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Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection

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Abstract
Background Endoscopic ultrasonography (EUS) has become a reliable method for predicting the invasion depth of early gastric cancer (EGC). This study evaluated the accuracy of EUS in identifying lesions meeting expanded-indication criteria for endoscopic submucosal dissection (ESD) and analyzed clinicopathologic factors influencing the diagnostic accuracy of EUS in assessing tumor invasion depth.
Methods This study investigated 542 EGCs of 515 patients who underwent EUS pretreatment. The pretreatment EUS-determined diagnosis was compared with the final histopathologic evaluation of resected specimens, and the impact of various clinicopathologic parameters on diagnostic accuracy was analyzed.
Results The diagnostic accuracy of EUS in identifying lesions meeting expanded-indication criteria for ESD was 87.8% (259/295) for differentiated adenocarcinoma (D-type) 30 mm in diameter or smaller, 43.5% (10/23) for D-type tumor larger than 30 mm in diameter, and 75% (42/56) for undifferentiated adenocarcinoma (UD-type) 20 mm in diameter or smaller. Using multivariate analysis, the diagnostic accuracy of EUS in predicting tumor invasion depth was determined to be decreased significantly by ulcerous change and large tumor size (diameter, ≥30 mm).
Conclusion For patients with EGC, D-type lesions 30 mm in diameter or smaller and UD-type lesions 20 mm in diameter or smaller can be diagnosed with high accuracy by EUS, but larger D-type lesions (diameter, >30 mm) should be considered carefully in terms of EUS-based treatment decisions. Findings of ulceration and large tumors are associated with incorrect diagnosis of tumor invasion depth by EUS.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Endoscopic ultrasonography

The advent of endoscopic ultrasonography (EUS) has significantly improved the preoperative diagnosis and staging of upper gastrointestinal (GI) cancer [1–5]. Endoscopic ultrasonography is the most reliable nonsurgical method available for assessing primary tumor, with a high rate of accuracy in staging gastric cancer.

The previous classification system used with EUS tended to result in overstaging because of benign ulcerous change (open ulceration or ulcer scar), fibrosis, benign cystic glands in the submucosal layer, macroscopic findings, inflammatory changes, or an anomaly of the muscularis mucosae [5–8]. The problem of inaccurate staging may lead to the surgical treatment of mucosal cancers that actually are eligible for endoscopic resection.

Endoscopic submucosal dissection (ESD) currently is widely accepted as a standard treatment strategy for GI neoplasm, especially in early gastric cancer (EGC), without any risk of lymph node metastasis [9–11] because the ESD technique facilitates one-piece resection even in patients with large or ulcerous lesions [12–15]. Gotoda et al. [12] reported that differentiated adenocarcinoma (D-type) lesions 30 mm in diameter or larger were entirely free of nodal metastasis if they showed a lack of lymphatic-vascular capillary involvement and the submucosal penetration was 500 μm or less.

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More recently, Hirasawa et al. [16] reported that intramucosal undifferentiated adenocarcinoma (UD-type) 20 mm in diameter or smaller without lymphatic-vascular capillary involvement or ulcerous findings presents a negligible risk of lymph node metastasis. Therefore, it has become more important in treatment planning to determine the depth of invasion accurately before treatment. However, the accuracy of EUS has not been fully established for lesions with ulcerous findings and UD-type histology. Therefore, to determine the diagnostic efficacy of EUS for assessing such lesions for potential endoscopic therapy, we evaluated the accuracy of EUS in identifying lesions eligible for ESD based on expanded-indication criteria and analyzed clinicopathologic factors that influenced the diagnostic accuracy of EUS in predicting the depth of tumor invasion.

Patients and methods

Patients

A total of 542 EGCs were diagnosed by conventional endoscopy for 515 patients (385 men and 130 women with a mean age of 66.9 years (range, 35–90 years) who underwent EUS for pretreatment staging at the Division of Endoscopy, Cancer Institute Ariake Hospital of the Japanese Foundation for Cancer Research between April 2005 and March 2009. We performed EUS only for difficult cases such as those with suspected submucosal invasion, concomitant ulcerous findings, or large lesions detected by conventional endoscopy. All patients underwent curative treatment by either ESD or standard surgical intervention, and all lesions were evaluated by histopathologic examination.

EUS equipment and examination procedures

EUS procedure

The instrument used for the EUS examinations was the GFUM-2000 (Olympus, Tokyo, Japan) set at variable frequencies of 20 MHz or the miniprobe set at 20 MHz (Olympus). Instillation of nonaerated water was performed to improve transmission of the ultrasound beam. Patients were premedicated with local pharyngeal anesthesia and midazolam (3–5 mg intravenously), if needed, and placed in the left lateral decubitus position.

Under direct vision, the echoendoscope was advanced beyond the tumor. Acoustic coupling with the GI wall was obtained by instilling 200–400 ml of deaerated water in the gastric lumen or by a water-filled balloon on the instrument's tip. Endoscopic ultrasonography imaging was performed by the same group of endosonographers.

Definition and identification of cancer invasion depth by EUS

Tumor invasion depth was measured ultrasonographically. The gastric wall was assessed based on the standard five-layer sonographic structure [8, 17]. On the EUS image, the mucosal (M) layer is visualized as a combination of the first and second hypoechoic layers, and the submucosal (SM) layer corresponds to the third hyperechoic layer. The layer of the muscularis propria (MP) is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa, including the subserosa.

The tumor invasion depth assessed by EUS was classified according to a modification of the system proposed by Yanai et al. [8], as follows: EUS-M (lesion confined to sonographic layers 1 and 2), EUS-SM1 (lesion with changes in sonographic layer 3 but no deeper than 1 mm), EUS-SM2 (lesion with changes in sonographic layer 3 and deeper than 1 mm), or EUS-MP (lesion with changes in sonographic layer 4). The invasion depths of EGC on EUS images were interpreted by experts certified by the Japan Society of Gastrointestinal Endoscopy. In this study, EUS-M and EUS-SM1 were combined into the same classification (EUS-M/SM1) because conventional EUS has difficulty distinguishing M from SM1 [18].

Data analysis

Detailed information about the endoscopic images and results of the histopathologic examination were obtained from the medical records. Tumor location was categorized with reference to the longitudinal axis and cross-sectional circumference of the stomach. More specifically, the longitudinal axis of the stomach was divided into three sections (upper third containing the fundus, cardia, and upper body; middle third containing the midbody, lower body, and angle; and lower third containing the antrum and pylorus), and the cross-sectional circumference was divided into four sections (lesser curvature, posterior wall, greater curvature, and anterior wall).

Endoscopic findings related to the tumor were categorized according to the classification of the Japanese Gastric Cancer Association (JGCA) [9]. The macroscopic type was defined as protruded type (0-I and 0-I + IIa), elevated/flat type (0-IIa, 0-IIb, 0-IIa + IIb), depressed type (0-IIc, 0-III, 0-IIIc + III), and combined type (0-IIa + IIc or III).

All resected specimens were sectioned into 2- to 5-mm slices and evaluated histopathologically based on the Japanese Classification of Gastric Carcinoma of the JGCA (D-type or UD-type) [9, 19]. Tumors of the UD-type lacked gland formation and included poorly differentiated mucinous adenocarcinoma and signet-ring cell carcinomas.

The depth of submucosal invasion was subclassified histologically into one of two grades: penetration into the submucosal layer less than 500 μm from the muscularis mucosa (SM1) or penetration of 500 μm or deeper (SM2) [9]. Tumor size and pathologic ulceration were determined histopathologically, and the size of the resected specimen was recorded as the largest measured diameter.

We analyzed the diagnostic accuracy of EUS in determining whether lesions met the expanded-indication criteria for ESD in patients with EGC and the clinicopathologic factors affecting the diagnostic accuracy of EUS in measuring the invasion depth of EGC.

Statistical analysis

Statistical evaluations were performed using the chi-square test, Fisher's exact test, *t*-test, or Mann–Whitney *U* test. Various risk factors also were evaluated using logistic regression. The level of significance was set at a *p* value less than 0.05. Statistical analyses were performed with StatView software (SAS Institute, Cary, NC, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Cancer Institute Ariake Hospital of the Japanese Foundation for Cancer Research.

Results

Demographic, endoscopic, and histologic characteristics

Tables 1 and 2 describe the baseline characteristics of the study population and the clinicopathologic features of the enrolled patients' EGCs. The median age of the patients was 67 years (mean, 66.9 ± 10.4 years; range, 35–90 years), and the male:female ratio was 2.96:1 (385:130). The median tumor diameter was 18 mm (mean, 22.4 ± 17.7 mm; range, 2–150 mm). Of the 542 lesions, 116 (21.4%) had concomitant ulcerous findings, and histologic examination showed that 21 lesions (3.9%) had heterotopic gastric glands (HGGs) beneath the tumor.

Diagnostic accuracy of EUS in assessing tumor invasion depth

The overall accuracy of EUS in predicting the depth of tumor invasion was 81.7% (443/542). As shown in Table 3, 434 lesions were diagnosed by EUS as having an invasion depth of M/SM1 (EUS-M/SM1 lesions) compared with the following pathologically determined depth of invasion: M for 344 lesions (79.3%), SM1 for 27 lesions (6.2%), SM2 for 58 lesions (13.4%), and MP for 5 lesions (1.1%). Among the 101 EUS-SM2 lesions, the pathologic depth was M for 25 lesions (24.7%), SM1 for 5 lesions (5%), SM2 for 67 lesions (66.3%), and MP for 4 lesions (4%). Among the 7 EUS-MP lesions, the pathologic depth was M for 1 lesion (14.3%), SM1 for 0 lesions (0%), SM2 for 1 lesion (14.3%), and MP for 5 lesions (71.4%).

Table 1 Baseline characteristics of study patients and their early gastric cancer (EGC) lesions

Patient characteristics	
n	515
Age (years)	
Mean ± SD	66.9 ± 10.4
Median (range)	67.0 (35–90)
Gender: *n* (%)	
Male: *n*	385 (64.8)
Female: *n*	130 (25.2)
Lesion characteristics	
n	542
Histologic depth: *n* (%)	
M	370 (68.3)
SM1 (<500 μm)	32 (5.9)
SM2	126 (23.2)
MP	14 (2.6)

SD standard deviation, *M* mucosal, *SM1* submucosal layer less than 500 μm from the muscularis mucosa, *SM2* submucosal layer penetration of 500 μm or deeper, *MP* muscularis propria

Diagnostic accuracy of EUS in identifying expanded-indication criteria for ESD

D-type tumor 30 mm in diameter or smaller

As shown in Table 4, among the patients with D-type lesions 30 mm in diameter or smaller, 87.8% (259/295) of the EUS-M/SM1 lesions, irrespective of ulcerous findings, corresponded to lesions classified as M or SM1 histopathologically and therefore met the expanded-indication criteria for ESD. In addition, 62.5% (30/48) of the EUS-SM2 lesions were confirmed to be nonindication lesions by histopathologic examination.

D-type tumor larger than 30 mm in diameter

As shown in Table 5, among the patients with D-type lesions larger than 30 mm in diameter, 43.5% (10/23) of the EUS-M/SM1 lesions without ulcerous findings [UL(−) lesions] corresponded to histologically classified M UL(−)

Table 2 Characteristics of early gastric cancer (EGC) lesions and accuracy of assessing invasion depth by endoscopic ultrasonography (EUS)

Lesion characteristics	Overall	Accurate assessment	Inaccurate assessment	*p* Value
n (%)	542	443 (81.7%)	99 (18.3%)	
Tumor size (mm)				
Mean ± SD	22.4 ± 17.7	19.9 ± 14.0	26.6 ± 19.8	0.0003
Median (range)	18.0 (2.0–150.0)	16.0 (2.0–150.0)	20.0 (4.0–120.0)	
Longitudinal locations: *n* (%)				
Upper third	139	107 (77.0)	32 (23.0)	0.0961
Middle third	134	115 (85.8)	19 (14.2)	0.1970
Lower third	269	222 (82.5)	47 (17.5)	0.7307
Cross-sectional locations: *n* (%)				
Lesser curvature	184	145 (78.8)	39 (21.2)	0.1952
Greater curvature	84	71 (84.5)	13 (15.5)	0.6434
Anterior wall	96	79 (82.3)	17 (17.7)	>0.9999
Posterior wall	178	149 (83.7)	29 (16.3)	0.4780
Macroscopic type: *n* (%)				
Elevated/flat	65	56 (86.2)	9 (13.8)	0.3949
Depressed	414	339 (81.9)	75 (18.1)	>0.9999
Protruded	21	16 (76.2)	5 (23.8)	0.5604
Combined	42	33 (78.6)	9 (21.4)	0.5344
Pathologic findings: *n* (%)				0.5962
Differentiated (D)-type (well, moderate, papillary)	417	339 (81.3)	78 (18.7)	
Undifferentiated (UD)-type (sig, por, muc)	125	105 (84.0)	20 (16.0)	
Ulcerous findings: *n* (%)				0.0017
Present	116	83 (71.2)	33 (28.8)	
Absent	426	361 (84.7)	65 (15.3)	
Heterotopic gastric glands: *n* (%)				0.5604
Present	21	16 (76.2)	5 (23.8)	
Absent	521	428 (82.1)	93 (17.9)	

SD standard deviation, *sig*, *por*, *muc*

Table 3 Diagnostic accuracy of endoscopic ultrasonography (EUS) for all lesions: tumor invasion depth

EUS diagnosis	Pathologic depth				
	M	SM1	SM2	MP	Total
EUS-M/SM1	344	27	58	5	434
EUS-SM2	25	5	67	4	101
EUS-MP	1	0	1	5	7
Total	370	32	126	14	542

M mucosal, *SM1* submucosal layer less than 500 μm from the muscularis mucosa, *SM2* submucosal layer penetration of 500 μm or deeper, *MP* muscularis propria

lesions. In addition, 71.4% (10/14) of the EUS-M/SM1 lesions with ulcerous findings [UL(+) lesions] and 68.6% (24/35) of the EUS-SM2 lesions were confirmed histopathologically to be nonindication lesions.

Table 4 Diagnostic accuracy of endoscopic ultrasonography (EUS) for differentiated (D)-type lesions 30 mm in diameter or smaller: indications for endoscopic submucosal dissection (ESD)

EUS diagnosis	Pathologic depth				
	M/SM1 UL(−)[b]	M/SM1 UL(+)[b]	SM2	MP	Total
EUS-M/SM1, UL(−)[a]	191	22	27	0	240
EUS-M/SM1, UL(+)[a]	32	14	8	1	55
EUS-SM2	7	11	28	2	48
EUS-MP	0	0	0	1	1
Total	230	47	63	4	344

M mucosal, *SM1* submucosal layer less than 500 μm from the muscularis mucosa, *SM2* submucosal layer penetration of 500 μm or deeper, *MP* muscularis propria, *UL(−)* lesions without ulcerous findings, *UL(+)* lesions with ulcerous findings

[a] Expanded-indication criteria for ESD

[b] Expanded histological criteria for ESD

Table 5 Diagnostic accuracy of endoscopic ultrasonography (EUS) for differentiated (D)-type lesions more than 30 mm in diameter: indications for endoscopic submucosal dissection (ESD)

EUS diagnosis	Pathological depth				
	M UL(−)[b]	M UL(+)	SM	MP	Total
EUS-M/SM1, UL(−)[a]	10	5	8	0	23
EUS-M/SM1, UL(+)	4	7	2	1	14
EUS-SM2	11	1	21	2	35
EUS-MP	0	1	1	0	2
Total	25	14	32	3	74

M mucosal, *SM1* submucosal layer less than 500 μm from the muscularis mucosa, *SM2* submucosal layer penetration of 500 μm or deeper, *MP* muscularis propria, *UL(−)* lesions without ulcerous findings, *UL(+)* lesions with ulcerous findings

[a] Expanded-indication criteria for ESD

[b] Expanded histological criteria for ESD

UD-type tumor 20 mm in diameter or smaller

As shown in Table 6, among the patients with UD-type lesions 20 mm in diameter or smaller, the accuracy of EUS in predicting the depth of tumor invasion was 86.4% (70/81), and 75% (42/56) of the EUS-M/SM1 UL(−) lesions corresponded to histologically classified M UL(−) lesions. In addition, 87.5% (8/9) of the EUS-M/SM1 UL(+) lesions and 100% (18/18) of the EUS-SM2 lesions were confirmed histopathologically to be nonindication lesions.

Uni- and multivariate analyses of various clinicopathologic factors affecting the diagnostic accuracy of EUS in EGC

In univariate analysis, the diagnostic accuracy of assessing invasion depth was significantly decreased for larger EGCs

Table 6 Diagnostic accuracy of endoscopic ultrasonography (EUS) in undifferentiated (UD)-type lesions 20 mm in diameter or smaller: indications for endoscopic submucosal dissection (ESD)

EUS diagnosis	Pathologic depth				
	M UL(−)[b]	M UL(+)	SM	MP	Total
EUS-M/SM1 UL(−)[a]	42	6	8	0	56
EUS-M/SM1 UL(+)	1	4	1	1	7
EUS-SM2	0	1	17	0	18
EUS-MP	0	0	0	0	0
Total	43	11	26	1	81

M mucosal, *SM1* submucosal layer less than 500 μm from the muscularis mucosa, *SM2* submucosal layer penetration of 500 μm or deeper, *MP* muscularis propria, *UL(−)* lesions without ulcerous findings, *UL(+)* lesions with ulcerous findings

[a] Expanded-indication criteria for ESD

[b] Expanded histological criteria for ESD

Table 7 Multivariate logistic regression analysis for misdiagnosis

	OR (95% CI)	*p* Value
Ulcerous findings	1.899 (1.146–3.144)	0.0231
Tumor size (≥30 mm in diameter)	2.334 (1.385–3.933)	0.0024

OR odds ratio, *CI* confidence interval

($p = 0.0003$) and tumors with concomitant ulcerous findings ($p = 0.0017$) (Table 2). In multivariate logistic regression analysis, the diagnostic accuracy of EUS in predicting tumor invasion depth was significantly decreased by the presence of ulcerous findings [odds ratio (OR), 1.899; 95% confidence interval (CI), 1.146–3.144; $p = 0.0231$] and a tumor size of 30 mm or more (OR, 2.334; 95% CI, 1.385–3.933; $p = 0.0024$) in the study population (Table 7).

Discussion

Once a diagnosis of EGC is suspected based on endoscopic and histopathologic findings, accurate staging becomes fundamental to determining the most appropriate management plan. Currently, EUS is the most reliable method used to predict the depth of gastric cancer with high accuracy and a low chance of over- or understaging [20]. The accuracy of EUS for staging gastric cancer, as reported by different investigators, ranges from 64.8 to 92% [6–8, 20–22].

We performed EUS only for difficult cases, such as those with suspected submucosal invasion or concomitant ulcerous changes or large lesions. However, the overall rate for accurate prediction of tumor invasion depth was 81.7%, which is compatible with other reports.

The reported accuracy rates for tumor depth assessment by EUS are 75% for mucosal and 62% for submucosal cancers [23]. Even currently, it still is difficult to diagnose minimal submucosal invasion preoperatively, and overstaging is common [8]. However, more precise identification of tumor depth such as confinement to the mucosal layer, minimal invasion into the submucosal layer, or massive invasion into the submucosal layer becomes indispensable for the appropriate selection of patients for endoscopic resection treatment.

In our study, among the D-type lesions 30 mm in diameter or smaller, 87.8% (259/295) of the EUS-M/SM1 lesions, irrespective of ulcerous findings, corresponded to M or SM1 lesions histopathologically, which represent an expanded indication for ESD. However, among the D-type lesions larger than 30 mm in diameter, only 43.5% (10/23) of the EUS-M/SM1 UL(−) lesions corresponded histopathologically to this expanded-indication criteria.

Kida et al. [24] reported that three-dimensional EUS (3D-EUS) provided a practical way to diagnose small invasion of tumors larger than 500 μm with an accuracy of 78.7% when EGC had no ulcerous changes, suggesting that 3D-EUS may be more useful and more accurate for diagnosis. However, even with the use of 3D-EUS, differentiating the minute gastric cancer invasion of ulcer fibrosis from ulcer fibrosis alone has been problematic [24].

With regard to large lesions, we often cannot recognize the morphologic findings associated with submucosal or deeper invasion, so it is possible that these lesions were not scanned appropriately by EUS. Therefore, we recommend curative endoscopic resection for patients with a diagnosis of EUS-M/SM1 lesions irrespective of ulcerous findings of D-type EGCs 30 mm in diameter or smaller and surgical management of cases with a diagnosis of EUS-SM2. Because endoscopic treatment might be insufficient for large EGCs, EUS-based treatment decisions about D-type lesions larger than 30 mm in diameter should be made cautiously.

Among the UD-type lesions 20 mm in diameter or smaller, 75% (42/56) of the EUS-M/SM1 UL(−) lesions corresponded to histologically classified M UL(−) lesions, which meets expanded-indication criteria for ESD, and 96.3% (26/27) of the lesions evaluated as deeper than EUS-SM2 or having ulcerous changes were classified histopathologically as nonindication lesions. Thus, 3D-EUS may be a more useful method for staging such lesions.

Recently, three reports showed that respective curative resection rates of 55% [25], 67% [26], and 79% [27] were achieved by ESD for UD-type lesions 20 mm in diameter or smaller after a pretreatment diagnosis of intramucosal cancer without ulcerous findings. Thus, therapeutic or diagnostic ESD also might be advisable to prevent excessive surgery in cases with a diagnosis of EUS-M/SM1 provided the histopathologic diagnosis is determined by expert GI pathologists.

Logistic regression analysis showed that ulcerous findings and large tumor size (diameter, ≥30 mm) were factors associated with incorrect diagnosis by EUS in the current study. The lesions with ulcerous change diagnosed as EUS-SM2 tended to include many intramucosal cancers. It was difficult to differentially diagnose tumor invasion, benign ulcers, or fibrosis in the submucosal layer, so four MP cancers were diagnosed as EUS-M/SM1 in the lesions with ulcerous findings. Therefore, anti-ulcer drugs, including proton pump inhibitors, should be administered for concomitant open ulcers of EGCs, followed by reassessment when ulcer healing has been achieved.

It is reported that the histologically classified UD-type tumor is a significant factor associated with misdiagnosis by EUS [8, 22], although the difference did not reach statistical significance in the current study. The D-type tumor tends to be characterized by expansion of the tumor nodule or mass, whereas the UD-type tumor tends to be characterized by diffuse infiltration of tumor cells individually or in small nests, a feature difficult to detect by EUS [28, 29] and thus a possible cause of misdiagnosis. This difference also did not reach statistical significance in the current study.

When tumors are located in the upper third of the stomach, the diagnostic accuracy of EUS is lower because of technical problems associated with scanning this part of the upper GI tract and difficulty achieving the necessary pool of nonaerated water in the stomach's upper third, especially in the lesser curvature. The diagnostic accuracy also tends to be lower when HGGs are located beneath the tumor. The prevalence of HGGs in the general population is estimated to be 4 to 10.7% [30]. In the current study population, HGGs were seen beneath the tumor in 3.9% of the patients (21/542), a proportion that excluded cases in which HGGs were not seen beneath the tumor but recognized in another area.

It is difficult to distinguish HGGs from tumor invasion on EUS images because these HGGs are depicted as a hypoechoic or anechoic structure of the same echo level as a tumor. In addition, cancer cells sometimes invade to the submucosa thorough HGGs, which is difficult to detect by EUS (Figs. 1, 2). Moreover, it should also be remembered that diffuse HGGs in the submucosa have the potential to increase the risk of multiple gastric cancers [30, 31].

In conclusion, endoscopic treatment should be considered for both EUS-M/SM1 lesions irrespective of ulcerous findings for D-type EGCs 30 mm in diameter or smaller and EUS-M/SM1 UL (−) lesions in UD-type EGCs 20 mm in diameter or smaller. All EUS-SM2 lesions should be treated surgically. Larger D-type lesions (diameter >30 mm) should be considered carefully, particularly in

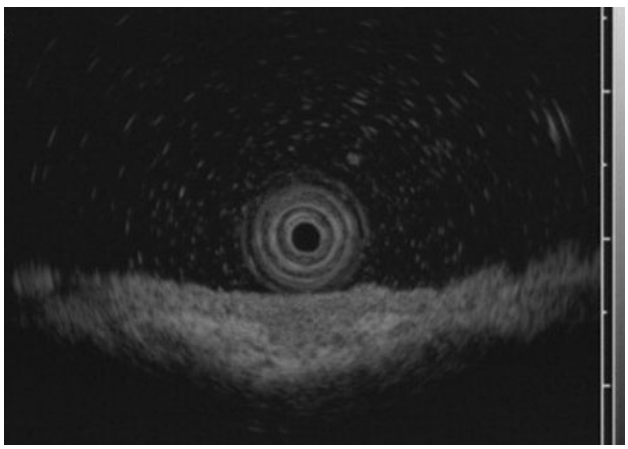

Fig. 1 Endoscopic ultrasonography (EUS) findings of early gastric cancer (EGC) accompanied by heterotopic gastric glands (HGGs)

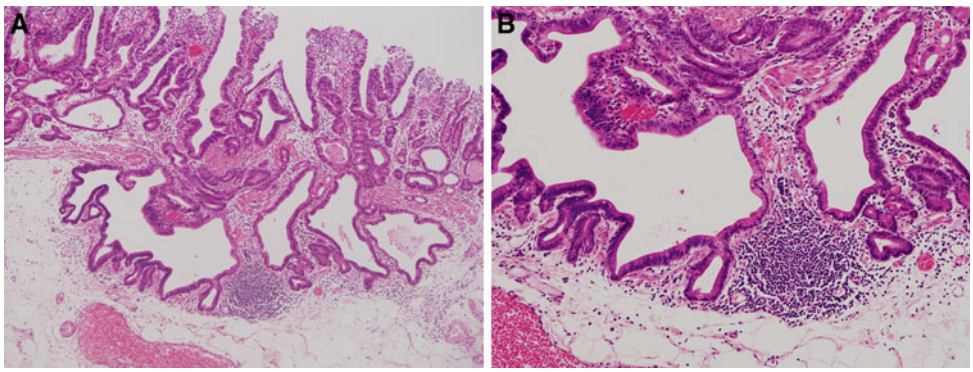

Fig. 2 Pathologic findings showing that cancer cells invaded to SM2 through the heterotopic gastric glands (HGGs). **A** Hematoxylin and eosin stain, ×100. **B** Hematoxylin and eosin stain, ×400

making decisions about the treatment method based on pretreatment staging by EUS. Findings of ulceration and large tumor size are associated with an incorrect diagnosis of tumor invasion depth by EUS.

Disclosures Kazuhisa Okada, Junko Fujisaki, Akiyoshi Kasuga, Masami Omae, Kazuhito Yoshimoto, Toshiaki Hirasawa, Akiyoshi Ishiyama, Yorimasa Yamamoto, Tomohiro Tsuchida, Etsuo Hoshino, Masahiro Igarashi, and Hiroshi Takahashi have no conflicts of interest or financial ties to disclose.

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