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Differential Diagnosis of Thickened Gastric Wall Between Hypertrophic Gastritis and Borrmann type 4 Advanced Gastric Cancer

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Differential Diagnosis of Thickened Gastric Wall Between Hypertrophic Gastritis and Borrmann type 4 Advanced Gastric Cancer

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Abstract

Backgrounds

Accurately diagnosing diffuse gastric wall thickening is challenging for endoscopists. Hypertrophic gastritis (HG), while benign, mimics the morphology of advanced gastric cancer Borrmann type 4 (AGC B-4). We compared the features of endoscopy and endoscopic ultrasonography (EUS) between HG and AGC B-4.

Methods

We retrospectively investigated patients who underwent EUS for thickened gastric wall between January 2000 and December 2021. Among them, those with HG or AGC B-4 were selected. All diagnoses of AGC B-4 were pathologically confirmed. Endoscopy was performed to determine the presence of ulceration and antral wall thickening. In EUS, 5-layered gastric layers at the most thickened fold were evaluated by measuring the thickness of the proper muscle (PM) and total wall layers, and the location of hypoechoic disruption of the 5-layered gastric wall structure was initially assessed.

Results

Fifty patients with HG and 115 patients with AGC B-4 were included. Male dominance was observed in AGC B-4, as well as significantly lower hemoglobin, albumin levels. AGC B-4 had a significantly higher rate of antral wall thickening and presence of ulceration than HG. Destruction of the proper muscle (PM) layers was only observed in AGC B-4, and the PM was significantly thicker in AGC B-4. In pathologic diagnosis in AGC B-4, if there were ulcers, forcep biopsy showed excellent success rate. However, since only a 42.6% success rate in patients without ulcers, so additional modalities were required. When we plotted the receiver operating curve to distinguish between AGC B-4 and HG based on PM thickness, 2.39 mm was the cut-off value. The multivariable analysis showed that thickened PM layer and presence of ulceration were significant risk factors for the diagnosis of AGC B-4.

Conclusion

Significant differences in baseline characteristics and laboratory findings were observed between HG and AGC B-4. In AGC B-4 without ulceration, other diagnostic modalities than forcep biopsy might be required for pathologic confirmation. PM layer 2.39 mm was the cut-off value to distinguish the diseases and the presence of thickened PM and ulceration should make AGC B-4 more suspicious.
Keywords: Endoscopic ultrasonography; Gastritis; Gastric neoplasms

Introduction

An accurate diagnosis of diffuse gastric wall thickening is challenging for endoscopists since appropriate biopsy sampling is challenging [1]. Causes of diffuse gastric wall thickening include rugal hypertrophic gastritis, amyloidosis involving the stomach, Zollinger-Ellison syndrome, lymphoma, and gastric cancer [2-4]. Hypertrophic gastritis (HG) is a benign disease mimicking the morphology of diffuse infiltrative cancer such as advanced gastric cancer Borrmann type 4 (AGC B-4). Since the prognosis of advanced gastric cancer is poor, their timely and accurate diagnosis is of the utmost importance [5, 6].

Although endoscopic findings, including rigidity, luminal distensibility, and the presence of mucosal break or ulcer may aid in differentiation [7, 8], endoscopic ultrasonography (EUS) can potentially assist in evaluating the gastric wall [9-15]. In AGC B-4, obtaining adequate tissue with forceps biopsy for pathologic diagnosis is challenging because of the deeply penetrative characteristics of diffuse infiltrative cancer beneath the mucosa [1, 16]. Accordingly, various diagnostic methods are utilized, including strip biopsy, unroofing biopsy, EUS-guided fine needle aspiration/biopsy (EUS-FNA/B), or, ultimately, surgery [10].

An endoscopic biopsy can generally confirm the diagnosis without these modalities, while typical EUS findings can help differentiate the two diseases. However, in the case of early-stage AGC B-4, in which no malignant cells were found in repeated endoscopic biopsies or in which cancer invasion was limited to the muscularis propria layer without significant thickening, an early diagnosis might be delayed even if typical findings were seen in the endoscopy, which may also affect the prognosis of the patient. Therefore, we aimed to analyze the endoscopic and endosonographic features of HG and AGC B-4 and identify adequate diagnostic methods for the pathologic diagnosis of AGC B-4.

Methods

Patients

We retrospectively investigated patients who underwent EUS for the differential diagnosis of thickened gastric wall between January 2000 and December 2021 at Asan Medical Center. Medical history, clinical symptoms, laboratory findings, *Helicobacter pylori* (*H. pylori*) infection status,

endoscopic findings, pathologic results, EUS findings, and final diagnosis were reviewed from electronic medical records. Patients diagnosed with HG or AGC B-4 were selected, while those with other diagnoses were excluded. All diagnoses of AGC B-4 were pathologically confirmed. Most patients with HG were followed up at the hospital and confirmed to be stable without disease progression. Biopsy report showed chronic active gastritis with foveolar epithelial hyperplasia in patients with hypertrophic gastritis. Patients of AGC B-4 were classified according to the preservation of the 5-layered gastric wall structure on EUS and the presence of ulceration on endoscopy, respectively. This study was approved by the Institutional Review Board of Asan Medical Center (Approval number: 2021-1434).

Endoscopic examination

All patients underwent EGD for evaluation of disease involvement. The presence of diffuse wall thickening was evaluated and if abnormal wall thickening was observed in the antrum, an antral wall thickening was defined (Figure 1). In addition, if there was an erosion or ulceration between or on the thickened wall, defined as 'ulcer', was conducted. Ulcers unrelated to disease involvement, such as peptic ulcer, were excluded. In almost all patients, diffuse wall thickening could be seen on the official CT reading (99.1%) (Supplementary table 1).

Endo-ultrasonographic examination

Experienced endoscopists performed EUS with radial/linear echoendoscope or miniprobe. All patients were sedated using intravenous midazolam before the procedure, and the lumen of the stomach was filled with 300–600 mL of deaerated water. Next, 5-layered gastric layers at the most thickened fold were evaluated by measuring the thickness of the proper muscle (PM) and total wall layers, and the location of hypoechoic disruption of the 5-layered gastric wall structure was initially assessed by endosonographers. And later these findings were retrospectively reviewed again by experienced endosonographer (D.H.K) with more than 15 years of experience. Total wall thickness was defined as thickness from the luminal to the extraluminal border. The maintained PM layer and subserosal layers

were defined as a ‘preserved wall layer’, and disruption to the two layers was defined as a ‘destructed wall layer’ (Figure 2). The presence of ascites was also evaluated.

Method of biopsy

Endoscopic forceps biopsy, EUS-guided fine needle aspiration or biopsy (EUS-FNA/B), endoscopic mucosal resection (EMR) and unroofing biopsy, surgery, and other methods including ascites cytology and skin biopsy were performed for pathologic evaluation. EUS-FNA/B was conducted using a linear array echoendoscope at the thickened layers with 19- or 22-gauge needles. EMR or unroofing biopsy was performed using an electrocautery snare or knife for mucosal resection with or without submucosal injection of the saline–epinephrine solution. The success rate of each biopsy method, defined as the number of attempts divided by successful cases, was evaluated.

Statistical methods

All continuous variables are summarized using mean and standard deviation (SD) or median and interquartile range (IQR) when they did not present with a normal distribution. Categorical variables are presented as percentages. Student’s *t*-test was used to compare the thickness of each layer between the groups. Values of $p < 0.05$ were considered significantly different. Receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal PM layer thickness to predict AGC. We selected the significant factors such as thickened PM layer, sex, abdominal pain, weight loss, nausea or vomiting, antral wall thickening, and presence of ulceration and conducted a univariate analysis. Multivariable logistic analysis was performed in patients with AGC B-4 and a preserved wall layer and HG because measuring the PM layer in AGC B-4 with a destructed wall layer is insufficient. Statistical analyses were performed using Statistical Analysis System (SAS) software.

Results

Baseline characteristics

We identified 194 patients with thickened gastric fold who underwent EUS. Among them, we excluded those with normal-like rugae on endoscopy or EUS (n=8), early gastric cancer (n=2), other Borrmann type AGC (n=6), and lymphoma (n=13). The other Borrmann types were based on the post-operative pathologic report. A total of 50 and 115 patients were diagnosed with HG and AGC B-4, respectively. Patients with AGC B-4 were classified according to the presence of ulceration and preservation of the wall layer (Figure 3).

The ratio of males to females in patients with AGC B-4 was 72:43. In contrast, female dominance was observed among those with HG (14:36). Clinical manifestations, including weight loss, nausea or vomiting, and dyspepsia were significantly more common in patients with AGC B-4 than in those with HG. However, *H. pylori* infection was significantly more prominent in patients with HG than with AGC B-4 (80.0% vs. 40.9%, $p < 0.001$). Laboratory findings showed significant lower hemoglobin and total albumin levels in patients with AGC B-4 than with HG (14.6 vs. 12.9, $p < 0.001$ and 4.2 vs. 3.9, $p = 0.047$) (Table 1).

Endoscopic findings

A significantly higher rate of antral wall thickening was associated with AGC B-4 than HG (39.1% vs. 4.0%, $p < 0.001$). There were also significantly more ulcerations in patients AGC B-4 than with HG (59.1% vs. 4.0%, $p < 0.001$) (Table 2).

Endosonographic findings

Patients with destructed layers were only identified in the AGC B-4 group (n=50). A mini probe, linear probe, and radial probe were used for diagnosis. EUS revealed significant differences in total wall thickness between AGC-B4 with persevered and destructed wall layers and HG (9.6 [8.5–14.0] vs. 14.3 [11.5–18.8] vs. 9.9 [6.9–14.4) mm, $p < 0.001$). AGC B-4 with a preserved wall layer showed a significantly larger value in PM thickness than that of the HG (3.9 (2.9–4.8) vs. 1.2 [0.9–1.7] mm, $p < 0.001$). In the presence of ascites, there were significantly more patients in AGC B-4 with a destructed

wall layer than with a preserved wall layer (14.0% vs. 1.5%, $p = 0.001$). No ascites was observed in HG (Table 3).

Diagnostic methods of AGC B-4

Patients with AGC B-4 with ulcers showed significantly higher success rates, especially in forceps biopsy, than those without ulcers (92.6% vs. 42.6%, $p < 0.001$). In AGC B-4 without ulcer, since forcep biopsy showed lower success rate (42.6%), additional advanced methods other than forcep biopsy were required for pathologic diagnosis, including EUS-FNA/B, EMR, unroofing biopsy, surgery, or extra-gastric pathologies such as ascites cytology or skin biopsy. In the case of EUS-FNA/B, it showed a 50.0% of success rate. EMR or unroofing biopsy showed 75.0% and 50.0% success rates in patients without and with an ulcer, respectively (Table 4).

ROC for prediction of advanced gastric cancer

The ROC curve according to the thickness of total wall layers and PM layer among patients with preserved wall layer was shown in Figures 4-A, and B. The AUCs were 0.5295 and 0.9877, respectively. The cutoff value for the PM layer predicting AGC B-4 with preserved wall layer was 2.39 mm, and it showed the highest sensitivity and specificity with the value of 0.92 and 1.00, respectively.

Multivariable logistic analysis

In the univariate analysis, thickened PM layer (≥ 2.39 mm), male sex, weight loss, antral wall thickening, and ulceration significantly increased the risk of AGC B-4 with a preserved wall layer. In the multivariable analysis, thickened PM layer (OR 637.08, 95% CI: 37.88–10714.97, $p < 0.001$) and presence of ulceration (OR 48.62, 95% CI 2.61–906.81, $p = 0.009$) were significant risk factors for AGC B-4 with a preserved wall layer (Table 5).

Discussion

Gastric cancer is approximately twice as common in males than females and can cause various

symptoms, including nausea, vomiting, and weight loss after progression [17-20]. In our study, patients with AGC B-4 showed male dominance and presented with symptoms such as weight loss, nausea, vomiting, or dyspepsia compared with those with HG. Hypoacid status caused by *H. pylori* infection is associated with HG, which showed a significantly higher rate of *H. pylori* than AGC B-4 [21]. Some patients in the AGC B-4 groups who underwent upfront surgery or were admitted to the oncology department for chemotherapy were not evaluated for *H. pylori* infection.

Akbas et al. previously reported that antral wall thickening in CT (13.68 mm vs. 9.22 mm, $p < 0.05$), lower hemoglobin (10.78 g/dL vs. 12.64 g/dL, $p < 0.05$), and lower albumin level (4.2 mg/dL vs. 3.9 mg/dL, $p = 0.047$) were more frequently observed in malignant gastric disease compared with benign gastric disease [22]. In our study, Hb levels of AGC B-4 were significantly lower than that of HG.

A previous study demonstrated that patients with Menetrier's disease had diffuse thickening of the gastric wall, often with antral sparing [23]. In our study, most cases of HG did not have antral wall thickening, while AGC B-4 had significantly higher rate of it. Accordingly, if antral wall thickening was noted, it might suggest a higher possibility of malignant disease than benign disease.

A few studies reported that the average gastric wall thickness in trans-abdominal ultrasonography was approximately 4–7 mm, and Rapaccini et al. suggested further evaluation for pathologic tests when the gastric wall is greater than 7 mm on CT [24-26]. Tongdee et al.proposed an antral thickness of 10 mm as a cut-off point criterion for differentiating malignancy and non-malignancy conditions [27] and Lim et al. have shown that gastric wall thicknesses greater than 9.8 mm and thickened muscularis propria on EUS suggest the possibility of malignant disease [13]. However, most patients had a wall thickness greater than 10 mm in our study. In addition, when plotting the ROC curve for total wall thickness and AGC, a value close to a straight line was observed (Figure 4-A), suggesting that total wall thickness alone could not predict malignancy. On the other hand, when the ROC curve for the PM layer thickness was drawn, the value of the AUC was 0.987 for predicting malignancy, and as a cut-off point, a PM layer of 2.39 mm showed the highest sensitivity and specificity, strongly suggesting malignancy (Figure 4-B). There were no cases of HG in the destructed PM layer, indicative of malignancy.

Since standard forceps biopsy in thickened gastric wall could frequently show a negative result for

malignancy [9, 16], many studies have reported on the efficacy of EMR, unroofing biopsy, or EUS-FNA/B as a diagnostic method [10]. In our study, we divided the approaches into patients with or without ulcers on endoscopy. In patients with ulcers, a simple forceps biopsy of the ulcer showed a 92.6% success rate, so advanced biopsy methods were not required. In contrast, the yield of biopsy forceps fell to 42.6% in patients without ulcers, so other diagnostic methods were required. The success rates of EUS-FNA/B and EMR and unroofing biopsy were 50% (5/10) and 70.0% (14/20), respectively. Although a study reported an EUS-guided biopsy accuracy rate of 38–98% in the thickened gastric wall [10], this result was likely due to the difficulty of targeting the PM layer, and the number of cases was too insufficient to analyze in our study.

There are a few limitations to this study. First, since the EUS procedure was initially performed by multiple endoscopists and retrospectively reviewed later by one endosonographer, interobserver variation could be occur. However, these interobserver variation could be minimized because they have more than at least 5 years of experience in performing and interpreting EUS. Second, given the inconsistency of the thickness of every wall layer, measurements should have been taken at multiple sites and compared using the average. However, although this was not performed, we repeatedly observed multiple sites with long inspection times and tried to measure the thickness of the stomach wall at the site considered the thickest. Third, only AGC B-4 and HG were targeted in our study. Comparing the result with other malignant diseases in which the gastric wall is thickened, such as lymphoma or metastatic cancer, is warranted. Fourth, given this was a retrospective study in a single center with a small patient population, a multicenter prospective study is warranted.

In conclusion, sex, clinical symptoms, low hemoglobin, and albumin values significantly differed between HG and AGC B-4. AGC B-4 had a significantly higher rate of antral wall thickening and the presence of ulcers than HG. Destructed wall layers and 2.39 mm of PM thickness as a cut-off value are strongly indicative of AGC B-4. Forceps biopsy at the ulcer showed an excellent pathologic success rate in AGC B-4 with ulcer. Therefore, we propose EUS as a highly prognostic method for malignancy in patients with thickened PM layers of more than 2.39 mm or with an ulcer on endoscopy.

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Table 1. Baseline characteristics of patients with Borrmann type 4 advanced gastric cancer and hypertrophic gastritis

Characteristics	AGC B-4 (n=115)	Hypertrophic gastritis (n=50)	*p*-value
Age at diagnosis (years)	55.0 (44.5–64.0)	50.5 (43.0–60.0)	0.164
Sex (M / F)	72 / 43	14 / 36	< 0.001
Symptom			
Pain	52 (45.2%)	16 (32.0%)	0.158
Weight loss	56 (48.7%)	6 (12.0%)	< 0.001
Nausea or vomiting	23 (20.0%)	3 (6.0%)	0.042
Dyspepsia	45 (39.1%)	6 (12.0%)	0.001
Underlying disease			
Hypertension	20 (17.4%)	12 (24.0%)	0.440
DM	10 (8.7%)	7 (14.0%)	0.452
Chronic kidney disease	1 (0.9%)	2 (4.0%)	0.454
Liver cirrhosis	2 (1.7%)	2 (4.0%)	0.751
CVA	1 (0.9%)	0 (0.0%)	1.000
Angina	4 (3.5%)	0 (0.0%)	0.433
Thyroid disease	2 (1.7%)	0 (0.0%)	0.870
Family history of gastric cancer	18 (15.7%)	5 (10.0%)	0.472
H. pylori status			< 0.001
Infected	47 (40.9%)	40 (80.0%)	
Non-infected	18 (15.7%)	2 (4.0%)	
Previously treated	0 (0.0%)	1 (2.0%)	
Unknown	50 (43.5%)	7 (14.0%)	
Laboratory findings			
Hemoglobin (g/dL)	12.9 (12.1–14.3)	14.6 (13.4–16.2)	< 0.001
Albumin (g/dL)	3.9 (3.7–4.2)	4.2 (3.8–4.3)	0.047
Total protein (g/dL)	7.0 (6.5–7.4)	7.1 (6.9–7.7)	0.021

AGC B-4 Advanced gastric cancer Borrmann type 4; DM, diabetes mellitus; CVA, cerebro vascular accidents; *H.pylori, Helicbacter pylori.*

Table 2. Endoscopic findings of patients with Borrmann type 4 advanced gastric cancer and hypertrophic gastritis

Endoscopic findings	AGC B-4 (n=115)	Hypertrophic gastritis (n=50)	*p*-value
Location			< 0.001
Antral wall thickening	45/115 (39.1%)	2/50 (4.0%)	
Presence of ulceration			< 0.001
Present	68/115 (59.1%)	2/50 (4.0%)	
Absent	47/115 (40.9%)	48/50 (96.0%)	

AGC B-4, advanced gastric cancer Borrmann type 4.

Table 3. Endoscopic ultrasonographic findings of patients with Borrmann type 4 advanced gastric cancer and hypertrophic gastritis

	AGC B-4 with preserved layers (n=65)	AGC B-4 with destructed layers (n=50)	Hypertrophic gastritis (n=50)	*p*-value
EUS modalities				
Mini probe	36/65 (55.4%)	16/50 (32.0%)	19/50 (38.0%)	0.030
Linear probe	7/65 (10.8%)	3/50 (6.0%)	2/50 (4.0%)	0.351
Radial probe	41/65 (63.1%)	48/50 (96.0%)	40/50 (80.0%)	< 0.001
EUS findings				
Wall thickness (mm)	9.6 (8.5–14.0)	14.3 (11.5-18.8)	9.9 (6.9–14.4)	< 0.001
PM thickness (mm)	3.9 (2.9–4.8)	-	1.2 (0.9–1.7)	< 0.001
Wall < 2.39 mm	5 (7.7%)	-	49 (98.0%)	
Wall ≥ 2.39 mm	60 (92.3%)	-	1 (2.0%)	
Presence of ascites	1 (1.5%)	7 (14.0%)	0 (0.0%)	0.001

AGC B-4, advanced gastric cancer Borrmann type 4; PM, muscularis proper layer; IQR, interquartile range.

Table 4. Diagnostic methods in advanced gastric cancer Borrmann type 4 according to presence of ulceration

	AGC B-4 without ulcer (n=47)	AGC B-4 with ulcer (n=68)	*p*-value
Method of diagnosis			< 0.001
Forceps biopsy	20 (42.6%)	63 (92.6%)	
EUS-FNB	4 (8.5%)	1 (1.5%)	
EMR or unroofing	12 (25.5%)	2 (2.9%)	
Surgery	9 (19.1%)	0 (0.0%)	
*Other	2 (4.3%)	2 (2.9%)	
Success rate of each method			
Forceps biopsy	20/47 (42.6%)	63/68 (92.6%)	< 0.001
EUS-FNB	4/8 (50.0%)	1/2 (50.0%)	1.000
EMR or unroofing	12/16 (75.0%)	2/4 (50.0%)	0.935

AGC advanced gastric cancer; B-4 Borrmann type 4; EUS-FNA endoscopic ultrasound-guided fine needle aspiration; EMR endoscopic mucosal resection; *Included analysis of ascites cytology (n=2), punch biopsy of metastatic lesion in the skin (n=1), later confirmed during chemotherapy (n=1); AP-CT, abdominal and pelvic computed tomography; PET-CT, positron emission tomography-computed tomography.

Table 5. Multivariable logistic analysis of risk factors for Borrmann type 4 advanced gastric cancer

Factors	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Thickened pm layer (≥ 2.39 mm)	588.21 (66.47–5201.31)	< 0.001	637.08 (37.88–10714.97)	< 0.001
Sex (male)	5.39 (2.4–12.08)	< 0.001		
Abdominal pain	1.51 (0.7–3.27)	0.295		
Weight loss	4.29 (1.59–11.56)	0.004		
Nausea or vomiting	3.19 (0.84–12.13)	0.089		
Antral wall thickning	12.28 (2.73–55.3)	0.001		
Presence of ulceration	31.71 (7.1–141.74)	< 0.001	48.62 (2.61–906.81)	0.009

OR, odds ratio; CI, confidence interval; IQR, interquartile range.

Supplementary table 1. Characteristics of patients of thickened gastric folds who ultimately diagnosed by surgery.

	No surgery (n=156)	Surgery (n=9)	*p* value
Age	53.0 (44.0-63.5)	55.0 (45.0-60.0)	0.618
Sex	76/80 (48.7%)	3/6 (33.3%)	0.579
Laboratory findings			
Hemoglobin	13.3 (12.3-14.8)	13.9 (12.0-14.2)	0.670
Albumin	4.0 (3.7-4.2)	3.9 (3.7-4.1)	0.891
Total protein	7.0 (6.6-7.4)	6.6 (6.4-7.7)	0.510
Endoscopic findings			
Antral involvement	42 (26.9%)	5 (55.6%)	0.141
Ulcer or erosion	70 (44.9%)	0 (0.0%)	0.021
Endoscopic ultrasonographic findings			
Total wall layer (mm)	11.3 (8.4-15.5)	13.4 (11.0-14.7)	0.366
PM wall layer (mm)	2.4 (1.3-4.1)	3.6 (3.2-5.0)	0.082
Preserved wall layer	110 (70.5%)	5 (55.6%)	0.564
Destructed wall layer	46 (29.5%)	4 (44.4%)	
Ascites	8 (5.1%)	0 (0.0%)	1.000
AP-CT findings			0.127
No evidence of diseases	1 (0.9%)	0 (0.0%)	
Thickened gastric wall	24 (22.6%)	1 (11.1%)	
Perigastric lymph node	30 (28.3%)	6 (66.7%)	
Peritoneal seeding or distant metastasis	51 (48.1%)	2 (22.2%)	
PET-CT			0.295
No uptake	8 (7.5%)	1 (11.1%)	
Increased gastric uptake	18 (17.0%)	4 (44.4%)	
Perigastric lymph node	22 (20.8%)	1 (11.1%)	
Peritoneal seeding or distant metastasis	33 (31.1%)	1 (11.1%)	
Not performed	25 (23.6%)	2 (22.2%)	

AP-CT Abdominopelvic-CT; PET-CT positron emission tomography CT

Figure legends

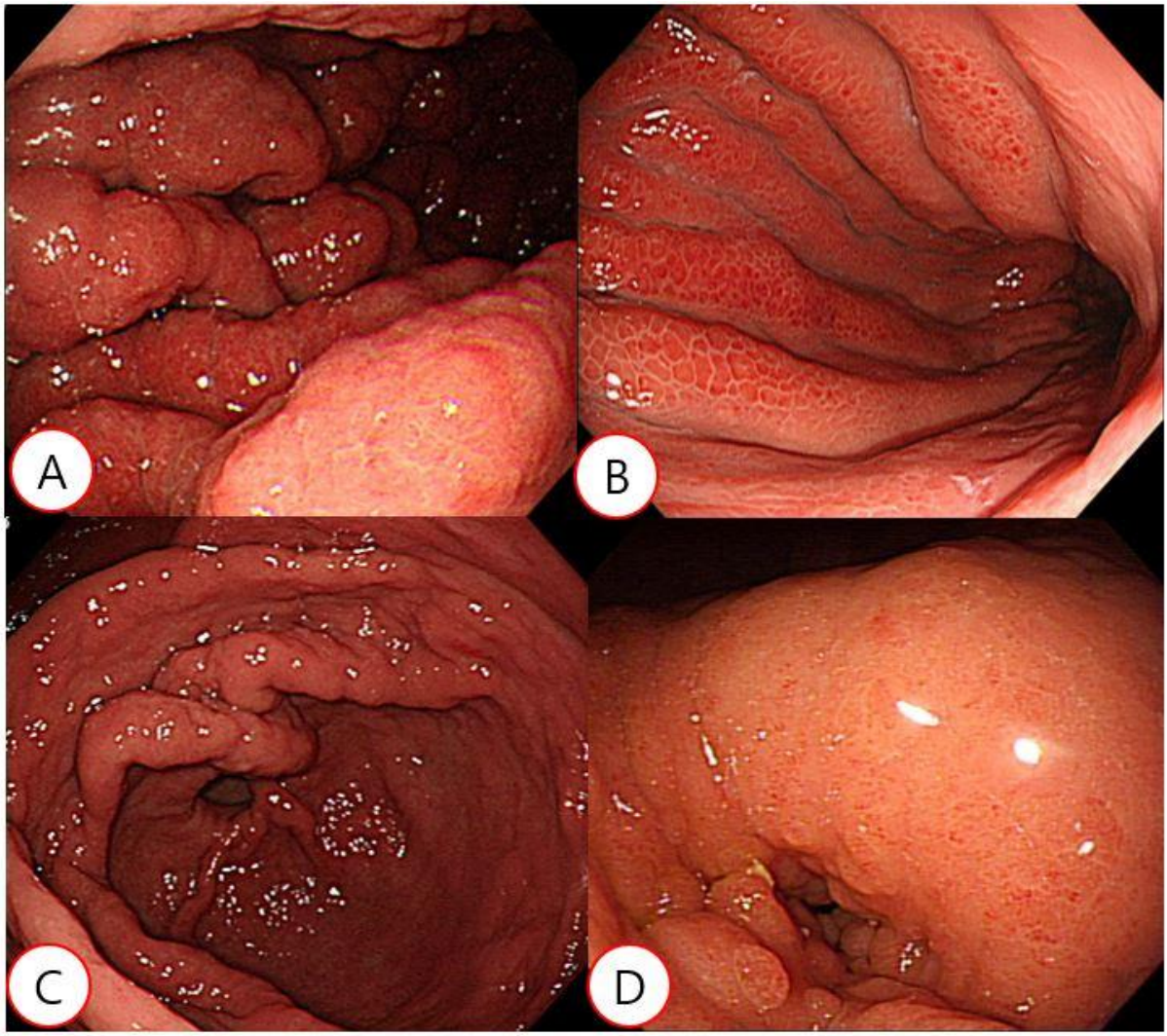


Figure 1. Endoscopic images of (A) thickened wall in a patient of hypertrophic gastritis, (B) thickened folds in a patient of advanced gastric cancer with Borrmann type 4, (C) case of antral wall thickening in a patient of hypertrophic gastritis, and (D) antral wall thickening in a patient of advanced gastric cancer with Borrmann type 4.

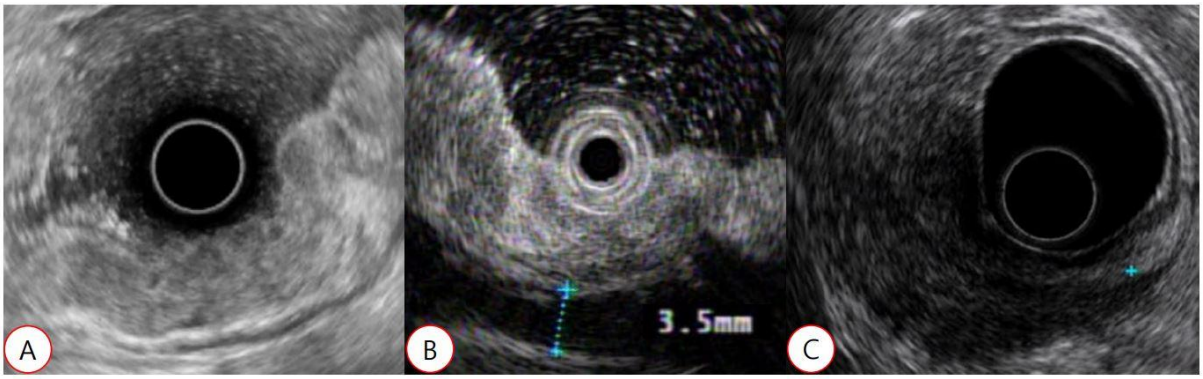


Figure 2. Endoscopic ultrasonographic images of patients diagnosed with hypertrophic gastritis (A), advanced gastric cancer with preserved wall layer (B), and with destructed wall layer (C).

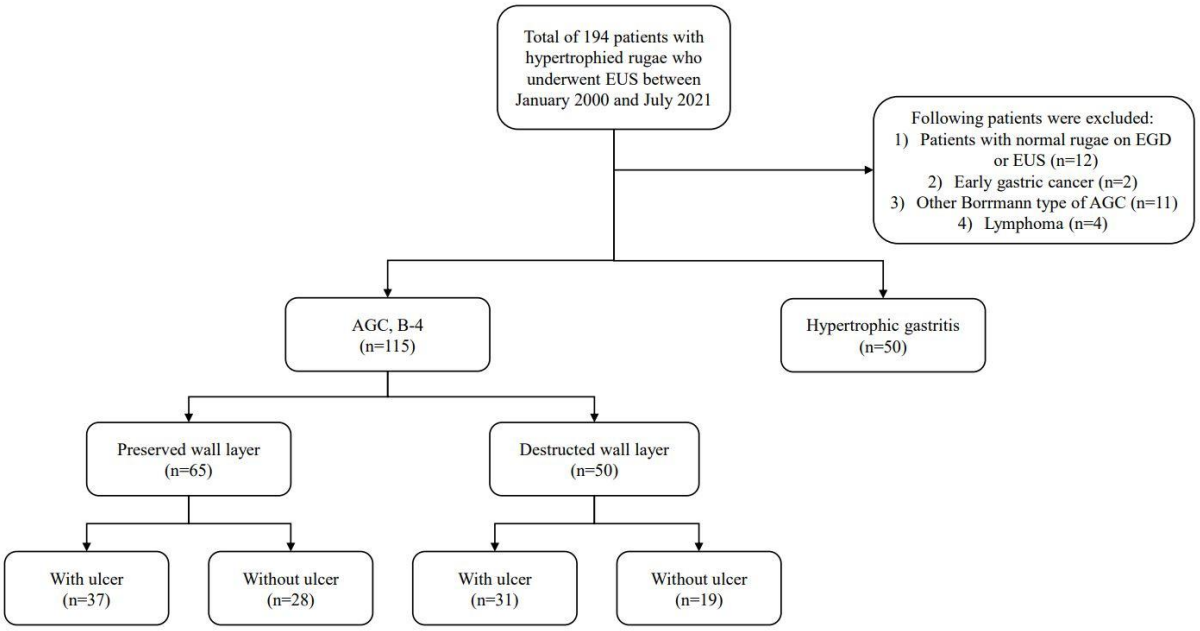


Figure 3. Flowchart of patients with hypertrophied rugae who underwent endoscopic ultrasound. EGD esophagogastroduodenoscopy;
EUS endoscopic ultrasound; AGC Advanced gastric cancer; B-4 Borrmann type 4

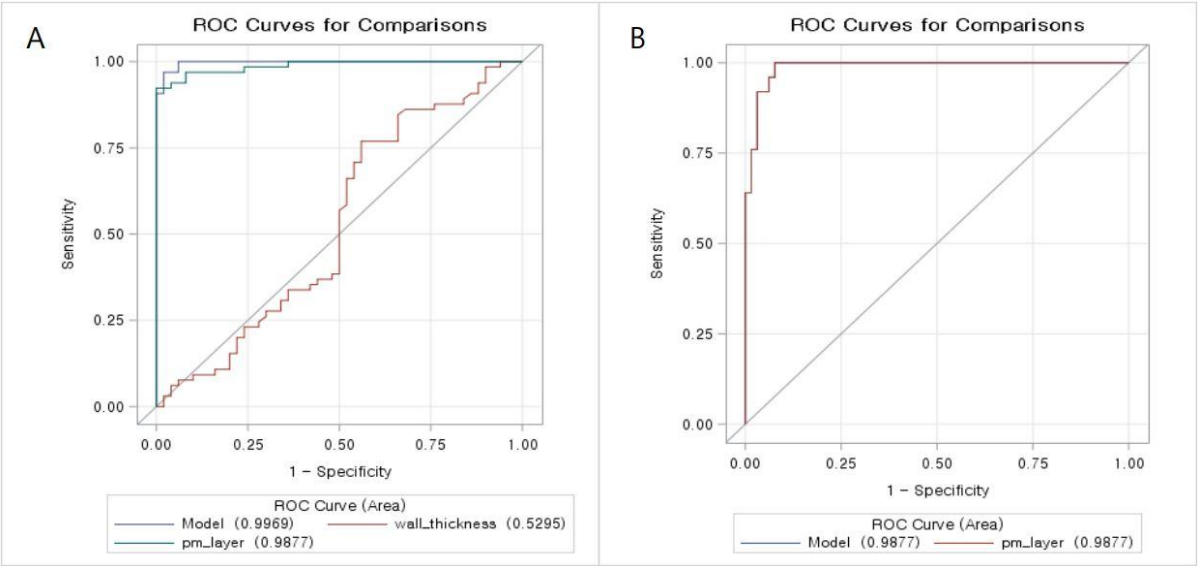
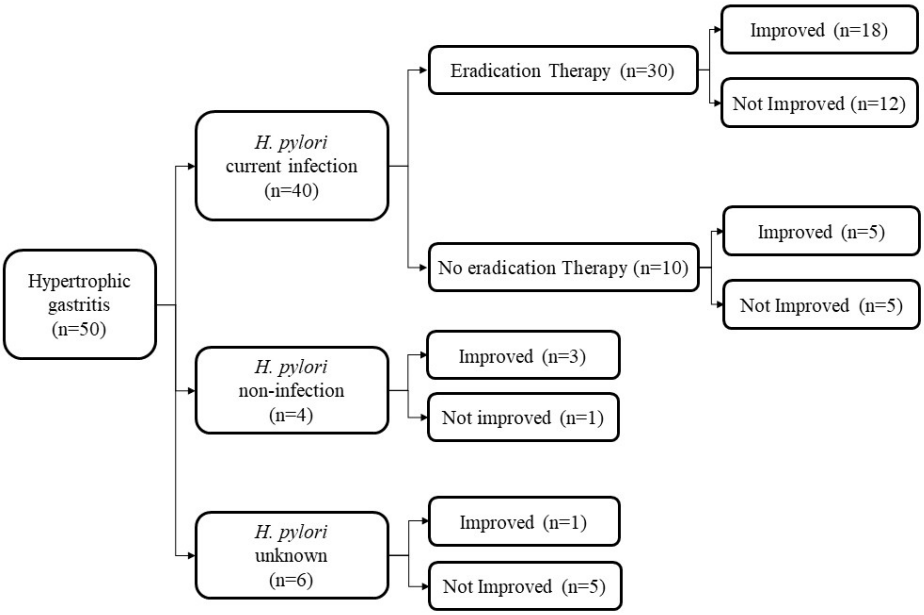


Figure 4. (A) Receiver operating characteristics curve (ROC) for prediction of advanced gastric cancer based on total wall thickness on endoscopic ultrasound between patients with advanced gastric cancer B-4 with preserved wall layer and hypertrophic gastritis. (B) ROC for prediction of advanced gastric cancer based on proper muscle thickness on endoscopic ultrasound between patients with advanced gastric cancer with preserved wall layer and hypertrophic gastritis.



Supplementary Figure 1. Flowchart of patients diagnosed with hypertrophic gastritis. Endoscopic improvement was defined as improvement of wall thickening at the follow-up endoscopy.