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A single center retrospective analysis of feasibility of diagnostic endoscopic resection for grade 1 or 2 gastric neuroendocrine tumors

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Currently, endoscopic resection is recommended for gastric neuroendocrine tumors (G-NETs) < 10 mm. However, a larger G-NETs can also be resected endoscopically. Here, we evaluated the feasibility of diagnostic endoscopic resection of G-NETs. We retrospectively analyzed 31 patients, diagnosed with grade 1 or 2 G-NETs at a single tertiary referral center, between January 2009 and December 2023. Outcomes analyzed included histopathology, complete resection, and metastasis rates. The mean follow-up period was 38.9 ± 38.4 months; mean size of G-NETs was 4.9 ± 3.4 mm, and the most size of G-NETs were < 10 mm (87.1%). The maximal NET diameter was 16 mm. Most NETs were grade 1 (type 1: 90.9%; type 3: 85.0%). None of the enrolled patients showed evidence of lymph node metastasis or local recurrence. Even in R1 resection (19.4%) showed no metastasis during follow-up without additional surgery. Recurrent or multiple G-NETs were observed only in patients with type 1 NETs (27.2%, 3/11). Modified endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) showed a 100% complete resection rate. After resection, grade 1 or 2 G-NETs had no lymph nodes or distant metastases during the follow-up period. This study suggests that G-NETs smaller than 16 mm can be considered for diagnostic endoscopic resection and this resection may be potentially definitive treatment.

Keywords Neuroendocrine tumor, Tumor grade, Stomach, Resection

The increasing utilization of diagnostic endoscopic examinations has resulted in a surge in the detection of gastric subepithelial tumors (SET). Consequently, the detection of gastric neuroendocrine tumors (G-NETs) has increased too. G-NETs develop from enterochromaffin-like cells in the gastric mucosa[1]. A well differentiated NET was previously called a carcinoid tumor, as it exhibited behavior akin to cancer[2]. Currently, all G-NETs are regarded as malignant tumors regardless of their size. The exact incidence of G-NETs remains unclear. Approximately, G-NETs comprise 1.8% of gastric tumors, with a reported annual incidence of 4.97 cases per 1,000,000 in the US[3]. Early detection of G-NETs is associated with a better survival rate[4–7]. The clinical presentation of G-NETs is nonspecific, and carcinoid syndrome is seldom observed. Therefore, G-NETs are usually diagnosed incidentally during endoscopic screening[7–17]. Generally, management plans of G-NET depend on the type (classified by serum gastrin level), maximal tumor diameter, endoscopic features (such as surface ulceration), pathological grade, lymphovascular invasion, and invasion depth. Clinically, G-NETs are classified into three distinct categories: type 1, 2, or 3. Type 1 is associated with atrophic gastritis and elevated gastrin levels, while type 2 is associated with high gastrin levels in gastrinoma or MEN-1. Type 3 is a sporadic form that is not associated with elevated gastrin, gastrinoma, or atrophy[18,19].

The first step in managing G-NETs is classifying them according to their serum gastrin levels. Hypergastrinemia is associated with type 1 and 2, which are usually small (< 10 mm) and multiple in numbers[8]. Patients with G-NET type 1 have an excellent prognosis with 5-year overall survival of up to 100%[20,21]. The characteristics of G-NET type 1 are indolent course, frequent multiple lesions (approximately 72.5%), and high recurrence rate (71.8%)[9].

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Endoscopic resection is the first treatment option for type 1 gastric NETs of < 20 mm, grade 1 or 2, and without evidence of lymph node metastasis[8]. Despite the differences exist depending on the literatures, surgical resection is also recommended for patients with tumors > 10–20 mm because of the risk of coexisting adenocarcinoma or metastasis[8]. G-NET type 2 is associated with Zollinger-Ellison syndrome or multiple endocrine neoplasm type 1[6,8]. Type 3 G-NETs usually develop sporadically and are not gastrin-dependent. Because the metastatic rate of G-NET type 3 is higher (approximately 50%) than that of G-NET type 1 and the worse long-term survival (5-year survival rate of 70%), radical surgical resection with lymph node dissection may be considered, especially for larger tumors (> 10–20 mm), atypical endoscopic surface features (ulceration), lymphovascular invasion, proper muscle invasion, and grade 3 NETs, which are known as high risk features of metastasis[8].

Smaller sized, low-to-intermediate grade G-NETs have recently exhibited favorable long-term outcomes after endoscopic or local resection[9,10,12,14,16]. Although favorable endoscopic resection outcomes have been reported, the selection of endoscopic or surgical resection criteria for patients with G-NETs ≥ 10 mm has not yet been confirmed[8,13,22]. There are some variations depending on literatures, endoscopic resection is generally recommended for G-NET less than 10 mm, but there is still controversy about the suitability of endoscopic resection for G-NET size 10–20 mm[19,23,24] .

Recent advancements in endoscopic resection techniques have enabled us the resection of gastric epithelial or submucosal tumors in one piece, regardless of tumor size. However, the decision to proceed with endoscopic resection depends on the status of lymph node metastasis. Abdominal computed tomography (CT) and endoscopic ultrasound (EUS) examinations cannot accurately predict the status of lymph node metastasis. Therefore, we depend on the higher risk factors associated with lymph node metastasis to guide treatment decisions. Although tumor size, proper muscle invasion, and irregular surface patterns, such as ulceration, can be determined during conventional endoscopic or EUS examination, pathologic factors, especially lymphovascular invasion and grade, can be confirmed only after resection. Generally, surgical treatment of G-NETs is associated with higher surgical complications and lower quality of life than endoscopic resection. Furthermore, if the tumor shows high pathological risk factors for metastasis after localized surgical resection of G-NETs, additional minimally invasive surgery for lymph node dissection may be challenging. Recent endoscopic resection results have demonstrated a lower risk of procedure related complications[25].

This study aimed to analyze the clinical outcomes of G-NETs to assess the risk of disease progression and the feasibility of diagnostic endoscopic resection of low-to-intermediate grade NETs. In particular, this retrospective analysis of the diagnostic endoscopic resection of G-NETs will help guide future management of 10–20 mm G-NETs.

Materials and methods

Patients

Between January 2009 and December 2023, 31 patients with G-NET (grades 1 or 2) who were confirmed through pathologic examination, were retrospectively enrolled from the patient database at Pusan National University Yangsan Hospital (Republic of Korea). Because this is a retrospective study, we did not include cases without pathologically diagnosed neuroendocrine tumor, and we excluded cases with grade 3 neuroendocrine tumor. All the patients underwent conventional endoscopy and abdominal CT. Serum gastrin levels were measured to determine the type of G-NETs. 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 neoplasia or Zollinger-Ellison syndrome. This study was approved by the Institutional Review Board (IRB) of Pusan National University Yangsan Hospital (IRB approval number 55-2024-066). The requirement for informed consent was waived by the Pusan National University Yangsan Hospital ethics committee because the patients' medical records were anonymized prior to analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki. A flowchart of the present study is shown in (Fig. 1).

Tumor characteristics

All data, including baseline characteristics, endoscopic morphologic features, presence of metastasis, treatment modalities, follow-up duration, presence of recurrence, and pathologic data (grade, invasion depth, and lymphovascular invasion), were reviewed retrospectively. Although the retrospective nature of the analysis resulted in a discrepancy in the EUS evaluation, with certain cases being assessed through EUS and others not, the subjects who did not undergo EUS were not excluded from the analysis. EUS was performed with a 20-MHz catheter probe (UM3D-DP20-25R; Olympus). Lesion size was measured from the resected specimen. Surface depression or ulceration was defined as the presence of ulceration or a depressed morphology at the top of the NET. Surface erosion was defined as a mucosal defect. Metastasis status was determined based on surgical results or radiological examinations such as abdominal CT. Typical endoscopic features of G-NETs are shown in (Fig. 2).

Treatment for gastric NETs

During the diagnostic workup, abdominal CT was required to evaluate possible intra-abdominal lymph node metastasis or distant metastasis. If metastatic lymph node enlargement was suspected, radical gastrectomy with lymph node dissection was recommended. For patients with localized G-NETs, decisions of endoscopic or surgical resection were made after discussions with the patients, endoscopists, and surgeons. Endoscopic resection was recommended when the tumor was < 10 mm in diameter and confined to the submucosa on EUS. If the patient declined surgical resection of a 10–20 mm diameter within the submucosa, we first performed endoscopic resection. All procedures were performed by a skilled endoscopist (defined as one with greater than 10 years of experience). Endoscopic resection methods were selected according to the endoscopist's decision or tumor characteristics. Six types of endoscopic resection techniques were utilized: endoscopic submucosal

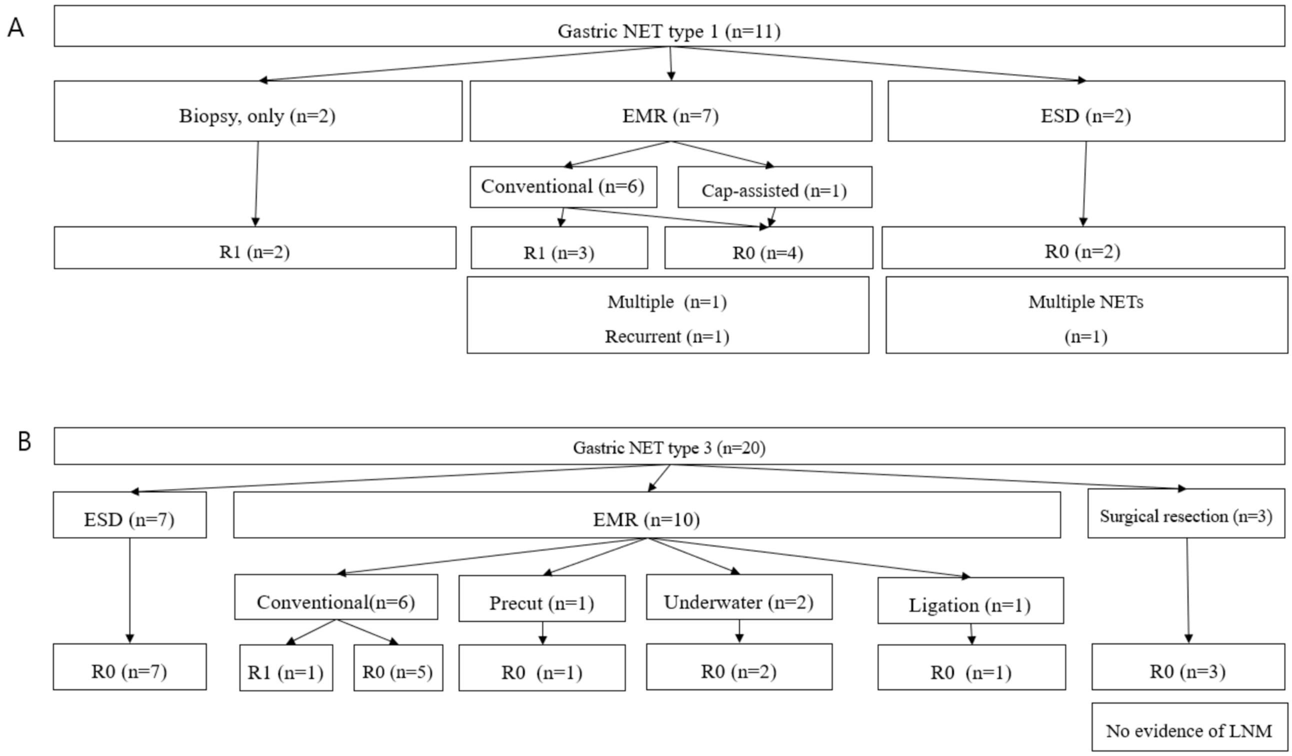


Fig. 1. Patients' management flow and outcomes. (**A**) gastric NET type 1. (**B**) gastric NET type 3. *NET* neuroendocrine tumor, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *R1* microscopic positive resection margin, *R0* negative resection margin, *LNM* lymph node metastasis.

dissection (ESD), modified endoscopic mucosal resection (EMR) techniques (such as EMR after precutting mucosa, band ligation-assisted EMR, cap-assisted EMR, underwater EMR), and conventional EMR. All endoscopic procedures were performed under conscious sedation with intravenous midazolam (3–8 mg) under close monitoring for oxygen saturation. The GIF-H260 or GIF-HQ290 scope (Olympus Optical, Tokyo, Japan) was used for the procedures. In the cases of EMR, the polypectomy snare which can maximally open up to 15 mm was used. In cased of precutting EMR or ESD, Dual Knife or IT knife 2 (Olympus Optical, Tokyo, Japan) was used. Cutting and coagulation were performed with the electrosurgical generator (ERBE VIO300D, Endocut Q mode, Effect 3, duration 2, or Swift coagulation 80 W, Erbe Co., Tubingen, Germany). All patients received an intravenous proton pump inhibitor (PPI) for 3 days and were maintained on per oral PPI for 3 months. All techniques were performed using standard method[26–28].

The various endoscopic treatment methods are shown in (Fig. 3). After resection, patients were recommended to undergo regular examinations at 6 to 12 month intervals, including endoscopic examination and abdominal CT. After endoscopic resection, we recommended additional surgical resection for NETs with a high pathologic risk of lymph node metastasis, including those with grade 3, lymphovascular invasion or incomplete endoscopic resection (R2 resection). If the patient refused resection, we followed the same schedule as mentioned above. All patients were followed at the same intervals (6 to 12 months) and with the same methods, regardless of whether they had R0 resection, R1 resection, or R2 resection without surgery.

Endoscopic procedure induced complications include perforation and bleeding. Perforation was defined as a hole observed during endoscopy or free air detected on abdominal radiography or CT scans. Major bleeding was defined as significant postprocedural bleeding, necessitating surgery or transfusion.

Pathologic evaluation

G-NETs were categorized into three grades based on the 2019 WHO classification[8]. G1 (low grade), defined as mitotic count <2 in 2 mm^2 and/or Ki-67 index $<3\%$ in hotspots with at least 500 cells. G2 (intermediate grade), defined as mitotic count between 2 and 20 in 2 mm^2 and/or Ki-67 index between 3 and 20% in hotspots containing at least 500 cells. G3 (high grade), defined as mitotic count >20 in 2 mm^2 and/or Ki-67 index $>20\%$ in hotspots with at least 500 cells. Two pathologists reviewed all tissue slides blindly. Discordant cases were re-evaluated under a multi-headed microscope to reach an agreement. Resected specimens were stretched, pinned, and fixed in formalin. Several immunohistochemical neuroendocrine markers, such as chromogranin A, synaptophysin, and CD56, were used to diagnose NET. All the resected specimens were histologically evaluated using light microscopy at low power and high magnification.

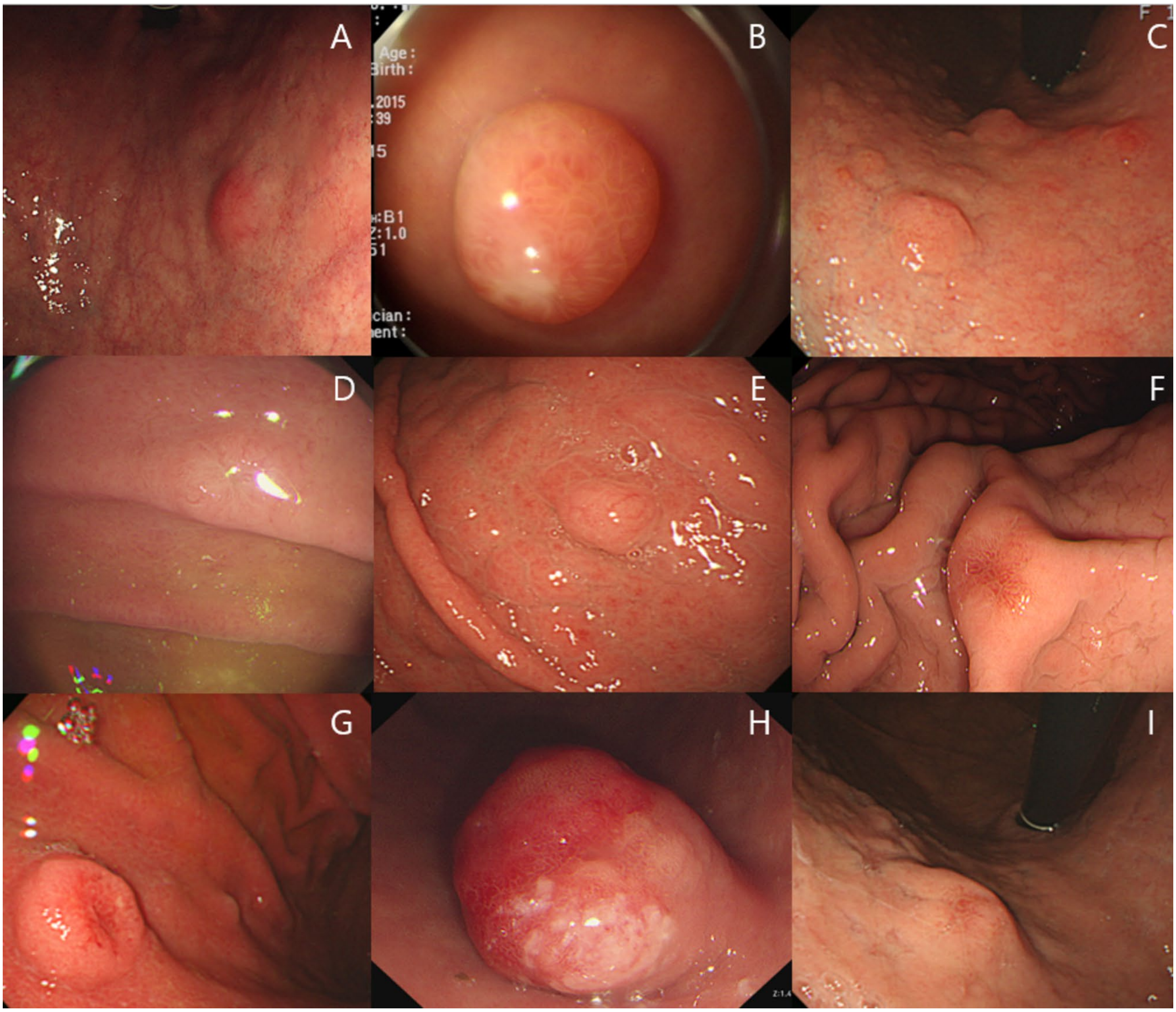


Fig. 2. Endoscopic findings of gastric neuroendocrine tumors. (**A**–**C**) illustrate type 1 G-NET. (**A**) Erythematous flat elevated sessile polyp. (**B**) Erythematous polyp with narrow neck. (**C**) Multiple erythematous small polyps. (**D**–**I**) are type 3 G-NET. (**D**) Minute submucosal tumor-like elevation with surface depression. (**E**) Polyp-like elevation with similar erythematous surface mucosa compared with the surrounding mucosa. (**F**) Submucosa tumor-like fold thickening with reddish surface depression. (**G**) Submucosal tumor with ulceration on the surface. (**H**) Large polyp-like elevated tumor with erythema and irregular surface with whitish exudate. (**I**) Broad-based submucosa tumor with surface erosion. *G-NET* gastric neuroendocrine tumor.

Statistical analysis
Data were presented as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. For continuous variables, the Student's t-test was performed. Univariate analysis was performed using the chi-squared test or Fisher's exact test for categorical variables. Statistical significance was set at $p < 0.05$. Statistical calculations were performed using PASW Statistics for Windows (version 22.0; SPSS Inc., Chicago, IL, USA).

Results
The mean age of patients with G-NET was 56.6 ± 2.1 years. In G-NET type 1, females were predominant (63.5%), whereas males were predominant in G-NET type 3 (65.0%). Most G-NETs were located in the middle and upper thirds of the stomach (67.7 and 22.6%, respectively). The mean tumor size was 4.9 ± 3.3 mm, with type 3 NETs being larger than type 1 (mean tumor size: 5.6 mm and 3.6 mm, respectively). Although all type 1 G-NETs were < 10 mm, four patients with type 3 NETs had tumor size ≥ 10 mm (20% of type 3). The largest tumor diameter was 16 mm (Fig. 3A). Most of the G-NETs were G1 tumors (total: 87.1%; type 1, 90.9%; and type 3, 85.0%). EUS was performed in more than half of the cases ($n = 18$, 58.1%). The mean resected size of the group without EUS

was smaller than the group with EUS (3.4 ± 1.8, 6.1 ± 3.84, Mean ± SD, respectively) suggesting that EUS was often omitted in the group with visually smaller lesions. CT scans were performed in all cases and there was no evidence of lymph node or distant metastasis on CT images. None of the enrolled G-NETs showed evidence of proper muscle invasion. Initial endoscopic biopsy was diagnostic in 93.5% of patients (Table 1).

Most G1 or G2-NETs were treated with endoscopic resection (90.3%) at first. Surgical resection was done in four patients. The first patient (grade 1, 5 mm; type 3) was diagnosed incidentally after a subtotal gastrectomy for gastric adenocarcinoma. Although the tumor in the second patient was 11 mm in size with surface ulceration (Fig. 2G), categorized as grade 1 with lymphovascular invasion, there was no evidence of lymph node metastasis after subtotal gastrectomy with lymph node dissection. Although the third patient's lesion was 19 mm in size, with surface erosion on EUS (Fig. 2I), the final surgical result was an 11 mm sized grade 2 NET without lymphovascular invasion or lymph node metastasis. The last patient who initially underwent EMR, underwent additional surgical resection because the NET was diagnosed as 16 mm in size with lymphovascular invasion (Figs. 2H and 3A). However, there was no evidence of lymph node metastasis after radical resection with lymph node metastasis.

Conventional EMR was the most common initial treatment for type 1 gastric NET. Marginal involvement was more common in type 1 gastric NET (lateral and vertical marginal involvement was 36.4 and 45.5%, respectively). All patients with marginal involvement were followed up without additional surgical treatment. In patients undergoing modified EMR or ESD, all NETs were resected pathologically completely (R0 resection rate: 100%). Mean follow-up period was 38.9 ± 38.4 months. No evidence of metastasis was observed during follow-up (Table 2).

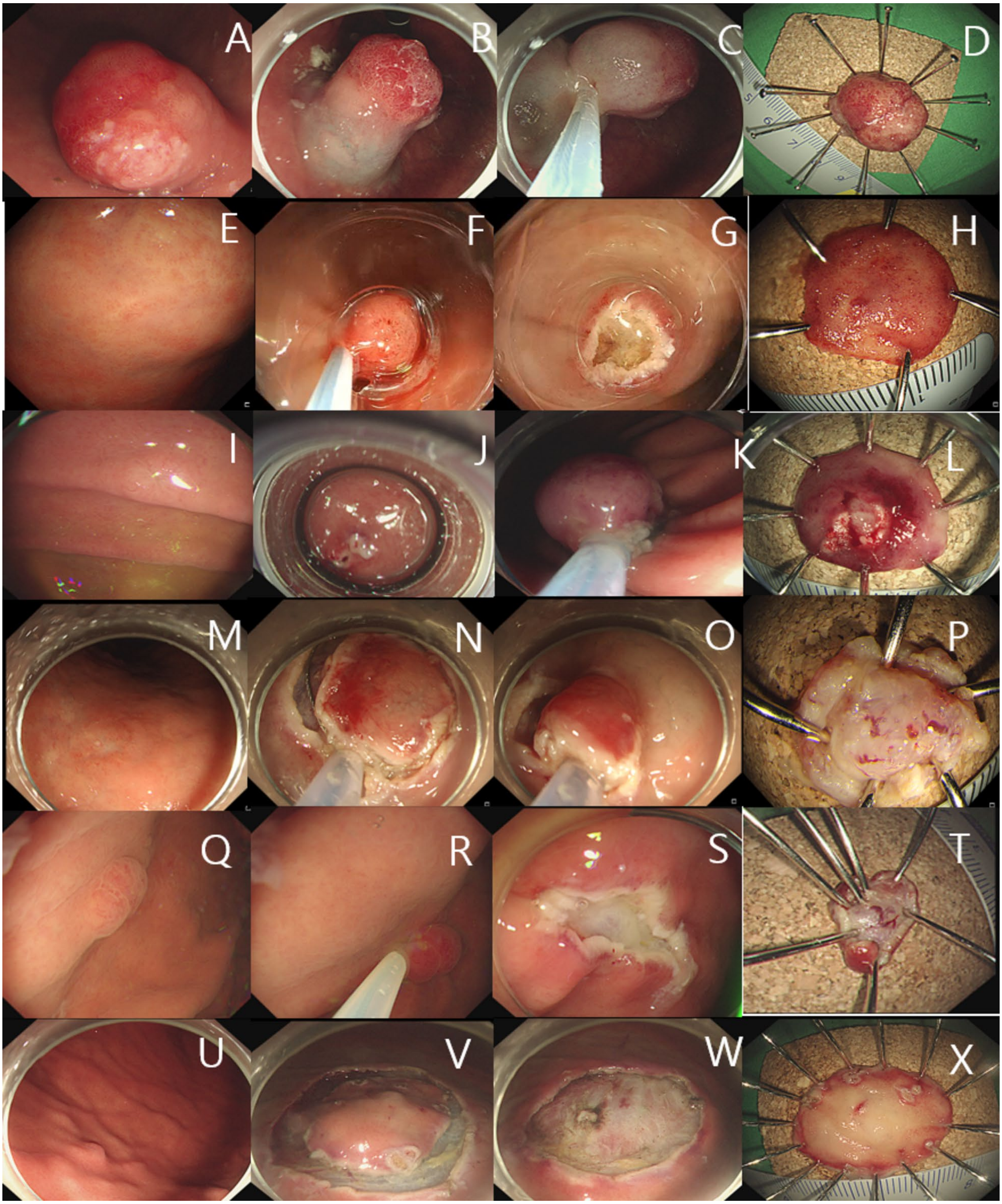
Discussion

This study primarily aimed to evaluate the feasibility of diagnostic endoscopic resection of grade 1 or 2 G-NETs. Ultimately, the study demonstrated that G-NETs ≤ 16 mm in maximal diameter showed no evidence of distant or lymph node metastasis after endoscopic or surgical gastrectomy with lymph node dissection. Generally, the decision of endoscopic resection depends on the G-NET type, size, pathologic grade, invasion depth, and lymphovascular invasion. In the case of G-NET, the disease is classified into three distinct clinical types (i.e., Type 1, 2, and 3). This variability contributes to the complexity of establishing a unifying treatment, which is further compounded by the disease severity associated with the pathological grade and tumor size. Although there are some variations in the available literature, for the small Type 1 G-NET, some studies recommend endoscopic resection, while others suggest a wait-and-see approach. For Type 3, some studies advocate for surgical intervention if feasible, while others recommend endoscopic resection for smaller G-NETs[19,23,24,29]. Based on the findings of the present study, low-to-intermediate grade G-NETs ≤ 16 mm can be managed through diagnostic endoscopic resection to examine the pathologic risk of lymph node metastasis.

Recently, local resection, especially endoscopic resection, has been recommended for malignant gastric tumors without a risk of lymph node metastasis. However, to date, there are no definitive diagnostic tools for the accurate prediction of lymph node metastasis, including EUS and abdominal CT. Therefore, there have been many reports on the risk factors for the prediction of lymph node metastasis. Endoscopic risk factors, such as NET size, surface ulceration, and proper muscle invasion, can be checked by endoscopic examinations, including EUS. However, pathological risk factors, including NET grade, lymphovascular invasion, and minute proper muscle invasion, can be confirmed after tumor resection. Recent guidelines recommend endoscopic or local surgical resection for gastric NETs with a size < 10 mm without surface ulceration. However, after surgical resection for gastric NETs with size ≥ 10 mm, with or without atypical surface ulceration/erosions, most patients show no evidence of lymph node metastasis after lymph node dissection, as in the present study. Therefore, we propose that endoscopic resection can be adapted for all gastric NETs within 16 mm, regardless of the overlying mucosa pattern for grade 1 or 2 NETs with no evidence of lymph node enlargement or distant metastasis on abdominal CT.

In this study, two small multiple polyp-like G-NET type 1 lesions were biopsied multiple times and followed up without NET-associated symptoms or mortality. Moreover, in patients with multiple prominent gastric NETs resected endoscopically, there was no evidence of NET-associated morbidity or mortality during the follow-up period. No G-NET type 1 were > 10 mm in size in this study. If type 1 G-NETs are not prominent and are only detected through endoscopic forceps biopsy, regular follow-up is the preferred management option instead of surgical gastric resection because of the indolence and overall good prognosis[10,30].

G-NET management guidelines recommend an endoscopic resection size limit of < 10 mm for type 3 NETs. However, after surgical resection, most NETs < 20 mm in size showed no evidence of lymph node metastasis, similar to the findings of the present study. A size limit of 10 mm may be too conservative as a cutoff for endoscopic resection. Some clinicians, particularly expert therapeutic endoscopists, believe that endoscopic resection methods should be considered for the treatment of malignant or premalignant tumors without the risk of lymph node metastasis. However, recent endoscopic resection methods should be regarded as the diagnostic method for evaluating the possible risk of lymph node metastasis at first rather than as a treatment method. If resected tissue specimens show complete resection (en-bloc resection with clear pathologic margin), confinement within the submucosa, low-to-intermediate grade NETs (grade 1 or 2), and no lymphovascular invasion, endoscopic resection can be regarded as curative. However, in cases of resected tissues showing a high risk of lymph node metastasis-related factors, such as incomplete resection (R2), proper muscle invasion, or high grade NET (grade 3), performing curative additional surgical resection is necessary because we diagnosed the G-NETs as a NET having a higher risk of lymph node metastasis. We propose that this is a reasonable approach for type 3 G-NETs because overtreatment with surgical resection may lead to potential postoperative complications and their impact on the patient's quality of life.



In the present study, four patients with ≥ 10 mm in size were identified. Among them, two patients diagnosed with suspicious grade 2 G-NET after endoscopic forceps biopsy, were treated by radical surgical resection with lymph node dissection and showed submucosal invasive NET without evidence of lymphovascular invasion or lymph node metastasis. Another patient treated with ESD showed no evidence of lymphovascular invasion (macro perforation was managed by endoscopic clip closure during the endoscopic procedure). The last patient was diagnosed with lymphovascular invasion after EMR, and additional radical surgical resection with lymph node dissection showed no evidence of lymph node metastasis. Therefore, radical surgical resection should be considered after pathological confirmation of endoscopically resected specimens.

An adequate endoscopic forceps biopsy of G-NETs is essential for grading NETs. As NETs are usually located in the deep mucosa or submucosa (rather than at the surface epithelium, such as adenocarcinoma), attention should be paid during endoscopic forceps biopsies. The diagnostic rate of endoscopic forceps biopsy for other

◀**Fig. 3**. Various endoscopic treatment methods for G-NETs. (**A–D**) indicate conventional EMR methods. A narrow-necked, subepithelial tumor (SET) is detected (**A**). After submucosal injection (**B**), electrosurgical snaring is performed (**C**). An en-bloc resection was achieved (**D**) E–H represent cap-assisted EMR. A erosive NET is seen (**E**). After submucosal injection, the crescent-shaped snare is positioned on the internal circumferential ridge at the tip of the oblique cap and snare is mounted at the ridge of the cap (**F**). Electrosurgical snaring is performed (**G**). An en-bloc resection was achieved (**H**). (**I–L**) show band-ligation-assisted EMR. A broad-based, submucosa tumor with surface erosion is seen (**I**). After submucosal injection, band-ligation is performed (**J**). Electrosurgical snaring is performed under the band (**K**). An en-bloc resection was achieved (**L**). M–P are precut EMR. A erosive NET is seen (**M**). After submucosal injection, circumferential mucosal incision was performed (**N**). After precut mucosal incision, snare resection was performed (**O**). An en-bloc resection was achieved (**P**). q–t illustrate underwater EMR. A polyp with reddish mucosa changes is seen (**Q**). After filling the lumen with distilled water, snaring was done without submucosal injection (**R**). Artificial ulcer bed was clear (**S**). An en-bloc resection was achieved (**T**). U-X illustrate ESD. A polyp with reddish mucosa changes is seen (**U**). After submucosal injection, circumferential mucosal incision was performed (**V**). After complete submucosal dissection, artificial ulcer bed is clear (**W**). En-bloc resection was done (**X**). *G-NET* gastric neuroendocrine tumor, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection.

	Type 1 (*n* = 11)	**Type 3 (*n* = 20)**	**Total (*n* = 31)**	***P* value**
Age, years, mean (SD)	57 (11.6)	56.4 (12.8)	56.6 (2.1)	0.907
Sex, Male, n (%)	4 (36.5)	13 (65.0)	17 (54.8)	0.153
Location, n (%)				0.391
Lower	0 (0)	3 (15)	3 (9.7)	
Middle	8 (72.7)	13 (65.0)	21 (67.7)	
Upper	3 (27.3)	4 (20)	7 (22.6)	
Endoscopic findings, n (%)				
Erythema, n (%)	11 (100)	18 (90)	29 (93.5)	0.278
Erosion, n (%)	1 (9.1)	9 (45.0)	10 (32.3)	0.041
Polyp-like, n (%)	10 (90.9)	8 (40.0)	18 (58.1)	0.006
Depression, n (%)	0 (0)	2 (10.0)	2 (6.5)	0.278
Grade, n (%)				0.639
Gr 1	10 (90.9)	17 (85.0)	27 (87.1)	
Gr 2	1 (9.1)	3 (15.0)	4 (12.9)	
Tumor size, mm, mean (SD)	3.64 (2.11)	5.65 (3.77)	4.94 (3.386)	0.114
Tumor size > 9 mm, n (%)	0 (0)	4 (20)	4 (12.9)	0.112
Biopsy, confirm, n (%)	11 (100)	18 (90)	29 (93.5)	0.527

Table 1. Baseline characteristics of gastric neuroendocrine tumors. *SD* standard deviation, *n* number, *Gr* grade.

gastric SETs is usually as low as 14–42% using bite-on-bite techniques[31,32]. However, in the present study, most of the patients with G-NET were diagnosed using endoscopic forceps biopsy (29/31, 93.5%). The majority of gastric SETs < 20 mm are recommended for periodic endoscopic follow-up rather than histologic diagnosis. This is based on the observation that the most common gastric SET, gastrointestinal stromal tumors (GIST), located in the deep proper muscle layer, are difficult to obtain tissue, and that small GISTs (< 2 cm) usually behave as benign[33]. Conversely, it is suspected that SETs are NETs, and it is essential to obtain sufficient tissue for a definitive diagnosis of G-NETs. Since NETs are usually located in the deep mucosal layer, subtle changes in the surface mucosa can be observed during meticulous endoscopic examination. Usually, G-NETs are accompanied by surface mucosal changes, including red or yellowish color changes. If multiple hyperplastic gastric polyp-like lesions are observed, multiple endoscopic forceps biopsies should be performed to rule out NETs.

Management decisions are difficult after R1 endoscopic resection of G-NETs. If remnant NETs are highly suspected after EMR (R2), additional ESD or endoscopic full thickness resection may be optional. However, most R1 cases of G-NETs show no visible remnant tissue after resection. Since NETs are located in the deep mucosa or submucosa, conventional EMR techniques are usually associated with marginal involvement after resection. Therefore, modified EMR techniques such as ligation-assisted EMR, cap-assisted EMR, underwater EMR, and ESD are more recommendable because of the relatively higher R0 resection rate than conventional EMR or polypectomy[10,14,20]. In this study, 12 conventional EMRs, 5 modified EMRs, and 9 ESDs were performed. NET originate from the submucosal layer, and it is necessary to resect the submucosal layer as close to the proper muscle as possible to achieve pathologic complete resection. Conventional EMR is characterized by its simplicity; however, it has difficulty capturing the deep submucosal layer. To overcome this obstacle, a modified EMR technique was introduced. Cap-assisted EMR utilizes a cap to suction and capture the deeper submucosal layer, band ligation EMR involves the placement of a band beneath the NET and the subsequent resection beneath

	Type 1 ($n = 11$)	Type 3 ($n = 20$)	Total ($n = 31$)
Initial treatment, n (%)			
Biopsy only	2 (18.2)	0 (0)	2 (6.5)
EMR	6 (54.5)	6 (30.0)	12 (38.7)
Cap-assisted EMR	1 (9.1)	0 (0)	1 (3.2)
Precut EMR	0 (0)	1 (5.0)	1 (3.2)
Underwater EMR	0 (0)	2 (10.0)	2 (6.5)
Ligation-assisted EMR	0 (0)	1 (5.0)	1 (3.2)
ESD	2 (18.2)	7 (35.0)	9 (29.0)
Operation	0 (0)	3 (15.0)	3 (9.7)
Depth of invasion, n (%)			
Mucosa	3 (27.3)	7 (35.0)	10 (32.3)
Submucosa	8 (72.7)	13 (65.0)	21 (67.7)
Lymphovascular invasion, n (%)	0 (0)	1 (5.0)	1 (3.2)
Marginal involvement, n(%)			
Lateral margin involvement	4 (36.4)	1 (5.0)	5 (16.1)
Vertical margin involvement	5 (45.5)	1 (5.0)	6 (19.4)
R0, n (%)	6 (54.5)	19 (95.0)	25 (80.6)
Surgical resection, n (%)	0 (0)	4 (20)	4 (12.9)
Follow-up, months (SD)	51.3 (48.8)	32.1 (30.6)	38.9 (38.4)
Submucosa invasion, n (%)	8 (72.7)	13 (65.0)	21 (67.7)
Lymphovascular invasion, n (%)	0 (0)	1 (5.0)	1 (3.2)
Recurrent lesions, n (%)	1 (9.1)	0 (0)	1 (3.2)
Multiple lesions, n (%)	2 (18.2)	0 (0)	2 (6.5)
Complication after endoscopic resection, n (%)	0	1[¶] (5.0)	1 (3.2)

Table 2. Results after treatment of gastric neuroendocrine tumors. *n* number, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *R0* negative resection margin, *SD* standard deviation. [¶]Macroperforation during ESD, successfully treated with endoscopic clipping.

the band. Precut EMR is a method of snaring already precut lesion, underwater EMR is a method that uses buoyancy to facilitate mucosal capture without submucosal injection. ESD offers the benefit of facilitating the acquisition of lateral and vertical margin uninvolvement due to dissection while maintaining direct visualization of the base of the NET. However, it is important to note that the procedure is technically challenging and carries a higher risk of complications when compared to EMR[34–36]. The present study results showed 100% R0 results for modified EMR and ESD. In particular, the 16 mm G-NET, the largest G-NET in this study, was removed by EMR, which is a G-NET with narrow neck (Fig. 3A), and therefore EMR was possible. In cases where the lesion size is larger than 10 mm and snaring may be technically difficult, it is necessary to select an appropriate resection method based on the shape of the lesion or the endoscopist's experience.

Some reports recommend no additional treatment for gastric NET type 1 lesions < 10 mm in size because of their indolent course after R1 resection[8]. In the present study, patients with no additional treatment after endoscopic forceps biopsy and R1 resected NET type 1 or 3 showed no NET-related morbidity or mortality during the follow-up period. For type 3 NET treated with R1 resection after endoscopic resection, the visible ulcer bed was clear in all patients. Surgical indications could be limited to NETs with visible remnant NETs after endoscopic resection (R2), proper muscle invasion, suspicious lymph node metastasis by CT or EUS, > 16 mm, grade 3, or lymphovascular invasion after endoscopic resection.

The present study has some limitations. First, because the data were analyzed retrospectively in a single academic referral center, a potential selection bias is an obstacle to generalizing these results. Prospective studies involving multiple institutions could provide more accurate data. In addition, the small number of cases included in the study ($n = 31$) may limit the generalizability of this study. For instance, one meta-analysis of type 1 G-NETs in 769 patients from 13 studies reported a 0.8% chance of lymph node metastasis, even in type 1 G-NETs measuring less than 10 mm. Overall similar, but this minor difference is mainly attributable to selection bias resulting from the study's limited sample size[37]. Second, the varying duration of follow-up among patients, coupled with the slow progression of low grade G-NETs, impedes the accurate examination of the recurrence rate. This is because of the number of cases was small, and those who were diagnosed earlier were followed longer, and those who were diagnosed more recently were followed for shorter periods. and the total number of cases was too small to categorize cases that were followed for more than a certain period of time. Third, as all data were restricted to the Republic of Korea, the metastatic rate may differ from that in other studies involving other ethnicities. Fourth, the incidence of lymph node metastasis or lymphovascular invasion was too low to perform multivariate analysis.

In conclusion, this study showed that patients with low-to-intermediate grade G-NETs ≤ 16 mm in size showed favorable clinical outcomes. Incomplete R1 resection of these G-NETs had no significant impact on the patient's clinical outcomes. A stepwise approach, utilizing more advanced resection techniques, such as conventional EMR, modified ligation-assisted EMR, ESD, and surgical resection, may be justified as a diagnostic and treatment management approach considering the low risk of lymph node metastasis for grade 1 or 2 G-NETs. This approach must balance the risk of lymph node metastasis and the procedure-related risk of complications. For patients with worse comorbidities or older patients, considering the risk of surgical complications and low quality of life, diagnostic endoscopic resection is preferable for all G-NETs of grade 1 or 2 ≤ 16 mm in size. Although there are some variations in the literature, endoscopic resection is recommended for G-NETs smaller than 10 mm, and endoscopic resection may be considered for G-NETs between 10 and 20 mm[19,23,24]. This study reports good results with endoscopic diagnostic resection of NETs up to 16 mm. However, multidisciplinary team discussions with the patients should be conducted.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

JO Jang and WJ Jang: writing and editing the manuscript equally; CW Choi and EJ Choi: conceptualization and approved the final article; JH Chung, SH Lee and SH Hwang; data collection and interpretation; SJ Kim, DG Ryu and SB Park; editing and reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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