associated with a higher risk of deep infiltration, LN and distant metastasis (24,25). In the present study, histologically submucosal NETs exhibited a higher level of differentiation, expansive growth and small diameter compared with deeper invasion NETs. In the deeper invasion NETs group, an infiltrative growth pattern and tumors of mixed and poorly differentiated type were more common than in the submucosal NETs group. These findings indicated that poorly differentiated NETs usually exhibit an infiltrative growth pattern and are more likely to invade the muscularis propria and deeper layer and exhibit LN and distal metastasis.

Thomas *et al* (26) analyzed 104 gastric carcinoids, the majority of which exhibited a diameter of  $< 2.0$  cm, and observed that the infiltration depth was restricted

Table II. Association between clinicopathological characteristics and depth of tumor invasion in 78 gastrointestinal NET patients.

Parameter	Patients, n	Submucosal NETs, n (%)	Deeper invasion NETs, n (%)	P-value
Gender				0.350
Male	42	11 (45.8)	31 (57.4)	
Female	36	13 (54.2)	23 (42.6)	
Age, years				0.409
>30	6	1 (4.2)	5 (9.3)	
31-60	33	14 (58.3)	19 (35.2)	
>60	39	9 (37.5)	30 (55.6)	
Tumor location				0.026
Esophagus	11	2 (8.3)	9 (16.7)	
Duodenum	6	2 (8.3)	4 (7.4)	
Stomach	30	6 (25.0)	24 (44.4)	
Colon	6	0 (0.0)	6 (11.1)	
Rectum	23	14 (58.3)	9 (16.7)	
Appendix	2	0 (0.0)	2 (3.7)	
Histopathological classification				<0.001
NET G1	20	20 (83.3)	0 (0.0)	
NET G2	29	3 (12.5)	26 (48.1)	
NEC	9	0 (0.0)	9 (16.7)	
MANEC	20	1 (4.2)	19 (35.2)	
Tumor diameter, mm				<0.001
≤10.0	20	20 (83.3)	0 (0.0)	
>10.0	58	4 (16.7)	54 (100.0)	
Macroscopic appearance				<0.001
0-Is type	18	18 (75.0)	0 (0.0)	
0-Is+IIc type	6	6 (25.0)	0 (0.0)	
Bormann's I type	18	0 (0.0)	18 (33.3)	
Bormann's II type	13	0 (0.0)	13 (24.1)	
Bormann's I+II type	11	0 (0.0)	11 (20.4)	
Bormann's III type	9	0 (0.0)	9 (16.7)	
Bormann's IV type	3	0 (0.0)	3 (5.6)	
Growth pattern				<0.001
Expansive	9	9 (37.5)	0 (0.0)	
Infiltrative	69	15 (62.5)	54 (100.0)	
Lymphatic-vascular involvement				<0.001
Absent	20	15 (62.5)	5 (9.3)	
Present	58	9 (37.5)	49 (90.7)	
Lymph node metastasis				<0.001
Negative	28	19 (79.2)	9 (16.7)	
Positive	50	5 (20.8)	45 (83.3)	
Distant metastasis				0.001
pM0	54	23 (95.8)	31 (57.4)	
pM1	24	1 (4.2)	23 (42.6)	

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma.

to the mucosa and submucosa. Soga (27) investigated 1,914 gastrointestinal carcinoids and hypothesized that the diameter of the tumor was closely associated with metastasis.

Gastrointestinal submucosa carcinoids exhibited a metastatic rate of 16.4% as a whole and minute carcinoids (≤5 mm) revealed a metastatic rate of 6.0% on average. In the present

Table III. Association between clinicopathological factors and LN metastasis in 24 patients with submucosal NETs.

Parameter	LN metastasis			P-value
	Patients, n	Negative, n (%)	Positive, n (%)	
Gender				0.209
Male	11	10 (52.6)	1 (20.0)	
Female	13	9 (47.4)	4 (80.0)	
Age, years				0.774
<30	1	0 (0.0)	1 (20.0)	
31-60	14	13 (68.4)	1 (20.0)	
>60	9	6 (31.6)	3 (60.0)	
Tumor location				0.231
Esophagus	2	2 (10.5)	0 (0.0)	
Duodenum	2	2 (10.5)	0 (0.0)	
Stomach	6	5 (26.3)	1 (20.0)	
Rectum	14	10 (52.6)	4 (80.0)	
Histopathological classification				<0.001
NET G1	20	19 (100.0)	1 (20.0)	
NET G2	3	0 (0.0)	3 (60.0)	
MANEC	1	0 (0.0)	1 (20.0)	
Tumor diameter, mm				0.238
≤5.0	7	7 (36.8)	0 (0.0)	
5.1-10.0	13	9 (47.4)	4 (80.0)	
>10.0	4	3 (15.8)	1 (20.0)	
Macroscopic appearance				0.799
0-Is type	18	15 (78.9)	3 (60.0)	
0-Is+IIc type	6	4 (21.0)	2 (40.0)	
Growth pattern				0.081
Expansive	9	8 (42.1)	1 (20.0)	
Infiltrative	15	11 (57.9)	4 (80.0)	
Envelope				0.607
Complete	6	6 (31.6)	0 (0.0)	
Incomplete	11	7 (36.8)	4 (80.0)	
N/A	7	6 (31.6)	1 (20.0)	
Lymphatic-vascular involvement				0.027
Absent	15	14 (73.7)	1 (20.0)	
Present	9	5 (26.3)	4 (80.0)	
Distant metastasis				0.049
pM0	23	19 (100.0)	4 (80.0)	
pM1	1	0 (0.0)	1 (20.0)	

NET, neuroendocrine tumor; LN, lymph node; MANEC, mixed adenoneuroendocrine carcinoma; N/A, not applicable.

study, the majority of lesions measuring <5.0 mm in diameter exhibited a slightly elevated macroscopic type and an expansive growth pattern without lymphatic-vascular involvement or distant metastasis. However, a high number of tumors measuring 5.1-10.0 mm in diameter exhibited an infiltrative growth pattern, lymphatic-vascular involvement and nodal metastasis. In the deeper invasion NETs group, all lesions measured >10.0 mm and exhibited an infiltrative growth pattern. This indicated that at the initial stage of growth

(≤5.0 mm in diameter), NETs exhibit an expanding growth pattern, and gradually develop an infiltrating growth pattern as the tumor increases in diameter (>5.0 mm). Subsequently, the tumor may invade through the submucosal layer, infiltrating the muscular and deeper layers. In addition, tumors may grow towards the mucosa in an elevated way, leading to mucosal erosions and ulcers (Borrmann's type II or III tumors). Thus, the present authors hypothesize that minute tumors with an expansive growth pattern present a relatively

Table IV. Kaplan-Meier survival analysis of gastrointestinal NETs patients with regard to clinicopathological factors.

Parameter	Patients, n	Median overall survival, months <sup>a</sup>	3-year survival rate, % <sup>a</sup>	95% CI	P-value
Gender					0.276
Male	42	80.4	-	70.2-90.6	
Female	36	73.5	-	60.1-87.0	
Age, years					0.089
<30	6	61.8	-	36.6-87.1	
31-60	33	88.9	-	79.4-98.4	
>60	39	66.2	-	54.1-78.4	
Histopathological classification					<0.001
NET G1	20	-	100.0	-	
NET G2	29	-	100.0	-	
NEC	9	-	44.4	-	
MANEC	20	-	85.0	-	
Depth of invasion					0.009
Submucosal	24	-	100.0	-	
Deeper invasion	54	-	83.3	-	

<sup>a</sup>Overall and 3-year survival could not be calculated for parameters where patients remained alive (marked by the symbol, -). NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; CI, confidence interval.

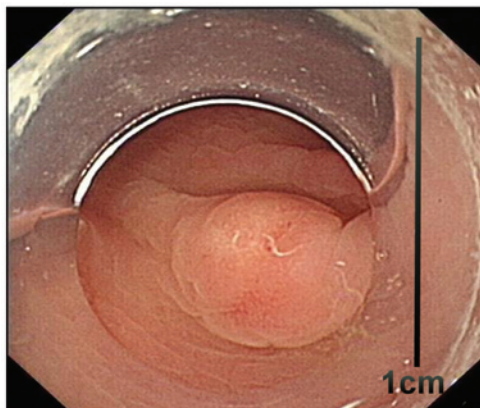


Figure 1. Endoscopic image of an early-stage gastrointestinal neuroendocrine tumor revealing a 0.6-cm lesion of slightly lifted type.

inert stage of tumor development and therefore, such tumors are suitable for endoscopic therapy.

At present, surgery is considered the curative treatment for NETs with muscular layer or deeper infiltration, with or without LN metastasis (13,28). Treatment for metastatic NETs includes, surgery, radiotherapy, chemotherapy and palliative care, depending on the individual case (28). If a tumor is limited to the mucosa or submucosa, it may be resected by surgery or by endoscopy using endoscopic mucosal resection or endoscopic submucosal dissection (15,16,29-31). Endoscopic resection is not only a curative method, but it also exhibits minimal trauma and a lower cost than other surgical procedures. For gastrointestinal epithelial tumors, if the tumor is diagnosed when limited to the mucosa or submucosa, >50% tumors are curable, with a 5-year survival rate of

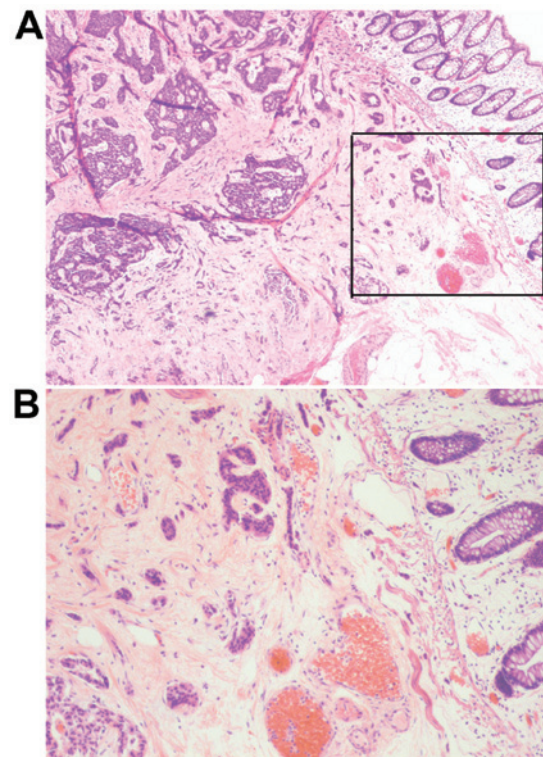


Figure 2. (A) Histological staining of an early-stage gastrointestinal neuroendocrine tumor measuring 0.6 cm in size and exhibiting an infiltrative growth pattern (hematoxylin and eosin staining; magnification, x40). (B) Magnified image of the panel delineated in part (A) (magnification, x100).

80-90% (32). Generally, the indicators for endoscopic resection are as follows: The gastrointestinal NET is limited to the mucosa or submucosa; the diameter of the tumor is <1.0 cm;

and there is no evidence of LN or distant metastasis (15,16). Certain studies have reported endoscopic resection for tumors measuring >1.0 cm in diameter (33-35). In the present study, 6 cases with lesions measuring ≤5.0 mm and 8 cases with 5.1-10.0-mm lesions in the submucosa were treated with tumor resection by endoscopy. A total of 5 patients underwent surgery following endoscopic resection for suspected positive margin or lymphatic-vascular involvement. No patients exhibited recurrence or metastasis during the follow-up period. These results indicated that surgery subsequent to endoscopic resection may achieve curable effects for patients with high risk factors. In the present study, submucosa NETs measuring 5.1-10.0 mm in diameter exhibited a high rate of lymphatic-vascular involvement (46.2%) and LN metastasis (30.8%), which suggests that the indicators for endoscopic resection of gastrointestinal NETs should be more stringent than that for early-stage gastrointestinal adenocarcinoma. For ≤5.0-mm lesions of the slightly elevated type, endoscopic resection is a safe treatment method, whereas for gastrointestinal NETs of 5.1-10.0 mm in diameter, endoscopic resection must be performed with caution.

In the present study, overall prognosis was favorable. Survival time was significantly higher in early-stage and lower grade tumors compared with later-stage and higher grade tumors. For gastrointestinal carcinomas, once the tumor has progressed out of the range of being resectable, the patient is expected to possess a relatively poor prognosis. Thus, earlier diagnosis and improved systemic treatment for advanced disease is urgently required.

In conclusion, the present retrospective study revealed that gastrointestinal submucosal NETs regularly exhibit a slightly elevated macroscopic type, and are usually small low-grade tumors. These features may aid oncologists to diagnose gastrointestinal NETs at an early stage. Gastrointestinal NETs of <5.0 mm in diameter with a slightly elevated macroscopic type may require endoscopic resection, while NETs measuring 5.1-10.0 mm in diameter must be considered carefully prior to attempting surgery, due to the potential risk of lymphatic-vascular involvement and LN metastasis.

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