

Clinical outcomes of gastroduodenal neuroendocrine tumors according to their WHO grade

A single-institutional retrospective analysis

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Abstract

The management of gastroduodenal neuroendocrine tumor (NET) has been controversial between radical surgical resection and local excision including endoscopic resection. A gastroduodenal NET grade (G), measured by their mitotic rate and Ki67 proliferation index, is important to predict prognosis. In this study, we aimed to compare the clinical outcomes of gastroduodenal NET according to grades in order to identify poor prognostic factors of gastroduodenal NETs. Fifty-four gastroduodenal NETs diagnosed between December 2008 and December 2020 in a tertiary referral hospital were retrospectively reviewed. The clinical outcomes of gastroduodenal NETs, according to tumor grades and factors associated with NET G2-3, were analyzed. A total of 52 gastroduodenal NET patients was enrolled. The mean follow-up period was 56.2 ± 40.1 months. The mean size of gastric and duodenal NET was 7.9 ± 11.0 mm and 9.8 ± 7.6 mm, respectively. During the study period, 72.7% (16/22) of gastric NETs and 83.3% (25/30) of duodenal NETs were G1. All G1 gastroduodenal NETs showed no lymph node or distant metastasis during the study periods. All G3 gastroduodenal NETs showed metastasis (one lymph node metastasis and 3 hepatic metastases). Among metastatic NETs, the smallest tumor size was a 13 mm gastric G3 NET. Factors associated with G2-3 NETs were larger tumor size, mucosal ulceration, proper muscle or deeper invasion, and lymphovascular invasion. A small-sized gastroduodenal NET confined to submucosa without surface ulceration may be suitable for endoscopic resection. After local resection of a gastroduodenal NET (G1) without lymphovascular and muscle proper invasion, follow-up examination without radical surgical resection can be recommended. G3 NETs may be treated by radical surgical resection, regardless of tumor size.

Abbreviations: CT = computed tomography, EMR = endoscopic mucosal resection, ENETS = European Neuroendocrine tumor Society, ESD = endoscopic submucosal dissection, EUS = endoscopic ultrasonography, G = grade, HPF = high power field, NET = neuroendocrine tumor, SET = subepithelial tumor, WHO = World Health Organization

Keywords: duodenum, neuroendocrine tumor, resection, stomach, tumor grade

1. Introduction

The WHO (World Health Organization) 2010 guidelines classified the previously called carcinoid tumor as well-differentiated neuroendocrine tumor (NET).^[1] Although the exact incidence of gastroduodenal NETs is uncertain, detection rates are reportedly increasing with the widespread use of endoscopic examinations, increased life expectancy, improved diagnostic modalities, diet changes, and environmental exposures. The

reported incidence of gastric NET in the US was 8.9 % of all gastrointestinal NETs, between 1992 and 1999.^[2] In South Korea, the National gastric cancer screening program has been recommending a biennial endoscopic screening examination for adults over 40 years, which has led to increased detection of early gastric cancer^[3] and gastroduodenal NETs.^[4] In past few decades, early detection of NETs has also been associated with improvement in survival rate of gastroduodenal NETs patients.^[4-7]

The authors have no conflicts of interest or financial ties to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The management of gastric NETs is somewhat different from other gastro-entero-pancreatic NETs, depending on the gastric NET types. Therefore, checking of gastric NET type using serum gastrin level is the first step. A type 1 gastric NET is associated with hypergastrinemia and chronic atrophic gastritis, while a type 2 gastric NET results in hypergastrinemia caused by Zollinger-Ellison syndrome or multiple endocrine neoplasia type 1. While type 1 and 2 gastric NETs are often small in size (<10mm) and multiple in numbers, type 3 gastric NETs are known to be solitary with normal serum gastrin level.^[8,9] Because most of the gastric type 1 NET usually show benign or indolent course, the spectrum of recommended therapies have ranged from radical surgical resection to “watch and wait”.^[10] However, for type 3 gastric NETs, radical surgical resection with lymph node dissection have been recommended, similar to gastric adenocarcinoma, because of their large size (over 20mm) and high rate of metastasis.^[8,11]

Clinical outcomes and prognosis of the NET are highly associated with tumor grade (G), which is classified according to their mitotic rate and Ki67 index.^[11] According to the WHO 2010 classification, gastro-entero-pancreatic NETs are classified as well-differentiated NET (G1-2) and poorly differentiated neuroendocrine carcinoma (G3) according to mitotic rates (>20/10 HPF, high power field) and Ki67 proliferation index of more than 20%.^[12] The recent 2019 WHO reclassification classified digestive NET as grade 1–3 and neuroendocrine carcinoma as small cell and large cell neuroendocrine carcinoma (Table 1). The WHO 2019 NET G3 and neuroendocrine carcinoma show mitotic rate > 20/HPF and Ki67 index > 20%,^[13] similar to the WHO 2010 NET G3. NET grades are highly associated with prognosis, and thus, low-grade NET and high-grade/neuroendocrine carcinoma should be considered as distinct clinic-pathological entities from disease management point of view.^[14] The 5 to 10-year survival rate of grade 1 gastro-enteric-pancreatic NETs is much better than grade 2-3 NETs.^[4] However, the natural history and clinical outcomes of these tumors have been poorly understood as they are uncommon. Therefore, the management strategy for gastroduodenal NETs has not been well established. Presently, for type 3 gastric NETs with normal serum gastrin level, and duodenal NET, radical surgical resection with lymph node dissection have been recommended as primary treatment.^[15] Local resection, including endoscopic resection of the NETs, is described as an optional treatment for small-sized gastroduodenal NETs confined to submucosa.^[8] Theoretically, all gastrointestinal malignant tumors without risk of lymph node metastasis may be treated by local resection including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and surgical local excision. However, no imaging modality has been established as a definitive tool for the evaluation of lymph node involvement status. Endoscopic ultrasonography (EUS), computed tomography (CT), and positron emission tomography can be used to predict lymph node metastasis, but there are limitations.^[16–18] Therefore, several factors have been used to predict the presence of lymph node metastasis of gastroduodenal NETs, such as size of tumor

(>20 mm), invasion depth (proper muscle or deeper invasion) and lymphovascular invasion.^[7,8,19]

Thus, the clinical features and biological behavior of low-grade gastroduodenal NETs remain unclear. In the present study, we wanted to know the clinical outcomes of gastroduodenal NET according to grades and to identify poor prognostic factors of gastroduodenal NETs.

2. Methods

2.1. Patients

Between December 2008 and December 2020, a total of 54 gastroduodenal NET patients were selected, retrospectively, from the patient database at the Pusan National University Yangsan Hospital. These included 22 gastric NETs and 32 duodenal NETs; 2 patients (two duodenal NETs) were excluded because of loss to follow-up. After exclusions, a total of 52 patients were reviewed and analyzed (Fig. 1). All patients were evaluated by conventional endoscopy, endoscopic ultrasonography (EUS), and abdominal computed tomography (CT). For patients with gastric NET, serum gastrin levels were checked to determine the type of gastric NET. An elevated serum gastrin level (> 90 pg/ml) was classified as type 1 and a normal serum gastrin level (<90 pg/ml) was classified as type 3. No patient had multiple endocrine neoplasias or Zollinger Ellison syndrome (type 2 gastric NET). This study was approved by the Institutional Review Board (IRB) of Pusan National University Yangsan Hospital (IRB approval number 05-2021-094). Informed consent was waived by the ethics committee (Institutional Review Board of Pusan National University Yangsan Hospital) because the subject's medical records were anonymized prior to analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Treatment for gastroduodenal NETs

Decision regarding endoscopic resection or surgical resection of localized tumors was made after discussion with patients, endoscopists, and surgeons. Endoscopic resection was recommended when the tumor was <10mm in diameter, and found confined to the submucosa on EUS, with no evidence of lymph node metastasis on the abdominal CT. If the patient refused surgical resection of a 10–20mm in diameter within submucosa, we tried endoscopic resection at first. For the location of lesions, we used different endoscopic resections. For gastric NETs, ESD techniques were preferred to EMR. But EMR techniques were preferred to ESD in duodenal NETs. All endoscopic procedures were performed under conscious sedation using intravenous midazolam (3–8 mg) under close monitoring with oxygen saturation. After resection, patients were recommended to undergo regular examinations at 6- to 12-month intervals, including an endoscopic examination and abdominal CT scan. For NETs located in the ampullary or periampullary regions, pylorus-preserving pancreaticoduodenectomy was performed. After endoscopic resection, we recommended additional surgical resection

Table 1

Classification of gastro-entero-pancreatic neuroendocrine tumors according to the World Health Organization 2019 guidelines.

	Differentiation	Grade	Mitotic rate	Ki 67 index, %
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3	Well differentiated	High	>20	>20
SCNEC	Poorly differentiated	High	>20	>20
LCNEC	Poorly differentiated	High	>20	>20
MINEN	Well or poorly differentiated	Variable	Variable	Variable

NET= Neuroendocrine tumour, SCNEC= Small-cell neuroendocrine carcinoma, LCNEC= Large-cell neuroendocrine carcinoma, MINEN= Mixed neuroendocrine–nonneuroendocrine neoplasm.

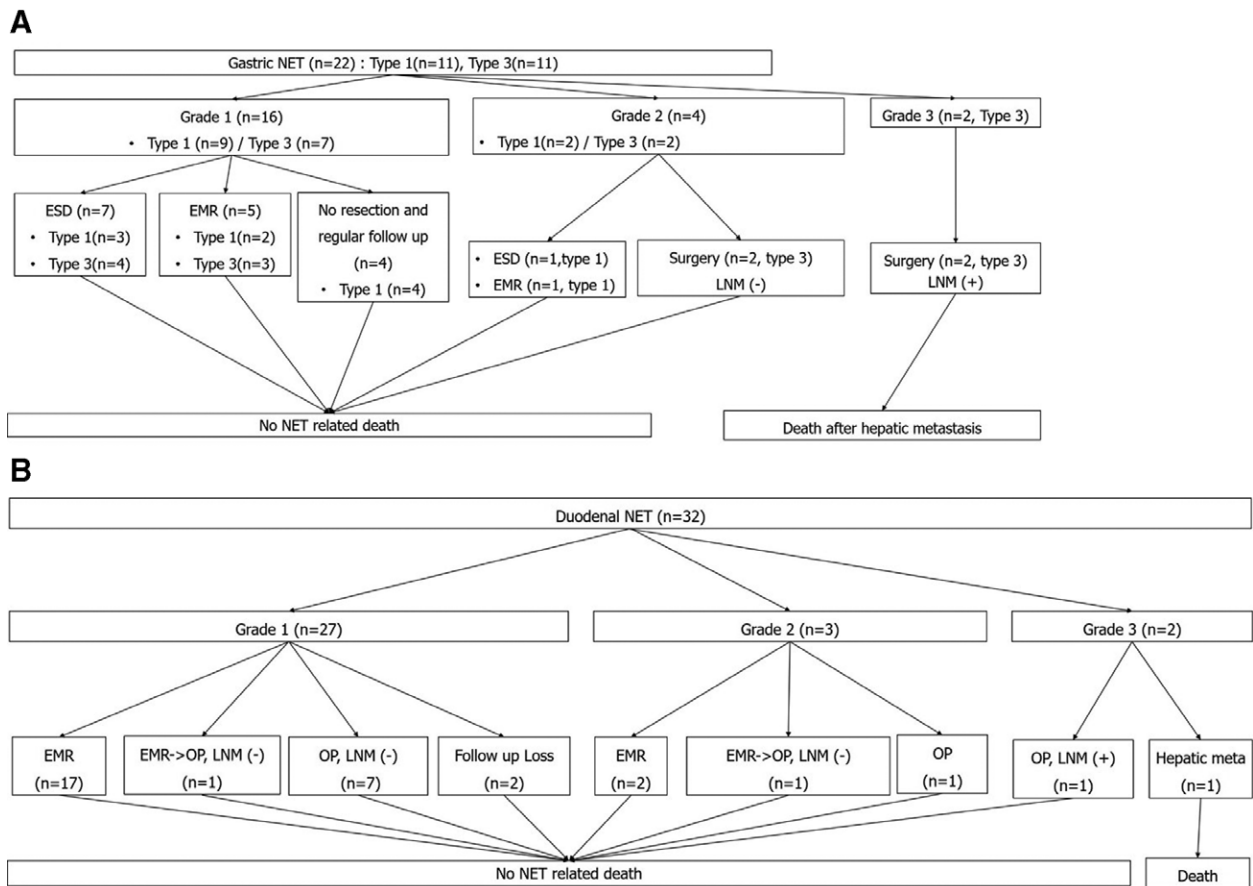


Figure 1. Study flow. (A) Gastric neuroendocrine tumor, (B) Duodenal neuroendocrine tumor). NET = neuroendocrine tumor, ESD = endoscopic submucosal dissection, EMR = endoscopic mucosal resection, LNM = lymph node metastasis, OP = operation.

for the lesions with high risk of lymph node metastasis such as grade 2 or 3, lymphovascular invasion, or incomplete endoscopic resection (R1 or R2 resection). If a metastatic lesion was found, systemic chemotherapy was done. The treatment flow chart is shown in Figure 1.

2.3. Pathologic evaluation

The gastroduodenal NETs patients were classified into 3 categories based on the WHO classification of 2010. All of the tissue slides were blindly reviewed by 2 pathologists. Discordant cases were reevaluated under a multi-headed microscope to reach an agreement. The resected specimens were stretched, pinned, and fixed with formalin. Several immunohistochemical neuroendocrine markers such as chromogranin A, synaptophysin and CD56, were used to diagnose NET. All resected specimens were evaluated histologically using light microscopy at low-power and high-power magnification.

2.4. Tumor characteristics

All data including the patients’ baseline characteristics, endoscopic morphologic features, presence of metastasis, treatment modalities, duration of follow up, presence of local recurrence, and pathologic data (lesion size, grade, invasion depth, and lymphovascular invasion) were reviewed retrospectively. The lesion size was measured from the resected specimen, or EUS and abdominal CT, if the tumor was inoperable. The surface depression or ulceration was defined by the presence of ulceration or depressed morphology on the top of NET. Surface erosion was defined as a mucosal defect

(Fig. 2). The status of metastasis was determined by pathologic results or radiologic examinations.

2.5. Statistical analysis

Data are represented as mean ± standard deviation for continuous variables, and number and percentage for categorical variables. For continuous variables, Student t-test was performed. Univariate analysis was performed with a Chi-square test or Fisher exact test for categorical variables. Variables were considered to be statistically significant if p < 0.05. Statistical calculations were performed with PASW Statistics for Windows, Version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

The mean age of gastric NET patients was 56.7 ± 12.8 years and male sex was 54.5% (12/22). Most gastric NETs were located in the body of the stomach (86.4%). The mean tumor size was 7.9 ± 11.0mm, with G2-3 NETs being larger than G1 (mean tumor size: 16.9mm vs 4.6mm, respectively). Most of type 1 gastric NETs (elevated gastrin level) were G1 tumors (9/11), while 2 were G2 tumors. Among type 3 gastric NETs, G1 tumors and G2-3 were 63.6 % (7/11) and 36.4 % (4/11), respectively. All G1 NETs are confined within the submucosa and 10mm or less in diameter. Among G3 tumors, 33.3% (2/6) of the tumors were located in the muscle proper or deeper, and these tumors showed lymph node and hepatic metastasis; the size of the metastatic gastric G3 NETs were 13mm (NET with lymph node metastasis) and 55mm (NET with hepatic metastasis), respectively. All G1 tumors were treated by endoscopic resection or

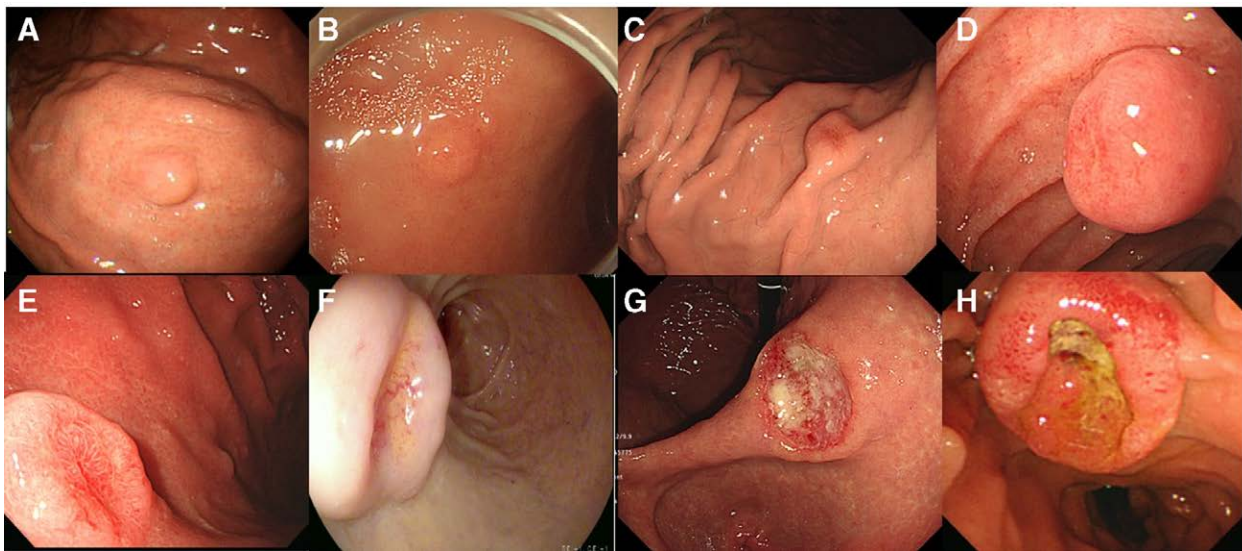


Figure 2. Endoscopic findings associated with foregut neuroendocrine tumors. A–B showed normal overlying mucosal surface (A: stomach body, B: duodenal bulb). C–D showed an erosive change of overlying mucosal surface (C: stomach body, D: duodenal 2nd portion), E–F showed depressive mucosal surface (E: stomach body, F: duodenal 2nd portion). G–H showed ulcerative surface (G: stomach angle, H: duodenal peri-ampullary portion)

simple regular surveillance for type 1 NETs. However, 66.7% of G3 tumors were treated by radical gastrectomy with lymph node dissection. Among endoscopic findings, surface ulceration was an important common observation for grade 2–3 NETs (Tables 2 and 3).

The mean age of duodenal NETs was 55.9 ± 13.0 years and male sex was 56.7% (17/30). The bulb of the duodenum was the predominant location and G1 was the most common grade. The average tumor size was 9.8 ± 7.6 mm and G2–3 NETs were larger than G1 (mean tumor size: 18.4 mm vs. 12.0 mm, respectively). Most of the G1 duodenal NETs were confined within submucosa (96.0%) and the largest tumor size was 25 mm. Among G3 tumors, 60.0% (3/5) of duodenal NETs were located in the muscle proper or deeper. Although the lymphovascular invasion was not found in G1 NETs, 80% of G2–3 NETs showed lymphovascular invasion (4/5) and 2 patients showed lymph node metastasis, and 1 patient showed hepatic metastasis. Most of the G1 NETs were treated by endoscopic resection (68.0%, 17/25) (Table 4).

The overall mean follow-up period was 56.2 ± 40.1 months. Among the endoscopic findings, tumor size and surface ulceration were different between G1 and G2–3 NETs. Among pathologic results, depth of invasion (muscle proper or deeper

invasion) and lymphovascular invasion were significant findings for G2–3 NETs. Among G1–2 NETs in the present study, there was no evidence of lymph node or distant metastasis, and no evidence of local recurrence. However, all G3 gastric NETs showed hepatic metastasis after surgical resection and 1 G3 duodenal NET showed lymph node metastasis, while another G3 duodenal NET showed hepatic metastasis in the initial evaluation (Fig. 1 and Table 5).

4. Discussion

The widespread use of endoscopic examination has led to early detection of small sized gastroduodenal NETs. The WHO 2010 graded gastro-entero-pancreatic NETs according to Ki67 proliferation index and mitotic rates. In the present study, most of the gastroduodenal NETs were G1 tumors. Reportedly, low-grade gastroduodenal NETs have indolent and nonaggressive features and show favorable clinical outcomes. No patients of the present study with grade 1–2 gastroduodenal NETs showed distant metastasis or lymph node metastasis. Moreover, no recurrence was observed after endoscopic or surgical resection of tumors in the grade 1–2 gastroduodenal NETs during the mean follow-up period of 56.2 months. However, all grade 3

Table 2

Baseline characteristics of gastric neuroendocrine tumors.

	G1 NET (n=16)	G2 NET (n=4)	G3 NET (n=2)	Total (n=22)	p value
Age, years, mean (SD)	57.1 (14.2)	53.8 (9.1)	59.5 (5.5)	56.7 (12.8)	0.08
Male Sex, n (%)	7 (43.8)	4 (100)	1 (50.0)	12 (54.5)	0.10
Gastrin level, n (%)					0.34
Elevated	9 (56.3)	2 (50.0)	0 (0)	11 (50.0)	
Normal	7 (43.8)	2 (50.0)	2 (100)	11 (50.0)	
Location of a lesion, n (%)					0.25
Antrum	3 (18.8)	0 (0)	0 (0)	3 (13.6)	
Body	13 (81.3)	4 (100)	2 (100)	19 (86.4)	
Endoscopic findings, n (%)					
Erosion	6 (37.5)	2 (50.0)	2 (100)	10 (45.5)	0.22
Depression	0 (0)	2 (50.0)	2 (100)	4 (18.2)	<0.01
Ulceration	0 (0)	0 (0)	2 (100)	2 (9.1)	0.02

G = grade, NET = neuroendocrine tumor, n = number, SD = standard deviation.

Table 3**Results after treatment of gastric neuroendocrine tumors.**

	G1 NET (n = 16)	G2 NET (n = 4)	G3 NET (n = 2)	Total (n = 22)	P value
Treatment modality, n (%)					<0.01
EMR	5 (31.3)	1 (16.7)	0 (0)	6 (27.3)	
ESD	7 (43.8)	1 (16.7)	0 (0)	8 (36.4)	
Follow-up	4 (25.0)	0 (0)	0 (0)	4 (18.2)	
Surgical resection	0 (0)	2 (50.0)	2 (100)	4 (18.2)	
Tumor size, mm, mean (SD)	4.6 (2.3)	8.0 (3.5)	34.0 (21.0)	7.9 (11.0)	0.02
Depth of invasion, n (%)					0.02
Mucosa or submucosa	16 (100)	4 (66.7)	0 (0)	20 (90.9)	
Proper muscle or deeper	0 (0)	0 (0)	2 (100)	2 (9.1)	
Lymphovascular invasion, n (%)	0 (0)	0 (0)	2 (100)	2 (9.1)	0.02
Lymph node metastasis, n (%)	0 (0)	0 (0)	2 (100)	2 (9.1)	0.02
Distant metastasis, n (%)	0 (0)	0 (0)	2 (100)	2 (9.1)	0.02

G = grade, NET = neuroendocrine tumor, n = number, SD = standard deviation, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection.

Table 4**Baseline characteristics of duodenal neuroendocrine tumors.**

	G1 NET (n = 25)	G2 NET (n = 3)	G3 NET (n = 2)	Total (n = 30)	P value
Age, years, mean (SD)	54.5 (12.8)	53.3 (3.4)	76.5 (4.5)	55.9 (13.0)	0.21
Male Sex, n (%)	15 (60.0)	1 (33.3)	1 (50.0)	17 (56.7)	0.47
Location of a lesion, n (%)					0.12
2nd portion	5 (20.0)	3 (60.0)	0 (0)	8 (26.7)	
Ampulla or periampullary	3 (12.0)	0 (0)	1 (50.0)	4 (13.3)	
Bulb	17 (68.0)	0 (0)	1 (50.0)	18 (60.0)	
Tumor size, mm, mean (SD)	8.1 (5.2)	11.7 (8.8)	28.5 (1.5)	9.8 (7.6)	<0.01
Depth of invasion, n (%)					<0.01
Mucosa or submucosa	24 (96.0)	2 (66.7)	0 (0)	26 (86.7)	
Proper muscle or deeper	1 (4.0)	1 (33.3)	2 (100)	4 (13.3)	
Lymphovascular invasion, n (%)	0 (0)	2 (66.7)	2 (100)	4 (13.3)	<0.01
Lymph node metastasis, n (%)	0 (0)	0 (0)	2 (100)	2 (6.7)	<0.01
Distant metastasis, n (%)	0 (0)	0 (0)	1 (50.0)	1 (3.3)	0.02
Treatment modality, n (%)					0.02
Chemotherapy	0 (0)	0 (0)	1 (50.0)	1 (3.3)	
EMR	17 (68.0)	1 (33.3)	0 (0)	18 (60.0)	
Surgical resection	8 (32.0)	2 (66.7)	1 (50.0)	11 (36.7)	
Endoscopic findings, n (%)					
Erosion	16 (64.0)	3 (100)	2 (100)	21 (70.0)	0.11
Depression	16 (64.0)	2 (66.7)	2 (100)	20 (66.7)	0.49
Ulceration	3 (12.0)	0 (0)	1 (50.0)	4 (13.3)	0.63

G = grade, NET = neuroendocrine tumor, n = number, SD = standard deviation, EMR = endoscopic mucosal resection.

Table 5**Characteristics of patients with metastasis (n = 4).**

Age	Sex	Location	Size (mm)	Grade	Initial treatment	Invasion depth	Lymphatic invasion	Site of metastasis	Follow-up (months)	Survival
65	F	Stomach, angle	13	3	STG with LD	Proper muscle	Yes	Lymph node and hepatic	28	Survived
54	M	Stomach, lower body	55	3	STG with LD	Serosa	Yes	Hepatic	10	Death
81	M	Duodenum, ampulla	27	3	PPPD	Serosa	Yes	Lymph node	60	Survived
72	F	Duodenum, bulb	30	3	Chemo-therapy	Proper muscle	Not checked	Hepatic	97	Death

F = female, M = male, STG = subtotal gastrectomy, LD = lymph node dissection, PPPD = pylorus preserving pancreaticoduodenectomy.

NETs showed lymph node metastasis or hepatic metastasis. Therefore, according to the present study, because the grade of gastroduodenal NET is important to predict the prognosis of gastroduodenal NETs, the G1 gastroduodenal NETs may be locally resected without wide surgical resection for lymph node metastasis, to preserve a better quality of life. However,

1 difficulty in this approach is that the determination of tumor grade can be difficult by endoscopic forceps biopsy specimen because of the small size. Thus, before deciding whether to perform radical surgical resection or local resection, accurate prediction of NET grade is important to avoid over- or under-estimated treatment.

Thus, endoscopic prediction of high-risk factors associated with higher grade gastroduodenal NETs is important. The present study along with other previous reports shows that small tumors are confined in the submucosa, and have a better prognosis and lower rate of lymph node metastasis.^[2,8,9,11,13,19–21] The first determinable factor during endoscopic examination is the tumor size, which can be measured during a conventional endoscopic examination or EUS (endoscopic ultrasound). During the conventional endoscopic examination, we can compare the tumor with endoscopic shaft diameter (about 10 mm) and endoscopic forceps jaw (closed 2–3 mm, open 5–7 mm). Although a EUS examination could measure the NET size, a study showed the mean difference between conventional endoscopic estimation and EUS was 3.3 mm. Therefore, if the gastroduodenal NETs showed intraluminal projection, the tumor size estimation by conventional endoscopic examination is a useful method. Most studies have reported small tumor size as <20 mm in diameter and these NETs could be a candidate for local resection.^[8,9,20,21] In the present study, 2 duodenal NET with grade 1 and 2, which were larger than 20 mm (25 mm and 24 mm in diameter, respectively), showed no lymph node metastasis. However, among grade 3 tumors, even a 13 mm diameter tumor showed muscle invasion and hepatic metastasis.

The prediction of invasion depth of gastroduodenal NETs may be another important consideration for predicting the tumor grade. Most studies, including the present study, reported that NETs confined in the submucosa have good prognostic outcome.^[8,9,20,21] The invasion depth prediction by conventional endoscopy is difficult because NETs are mainly located in the submucosa. More accurate estimation of invasion depth or status of lymph node metastasis may be possible by using the EUS than other radiologic image modalities. However, until now, the reported accuracy of the EUS is limited. A study reported that EUS can differentiate T1–2 from T3–4 gastric cancer with high accuracy (0.86) and overall sensitivity (0.91).^[22] In the evaluation of lymph node metastasis, EUS (0.91) was also more sensitive than CT (0.77) in a meta-analysis.^[18] Moreover, EUS can measure the exact size of tumors, which makes it favorable for the evaluation of NETs.

An additional important endoscopic finding is the morphologic changes of the overlying mucosa. Most benign subepithelial tumors (SETs) show normal-appearing overlying mucosa. However, potentially malignant SETs, such as high-risk gastrointestinal stromal tumors, lymphoma, SET like adenocarcinoma, and NETs can reveal changes in the overlying mucosa.^[23] In the present study, we checked for surface erosion, depression, and ulceration. The important endoscopic finding was the surface ulceration during initial endoscopic examinations. Surface ulceration of the SET is an important endoscopic feature because it implies that the malignant potential is high and definite pathologic diagnosis may be possible by endoscopic target biopsy on the ulcer base.

Among pathologic results, lymphovascular invasion is important in all malignant gastrointestinal tumors because it has been associated with a high rate of lymph node metastasis, even though abdominal radiologic images may show no evidence of lymph node metastasis.^[8,9,20,21] However, the presence of lymphovascular invasion can be examined after resection of tumors. Therefore, the detection of lymphovascular invasion before deciding the radical resection or surgical resection of gastroduodenal NETs is limited. So, endoscopic resection of the small-sized gastroduodenal NETs, probably confined to submucosa, is important as a diagnostic or therapeutic tool for gastroduodenal NETs. If the resected specimen shows G1 NET confined to submucosa without lymphovascular invasion, the endoscopic resection can be a curative treatment method. If the resected specimen shows higher grade NETs or lymphovascular invasion, we recommend radical surgical resection. Even if

the endoscopic resection of gastroduodenal NETs is incomplete, we can examine the tumor grade by examining the partially resected specimen or larger amount of tissue obtained during the endoscopic procedure. Therefore, we can determine which type of surgical maneuver to choose, between radical surgical resection and local excision.

The study has several limitations. First, because the data were analyzed retrospectively in a single academic referral center, possible selection bias is an obstacle to generalize these results. A prospective study from multiple institutions may provide more accurate data. Second, because the duration of follow-up is not the same in all patients and low-grade gastroduodenal NETs may progress slowly, the recurrence rate could not be examined accurately. Third, because all data were restricted to Korea, the behavior of metastatic rate may be different from other studies involving other ethnicities. Fourth, we used the WHO 2010 NET grading system instead of the new 2019 WHO classification. Therefore, some grade 3 NET could be classified as neuroendocrine carcinoma instead of grade 3 well-differentiated NET. However, the mitotic rate and Ki67 index is the same between the 2 categories. Moreover, additional pathologic evaluations over the metastatic diseases showed neuroendocrine carcinoma. Fifth, the incidence of lymph node metastasis or distant metastasis was too small to perform multivariate analysis.

Although the clinical course of low-grade gastroduodenal NET has not been fully characterized, most G1 gastroduodenal NETs have been regarded as more indolent courses than grade 2–3 or neuroendocrine carcinoma. Because of high metastatic rates of gastric type 3 and duodenal NETs, the current European Neuroendocrine tumor Society (ENETS) consensus guidelines recommend radical surgical resection with lymph node dissection. However, G1 gastroduodenal NETs with small size (<10 mm in diameter) confined to submucosa without lymphovascular invasion have been treated successfully by surgical wedge or endoscopic resection in several studies, including the present study.^[9,19,20] In the present study, the incidence of metastasis was absent for G1–2 gastroduodenal NETs, regardless of their size. Moreover, grade 2 gastroduodenal NET showed no lymph node or distant metastasis. However, another Korean study showed lymph node metastasis of grade 2 gastric NET despite small tumor size.^[21]

In summary, small gastroduodenal NETs confined to the submucosa without surface ulceration may be suitable for endoscopic resection. After local resection of a gastroduodenal NET (G1) without lymphovascular and muscle proper invasion, follow-up examination without radical surgical resection can be recommended. G3 NETs may be treated by radical surgical resection, regardless of tumor size. Further studies with a larger sample size will enable a more accurate recommendation.

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