

GASTROENTEROLOGY

Accuracy of high-frequency catheter-based endoscopic ultrasonography according to the indications for endoscopic treatment of early gastric cancer

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Key words

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Abstract

Background and Aim: The development of endoscopic treatment, such as endoscopic submucosal dissection, extends the indications for endoscopic resection in patients with early gastric cancer (EGC). Endoscopic ultrasonography (EUS) is the first-choice imaging modality for determining the depth of invasion of gastric cancer. The aim of the present study was to prospectively assess the accuracy of EUS for determining the depth of EGC, according to the accepted/extended indications.

Methods: We prospectively included a total of 181 lesions in 178 patients, with an endoscopic diagnosis of EGC, who underwent EUS for staging the depth of tumor invasion using a 20-MHz catheter probe. We investigated the accuracy of EUS for determining the depth of endoscopically-suspected EGC and then analyzed the difference in the accuracy of EUS according to the accepted/extended indications.

Results: Of the 178 patients, five patients were dropped because of the absence of final histological results. For the 176 lesions in 173 patients, the accuracy of EUS assessment for the depth of tumor invasion was 80.7% (142 of 176 lesions). The accuracy of EUS for the lesions with accepted indications and with extended indications was 97.6% (40 of 41 lesions) and 83.6% (46 of 57 lesions), respectively ($P = 0.040$). Of the lesions with extended indications, the accuracy of EUS decreased especially for the lesions with ulceration and those with minute submucosal invasion (79.2% and 42.9%, respectively).

Conclusions: The accuracy of EUS for the lesions with the extended indications was lower than that for the lesions with the accepted indications. In particular, lesions with ulceration and minute submucosal invasion should be carefully considered prior to endoscopic treatment by pretreatment EUS staging.

Introduction

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosa or submucosa, regardless of the presence or absence of lymph node metastasis.¹ Endoscopic treatment, such as endoscopic mucosal resection and endoscopic submucosal dissection (ESD), is currently the standard practice for a subgroup of patients with EGC in Korea and Japan.²⁻⁴ The Japanese Gastric Cancer Association has established the accepted indications for endoscopic resection of early gastric carcinoma: (i) differentiated-type adenocarcinoma; (ii) tumor less than 20 mm in diameter; and (iii) tumor invasion limited to the mucosa without any ulcerous changes and no expected lymph node metastasis.⁴ Recent clinical observations have found that the accepted indications for endoscopic resection can be too strict and can lead to unnecessary

surgery.⁴ Therefore, the extended indications for endoscopic resection have been proposed (Table 1): (i) intramucosal cancer, differentiated-type adenocarcinoma, no lymphatic-vascular invasion, with no ulceration and irrespective of tumor size; (ii) intramucosal cancer, differentiated-type adenocarcinoma, no lymphatic-vascular invasion, irrespective of ulceration and less than 3 cm in size; (iii) minute submucosal cancer (≤ 500 μ m penetration into the submucosa), differentiated-type adenocarcinoma, no lymphatic-vascular invasion, with no ulceration and less than 3 cm in size; and (iv) intramucosal cancer, undifferentiated-type carcinoma, no lymphatic-vascular invasion, with no ulceration and less than 2 cm in size.^{4,5}

With the increasingly widespread application of endoscopic resection for the treatment of EGC, precise pretreatment staging has become mandatory in order to assess the appropriateness of the

Table 1 Accepted and extended indications for endoscopic resection of early gastric cancer

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	Ulcer (–)		Ulcer (+)		SM ₁	≥SM ₂
	≤20	>20	≤30	>30	≤30	Any size
Differentiated						
Undifferentiated						

■, Guideline criteria for endoscopic mucosal resection; ■, Guideline criteria for endoscopic submucosal dissection; ■, Consider surgery; ■, Surgery.

procedure in relation to curative treatment.^{6–10} Endoscopic ultrasonography (EUS) is the first-choice imaging modality for determining the depth of gastric cancer invasion, and T-staging accuracy has been reported to be approximately 80%–90%.^{7,10,11} Compared to conventional EUS transducers, a high-frequency (≥15 MHz) catheter probe provides higher resolution images of the gastric wall and makes it possible to more accurately evaluate the depth of invasion.^{9,12,13}

The role of EUS is still not fully established for determining the depth of EGC according to the accepted/extended indications. Therefore, we prospectively investigated the accuracy of EUS for determining the depth of endoscopically-suspected EGC by using a high-frequency (20 MHz) catheter probe, and we then analyzed the difference in the accuracy of EUS according to the accepted/extended indications.

Methods

Patients

From January 2006 to December 2008, a total of 181 lesions in 178 patients (125 men and 53 women; age range: 32–82 years; mean age: 60 years) with an endoscopic diagnosis of EGC, who underwent EUS for staging the depth of invasion using a 20-MHz catheter probe, were prospectively included. All of the patients were suspected of having EGC endoscopically and had no evidence of distant metastasis by clinical examination, ultrasonography, and computed tomography.

The study was approved by the Institutional Review Board at Pusan National University Hospital (Busan, Korea) and informed consent was obtained from all of the patients.

EUS

EUS was performed with a radial-scanning, 20-MHz catheter probe (UM3D-DP20-25R; Olympus, Tokyo, Japan) by an experienced endosonographer (GH Kim), who had previously performed more than 500 examinations. The probe was passed through the instrument channel of a one-channel endoscope (GIF-H260; Olympus, Japan) or a two-channel endoscope (GIF-2T240; Olympus, Japan). All of the examinations were performed under intravenous conscious sedation (midazolam with or without meperidine). Scanning of the tumor was performed after filling the

stomach with 400–800 mL de-aerated water. Approximately 10–20 endosonograms were recorded for each patient, and these images were stored on magneto-optical disks. The probe yielded high-quality cross-sectional images of the gastric wall and was easily directed to the small cancer lesions under the direct vision of the endoscopist.¹³ According to the five-layer architecture of the gastric wall, the EUS images were interpreted with regard to tumor invasion (Fig 1,2). Upon EUS, the mucosa is visualized as a combination of the first and second hypoechoic layers, and the submucosa corresponds to the third hyperechoic layer. The muscularis propria is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa, including the subserosa.^{14–16} In addition, the fine hypoechoic layer between the second and third layers is considered to correspond to the muscularis mucosae.¹⁷ For lesions with ulcerous changes, a benign ulcer scar pattern, such as smooth tapering of the third layer, was considered to be the standard layer structure, and a method of pattern analysis was used to determine the depth of invasion.¹⁸ On the basis of these findings, the EGC lesions were classified into three groups: mucosal (EUS-M), submucosal (EUS-SM), or advanced (EUS-A). In addition, EUS-SM and EUS-A were integrated into non-mucosal.

Clinicopathological review

ESD or gastrectomy was performed within 2 weeks after EUS. The resected specimens were fixed in 10% buffered formalin. Carcinomas with adjacent non-neoplastic mucosa were serially cut parallel into 5-mm slices and embedded in paraffin; they were then sectioned and stained with hematoxylin–eosin for the histological examination. The clinicopathological findings, such as age, sex, macroscopic shape, tumor site, tumor size, histological type, depth of invasion, lymphovascular invasion, perineural invasion, and lymph node metastasis, were reviewed according to the Japanese Classification of Gastric Carcinomas.¹⁹ Lesions with ulceration or scarring from previous ulcerations (converging folds or deformity of the muscularis propria or fibrosis in the submucosal or deeper layer) within them were regarded as ulcerated lesions.⁵ The depth of submucosal invasion was measured from the muscularis mucosa to the point of the deepest penetration. The depth of submucosal penetration was classified into two subgroups: SM₁ (<500 μm penetration into the submucosa) and SM₂ (≥500 μm).⁵ The depth of tumor invasion was classified as mucosal, submucosal, or advanced (the tumor had invaded the muscularis propria or deeper).

Statistical analysis

The sensitivity, specificity, positive and negative predictive values, and the accuracy of the EUS assessment for mucosal cancer were calculated manually. The accuracy of EUS in relation to the clinicopathological features and according to the accepted and extended indications was assessed by using the χ^2 -test or Fisher's exact test. A *P*-value <0.05 was considered statistically significant. The statistical calculations were performed using SPSS version 12.0 for Windows software (SPSS, Chicago, IL, USA).

Results

Of the 178 patients, five patients were dropped from the analysis due to the absence of final histological results: two patients did not

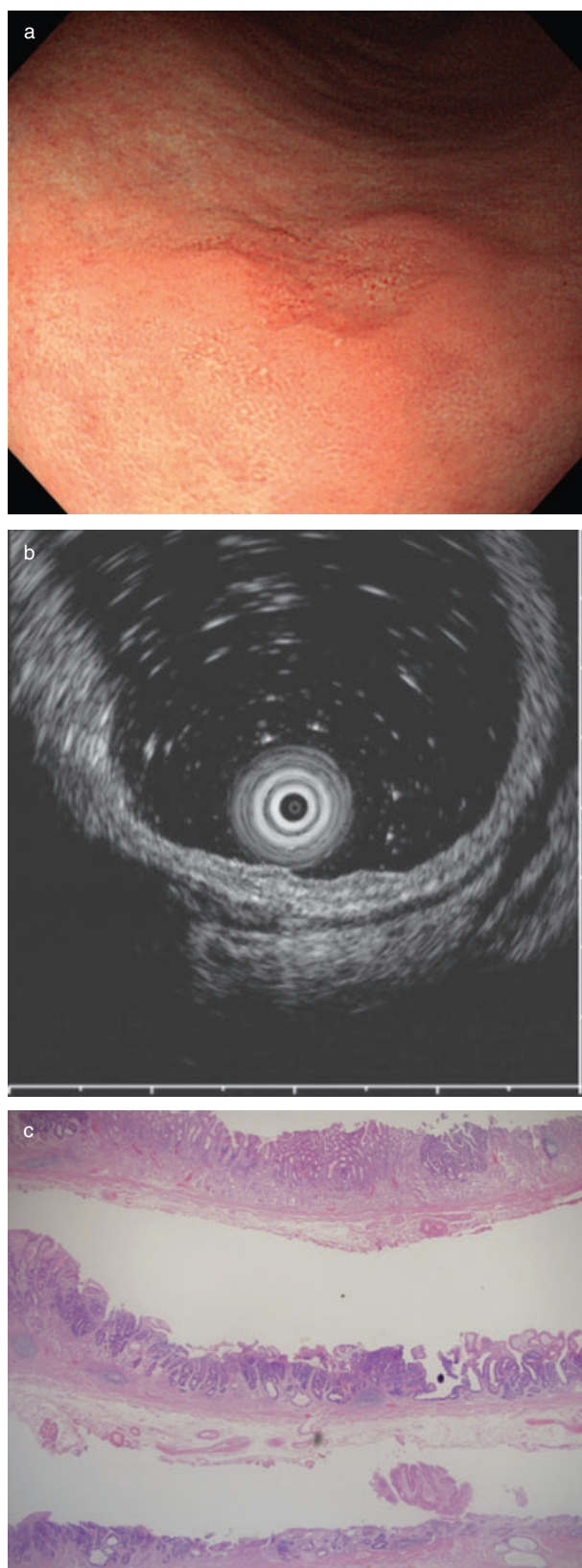


Figure 1 Early gastric cancer confined to the mucosa. (a) Gastroscopy shows a superficial depressed lesion in the antrum. (b) A 20-MHz endoscopic ultrasonography probe reveals a hypoechoic lesion in the mucosal layer. (c) Histological examination shows a differentiated adenocarcinoma confined to the mucosa, which has been removed by endoscopic submucosal dissection.

receive definite treatment because of their underlying liver cirrhosis, and the other three patients were lost to follow up after EUS. Finally, a total of 176 lesions in 173 patients (122 men and 51 women; age range: 32–82 years; mean age: 60 years) were included in this study. Sixty-six lesions were treated by ESD and 110 lesions were treated by operation.

For the 176 lesions, the accuracy of the EUS assessment for the depth of tumor invasion was 80.7% (142 of 176 lesions). The sensitivity and specificity of EUS assessment for mucosal cancer were 84% (105 of 125 lesions) and 80.4% (41 of 51 lesions), respectively. The positive predictive value, negative predictive value, and accuracy of the EUS assessment for mucosal cancer were 91.3% (105 of 115 lesions), 67.2% (41 of 61 lesions), and 83% (146 of 176 lesions), respectively (Table 2).

The accuracy of EUS was not different according to the location and size of cancer. The accuracy of EUS decreased for the lesions with a depressed or excavated morphology, those with concomitant ulceration, and those with undifferentiated histology (Table 3).

The accuracy of EUS was then reevaluated according to the accepted and extended indications for endoscopic resection (Table 4). The accuracy of EUS for the lesions with accepted indications and with extended indications was 97.6% (40 of 41 lesions) and 83.6% (46 of 57 lesions), respectively ($P = 0.040$). Of the lesions with extended indications, the accuracy of EUS decreased, especially for the lesions with ulceration and those with SM₁ invasion (79.2% and 42.9%, respectively). For the lesions that were not suitable for endoscopic treatment, the accuracy of EUS was 71.8% (56 of 78 lesions).

Discussion

In the present study, we first prospectively investigated the accuracy of EUS for endoscopically-suspected EGC by using a high-frequency (20 MHz) catheter probe. The accuracy of the EUS assessment for the depth of tumor invasion was 80.7%, which is similar to that of previous studies.^{6,9,18,20–22} Concomitant ulceration, an excavated morphology, and an undifferentiated histology decreased the accuracy of EUS in this study.

There have been reports on the difficulty of EUS diagnosis for lesions with ulcerous changes.^{6,9,18,20–22} To distinguish cancer invasion from ulcer fibrosis, we used a method of pattern analysis that was introduced by Kida *et al.*¹⁸ This pattern analysis was based on the fact that ulcer fibrosis always has a fan-shaped spread, while cancer invades in an arched-shaped spread. However, microinvasion into the ulcer fibrosis does not change the contours of the fan-shaped ulcer fibrosis, so the microinvasion is not detectable by EUS. By using this pattern analysis, they reported that the diagnostic accuracy for depressed-type EGC with ulceration was 76.1%.¹⁸ In our study, the accuracy rate of EUS was 69.9% for EGC with ulceration, which was significantly lower than that for

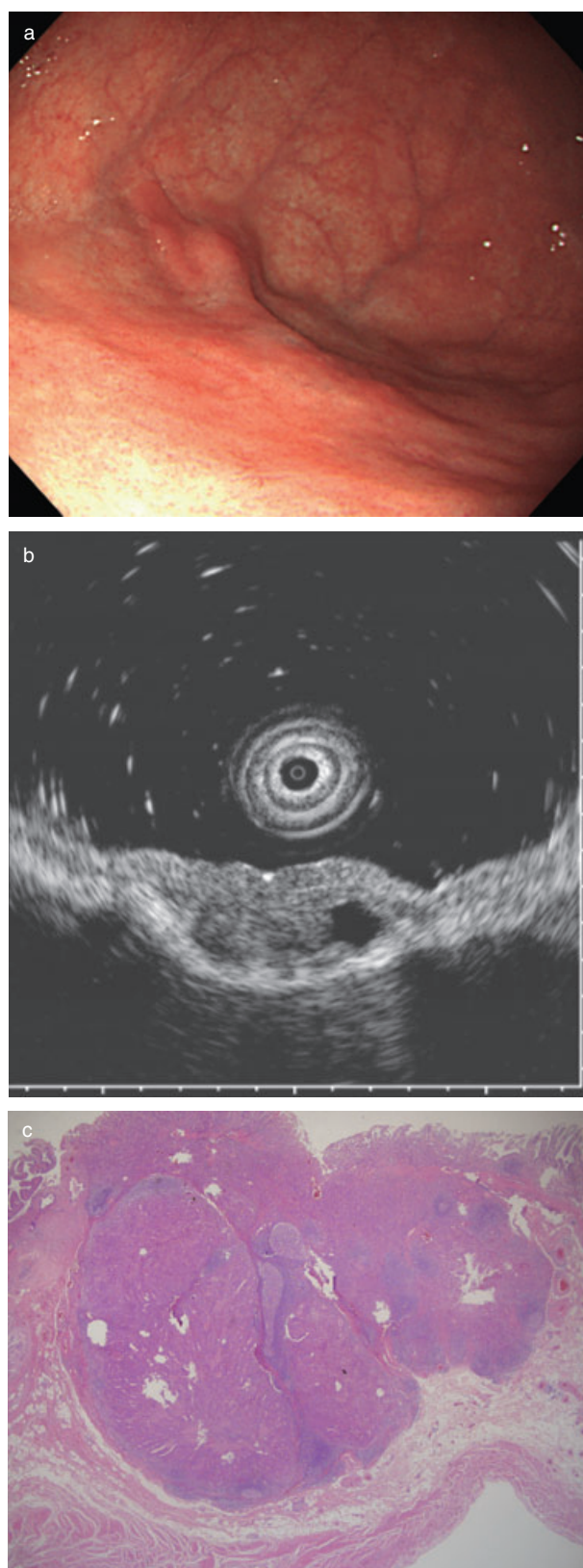


Figure 2 Early gastric cancer invaded into the submucosa. (a) Gastros-copy shows a superficial elevated lesion in the fundus. (b) A 20-MHz endoscopic ultrasonography probe reveals a hypoechoic tumor with a cystic area infiltrating into the submucosal layer. (c) Histological examination after surgical resection shows a differentiated adenocarcinoma with massive submucosal invasion.

EGC without ulceration. Contrast-enhanced EUS was suggested to be another method to improve the accuracy of EUS for lesions with ulcerous changes.²³ If the area of the carcinoma cells was selectively enhanced by intravenous contrast, it might contribute to distinguishing tumor invasions from fibrosis and lead to an accurate diagnosis for lesions with ulcerations.

The accuracy of EUS for the lesions with a depressed or excavated morphology was lower than that for the lesions with a flat or elevated morphology. This result was quite understandable because the depressed lesions usually showed a higher incidence of ulcerous changes.

In general, the accuracy of EUS for undifferentiated adenocarcinoma has been reported to be unfavorable.^{21,22} In this study, the accuracy of EUS for undifferentiated-type adenocarcinoma was also significantly lower than that for differentiated-type adenocarcinoma. However, for undifferentiated-type adenocarcinoma less than 2 cm and without ulcerous change, as one of the extended indications for ESD, the accuracy of EUS was 83.3%. Therefore, EUS could be useful to examine tumor invasion before ESD for undifferentiated-type adenocarcinoma less than 2 cm and without ulcerous change.

The previous studies that used conventional EUS transducers showed that a large tumor size was more frequently associated with an incorrect EUS diagnosis of the depth of tumor invasion.^{21,22} Although the conventional EUS can miss some lesions because of their small diameters and tight locations, the catheter probe system is able to demonstrate small lesions and examines suspicious foci that might invade most deeply under the direct vision of the endoscopist.¹³ This fact could explain our results where the EUS accuracy was not different according to the location and size of the cancer.

Second, we analyzed the differences in the accuracy of EUS according to the accepted/extended indications. The accuracy of EUS was high (97.6%) for the lesions with accepted indications. Of the lesions with extended indications, the accuracy of EUS for differentiated-type adenocarcinoma more than 2 cm and without ulcerous change was also high (95%). Therefore, we strongly recommend endoscopic treatment if a lesion with a differentiated-type adenocarcinoma and without ulcerous change is diagnosed as EUS-M. The accuracy of EUS was 79.2% for the lesions with differentiated-type adenocarcinoma less than 3 cm and with ulcerous change. Still, there has been no report about the accuracy of EUS according to the extended indications, so we could not directly compare our results with those of the previous reports. EUS would be useful in planning the treatment modality for the case of lesions with differentiated-type adenocarcinoma less than 3 cm and with ulcerous change.

However, the accuracy of EUS decreased for the lesions with SM₁ invasion (42.9%). Of the four misdiagnosed lesions, two had minute invasion of the tumor within a depth of about 200 μ m. Such

Table 2 Endoscopic ultrasonography (EUS) assessment of the depth of lesions with an endoscopically-suspected early gastric cancer

Histopathology	<i>n</i>	EUS		
		Mucosal	Submucosal	Advanced
Mucosal	125	105	20	0
Submucosal	44	10	34	0
Advanced	7	0	4	3
Total	176	115	58	3
Sensitivity for mucosal cancer	105/125 (84.0%)			
Specificity for mucosal cancer	41/51 (80.4%)			
Positive predictive value for mucosal cancer	105/115 (91.3%)			
Negative predictive value for mucosal cancer	41/61 (67.2%)			
Accuracy for mucosal cancer	146/176 (83.0%)			

Table 3 Accuracy of endoscopic ultrasonography (EUS) for predicting cancer invasion on the basis of the clinicopathological features

	Total	EUS		<i>P</i> -value
		Correct	Incorrect	
Location				0.803
Upper third	8	6 (75.0%)	2 (25.0%)	
Middle third	68	54 (79.4%)	14 (20.6%)	
Lower third	100	82 (82.0%)	18 (18.0%)	
Tumor size				0.334
<10 mm	29	27 (93.1%)	2 (6.9%)	
10–20 mm	59	46 (78.0%)	13 (22.0%)	
20–30 mm	44	34 (77.3%)	10 (22.7%)	
≥30 mm	44	35 (79.5%)	9 (20.5%)	
Gross findings				0.004
Flat/elevated	48	43 (89.6%)	5 (10.4%)	
Depressed	98	81 (82.7%)	17 (17.3%)	
Excavated	30	18 (60.0%)	12 (40.0%)	
Concomitant ulceration				0.003
Present	73	51 (69.9%)	22 (30.1%)	
Absent	103	91 (88.3%)	12 (11.7%)	
Histology				0.020
Differentiated	124	106 (85.5%)	18 (14.5%)	
Undifferentiated	52	36 (69.2%)	16 (30.8%)	

Table 4 Accuracy of endoscopic submucosal dissection (EUS) for predicting cancer invasion according to the accepted and extended indications for endoscopic resection

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	Ulcer (–)		Ulcer (+)		SM ₁	≥SM ₂
	≤20	>20	≤30	>30	≤30	Any size
Differentiated	40/41 (97.6%)	19/20 (95.0%)	19/24 (79.2%)	3/4 (75.0%)	3/7 (42.9%)	22/28 (78.6%)
Undifferentiated	5/6 (83.3%)	10/12 (83.3%)	9/18 (50.0%)		12/16 (75.0%)	

■, Guideline criteria for endoscopic mucosal resection; ■, Guideline criteria for endoscopic submucosal dissection; ■, Consider surgery; ■, Surgery.

minute invasion is difficult to diagnose and EUS resolution is approximately 0.2 mm on a 20-MHz probe.²⁴ Therefore, the limitation of EUS resolution would explain the decreased accuracy of EUS for the lesions with SM₁ invasion in this study.

This study was carried out prospectively, but there were some limitations. First, we included only the patients with endoscopically-suspected EGC who underwent EUS and ESD or gastrectomy, which might have introduced some bias. Second, due

to the limited depth of penetration of the 20-MHz probe, we could not evaluate lymph node metastasis. Third, EUS was performed under conventional endoscopy by an experienced endosonographer, so the interpretation of EUS images was possibly affected by the endoscopic appearance of the lesions and the experience of the endosonographer.²⁵

Accurately predicting the depth of tumor penetration in patients with EGC is very important for deciding the treatment modalities, such as endoscopic resection or surgery. According to our study, the accuracy of EUS for the lesions with the extended indications was lower than that for the lesions with the accepted indications. In particular, the lesions with ulceration and with SM₁ invasion should be carefully considered when deciding on endoscopic treatment by pretreatment EUS staging.

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