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ORIGINAL ARTICLE

Retrospective Study

What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?

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Abstract

AIM

To clarify the diagnostic efficacy and limitations of endoscopic ultrasonography (EUS) and the characteristics of early gastric cancers (EGCs) that are indications for EUS-based assessment of cancer invasion depth.

METHODS

We retrospectively investigated the cases of 153 EGC patients who underwent conventional endoscopy (CE) and EUS (20 MHz) before treatment.

RESULTS

We found that 13.7% were "inconclusive" cases with low-quality EUS images, including all nine of the cases with protruded (0-I)-type EGCs. There was no significant difference in the diagnostic accuracy

between CE and EUS. Two significant independent risk factors for misdiagnosis by EUS were identified-ulcer scarring [UL(+); odds ratio (OR) = 4.49, P = 0.003] and non-indication criteria for endoscopic resection (ER) (OR = 3.02, P = 0.03). In the subgroup analysis, 23.1% of the differentiated-type cancers exhibiting SM massive invasion (SM2) invasion (submucosal invasion $\geqslant$ 500 μm) by CE were correctly diagnosed by EUS, and 23.1% of the undifferentiated-type EGCs meeting the expanded-indication criteria for ER were correctly diagnosed by EUS.

CONCLUSION

There is no need to perform EUS for UL(+) EGCs or 0-I-type EGCs, but EUS may enhance the pretreatment staging of differentiated-type EGCs with SM2 invasion without UL or undifferentiated-type EGCs revealed by CE as meeting the expanded-indication criteria for ER.

Key words: Gastric cancer; Endoscopic ultrasonography; Invasion depth diagnosis; Conventional endoscopy; Endoscopic submucosal dissection

Core tip: With the increasingly expanded indications of endoscopic resection for early gastric cancer (EGC), the accurate diagnosis of the invasion depth has become more important in the pretreatment strategy. Although there have been many investigations comparing the efficacy of endoscopic ultrasonography (EUS) and conventional endoscopy (CE) for invasion depth diagnosis of EGCs, much controversy remains. Our results revealed that there is no need to perform EUS for EGCs that are protruded type or those that have an ulcer scar, but EUS may have an add-on effect in the pretreatment staging of differentiated-type EGCs diagnosed as SM2 (submucosal invasion $\geqslant$ 500 μm) and undifferentiated-type EGCs diagnosed by CE as meeting the expanded-indication criteria for endoscopic resection.

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INTRODUCTION

Until recently, the Japanese Gastric Cancer Treatment Guidelines[1] stipulated that mucosal lesions < 2 cm in size and without ulceration are indicated for endoscopic resection (ER). However, in response to a report by Gotoda *et al*[2] on the low incidence of lymph node metastasis from early gastric cancers (EGCs), the indications for ER described in those Guidelines have been expanded to include EGCs with a very low risk of lymph node metastasis. Another part of the rationale behind this decision was that endoscopic submucosal dissection (ESD), which was developed in Japan[3-7], has made *en bloc* resection possible for lesions of all sizes. Along with the expanded indications for the ER of EGCs, therefore, the accurate diagnosis of invasion depth has become a very important component of pretreatment strategies.

Conventional endoscopy (CE) remains a useful modality for detecting EGCs and gauging their invasion depth. Although there have been many investigations, mostly in Japan, of the ability of CE to gauge the invasion depth of mucosal (M) and submucosal (SM) invasive cancers, collectively the rate of successful depth measurement has ranged from 62% to 80%[8-10]. Thus it is sometimes difficult to establish diagnostic criteria for differentiating M from SM cancers by CE alone. Endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, and is thus sometimes used as an adjunct diagnostic tool for determining the depth of gastric cancer invasion.

Several studies have compared the accuracy of invasion depth measurement between CE and EUS, and some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth[11-14] whereas others did not[9,15]. Two recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of EGC invasion, and thus EUS may not be indispensable in the staging of EGCs[16,17]. It has also been reported that the accurate determination of invasion depth is difficult in cases with a large tumor size[11,15,18-21], upper location[15,18,20], depressed-type lesion[11,20], undifferentiated histology[15,21] or ulcerous finding (UL)[15,19,21,22].

There are also a number of practical technical difficulties that impede the production of suitable EUS images, and the use of poor-quality EUS images to determine the depth of EGCs may lead to incorrect results[23]. Unfortunately, most of the previous comparative studies (with the exception of the study by Tsujii *et al*[24]) analyzed only cases in which good-quality EUS images were obtained, and thus their findings may not show the true diagnostic capability of EUS in actual practice.

Along with the expanded indications for EGC dissection, it is expected that the number of ESDs of EGCs will increase, and the precise invasion depth staging of EGCs will therefore be important. Accordingly, the aims of the present study were to clarify: (1) the comparative diagnostic efficacies and limitations of EUS and CE for the pre-operative staging of EGC; and (2) the characteristic(s) of EGCs that are indications for the use of EUS as an adjunct diagnostic tool for measuring invasion depth.

MATERIALS AND METHODS

Patients

Between April 2012 and March 2015, 452 consecutive patients with a total of 510 neoplasias comprised of gastric adenomas and EGCs were treated with ESD (360 neoplasias) and surgery (150 neoplasias) at Hyogo College of Medicine Hospital in Nishinomiya, Japan. Among them, 153 EGCs in 140 patients were examined using both CE and EUS. Both the absolute-indication and the expanded-indication criteria for the ER of EGCs followed the Japanese Gastric Cancer Treatment Guidelines[1]. The absolute-indication criteria for ER are: M cancer, differentiated-type adenocarcinoma, UL(-), and < 2 cm in dia. The proposed extended-indication criteria for ER are as follows: (1) M cancer, differentiated-type adenocarcinoma, UL(-) and any tumor size; (2) M cancer, differentiated-type adenocarcinoma, UL(+) and < 3 cm in size; (3) minute submucosal cancer (< 500 μm invasion into the submucosa, SM1), differentiated-type adenocarcinoma and < 3 cm in size; and (4) M cancer, undifferentiated-type carcinoma, UL(-) and < 2 cm in size.

Written informed consent was obtained from all patients prior to the procedures and treatment, and the study design was approved by the Ethics Committee of Hyogo College of Medicine (No. 2109).

The CE and EUS diagnoses of the invasion depth of EGCs

When the invasion depth of an EGCs is being diagnosed, close endoscopic observation is necessary to adjust the air volume in the patient's stomach. The endoscopic criteria for cancer invasion in the present patient series were judged based on previous reports[8-10,15,24-26]. Briefly, in the CE diagnosis, the presence or absence of the following CE findings of SM massive invasion was determined: (1) irregular surface including nodules in the depressed area; (2) submucosal tumor-like elevation without flexibility; (3) abnormal converging folds such as clubbing and fusion; and (4) deep ulceration with marked marginal elevation. All endoscopic observations were performed by chromoendoscopy using an endoscope (GIF-Q260, H260, H260Z, H290Z, H290 or HQ290; Olympus Medical Systems, Tokyo) followed by EUS.

EUS was performed with a 20-MHz miniature probe UM-3R (Olympus Medical Systems), which was connected to an endoscopic ultrasonic observation unit (EU-M2000; Olympus Medical Systems). Approximately 200-500 mL of deaerated water was instilled in the stomach to improve the transmission of the ultrasound beam. In the EUS diagnoses, lesions confined to the 1st and 2nd sonographic layers were considered mucosal cancer. Massive submucosal invasion was defined as obvious irregular narrowing or budding into the 3rd sonographic layer as shown in previous reports[9-11,14,15,20,21,23-26].

In the UL(+) lesions, the previous criteria for EUS diagnosis were used[13,27]; namely, if a fan-shaped hypoechoic area was demonstrated in the 3rd layer, the lesion was defined as M/SM1, and when an arch-shaped hypoechoic area was observed in the 3rd layer, the lesions were regard as SM massive invasion (SM2). In the cases in which at least five layers of the gastric wall, including the lesion, were unclear and an assessment by EUS was difficult due to the low-quality image, the lesions were judged to be "inconclusive"[24].

It is very difficult to discriminate SM1 from M cancer even by CE or EUS, and the therapeutic strategies for these lesions are also similar. We therefore clinically divided these lesions into two groups: The M/SM1 group, for which ER may be suitable, and the SM2 group, for which surgery was indicated.

In this retrospective study, two endoscopists (Jiro Watari and Shigemitsu Ueyama) with 29 and 17 years of endoscopic practice experience, respectively and board certification from the Japan Gastroenterological Endoscopy Society independently reviewed the CE and EUS images without any pathologic information. The results were used for the calculation of interobserver agreement (κ value).

Histological evaluation

Resected specimens were sectioned at 2-mm intervals for ESD and 5-mm intervals for surgical resection. The histology, tumor location, gross morphologic type, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer[28]. We histologically classified the specimens into two groups based on their depth of submucosal invasion: Invasion into the SM1 (invasion < 500 μm) or SM2 (invasion ≥ 500 μm) layer. The largest measured tumor size of the resected specimen was recorded histologically as the tumor dia.

Statistical analysis

We assessed the data by performing the Mann-Whitney *U* test for comparisons between two independent groups, and the χ^2 test or Fisher's exact test was used to examine differences between two proportions. Statistical significance was defined as a P value < 0.05. Risk factors for the misdiagnosis of the depth of cancer invasion by EUS that were found to be significant with a P value of < 0.05 in a univariate analysis were entered into a multiple logistic regression model and analyzed using a backward approach. Odds ratios (ORs) and 95%CIs were calculated for each risk factor.

The interobserver agreement for the CE imaging and the EUS imaging evaluations was calculated by κσ statistics, which were interpreted as follows: Poor (≤ 0.2), mild (0.2-0.4), moderate (0.4-0.6), good (0.6-0.8), and excellent (0.8-1.0). Differences at P < 0.05 were considered significant. All statistical analyses were performed using the StatView software program, ver. 5.0 (SAS Institute, Cary, NC).

Table 1 Patient characteristics

Total no. of lesions (patients)	153 (140)
Mean (± SD) age, years	68.7 ± 10.4
Sex, male/female	102/38
Macroscopic type	
0-I /0-IIa/0-IIb /0-IIc	9/51/1/92
Location	
Upper/middle/lower	45/69/39
Mean (± SD) tumor size, mm	20.5 ± 14.4
Depth of invasion	
M/SM1/SM2	93/17/43
Histology	
Differentiated/undifferentiated	118/35
Ulcer scar	
Positive/negative	29/124
Criteria for endoscopic resection	
Absolute/expanded/non-indication	51/38/64

M: Mucosal cancer; SM1: Submucosal invasive cancer invaded into the submucosal layer < 500 μm from the muscularis mucosa; SM2: Submucosal invasive cancer with invasion of ⩾ 500 μm into the submucosal layer.

Table 2 Clinical characteristics of the 21 inconclusive cases

Tumor-related factors		No. of inconclusive cases (%)	*P* value
Macroscopic type			< 0.0001
I	(*n* = 9)	9 (100)	
IIa	(*n* = 51)	7 (13.7)	
IIc	(*n* = 92)	5 (5.4)	
Location			0.03
Upper	(*n* = 45)	3 (6.7)	
Middle	(*n* = 69)	8 (11.6)	
Lower	(*n* = 39)	10 (25.6)	
Histology			0.16
Differentiated	(*n* = 118)	19 (16.1)	
Undifferentiated	(*n* = 35)	2 (5.7)	
Ulcer scar			0.37
Positive	(*n* = 29)	2 (6.9)	
Negative	(*n* = 124)	19 (15.3)	
Criteria for ER			0.58
Absolute	(*n* = 51)	9 (17.6)	
Expanded	(*n* = 38)	5 (13.2)	
Non-indication	(*n* = 64)	7 (10.3)	

ER: Endoscopic resection.

RESULTS

Patient characteristics and clinicopathological data of EGCs

Table 1 shows the characteristics of the 140 patients and a summary of the 153 studied EGCs. The mean age of the patients was 68.7 ± 10.4 years (range 23-87 years), and women accounted for 27.1% of the patients. The mean tumor size was 20.5 ± 14.4 mm in dia. The numbers of lesions that met the absolute- and expanded-indication criteria for ER were 51 and 38 lesions, respectively. The lesions were located mainly in the middle portion of the stomach.

Clinical characteristics of the "inconclusive" cases

Twenty-one (13.7%) of the 153 EGCs were judged as "inconclusive". As shown in Table 2, all nine of the protruded-type (0-I) cancers yielded low-quality images. The inconclusive rate was significantly higher in the lower portion of the stomach than in other portions (P = 0.03). There was no significant difference in the inconclusive rate between the lesions with and without UL.

Comparison of EGC invasion-depth diagnoses between EUS and CE

The κ-values for the interobserver agreement for the invasion depth diagnosis between the two endoscopists were 0.78 (95%CI: 0.68-0.89) for EUS and 0.82 (95%CI: 0.72-0.92) for CE. Thus the interobserver agreement for invasion depth diagnosis by EUS and CE was good to excellent. When the results of the diagnostic accuracy by one endoscopist whose accuracy rate was higher than that of the other endoscopist were used in both modalities, the accuracy rate of EUS was 71.2% (109 of 153 lesions) (Table 3), and when the accuracy was calculated in 132 lesions (omitting 21 inconclusive cases), the rate increased to 82.6% (109 of 132).

The sensitivity of EUS for diagnosing M/SM1 lesions was 85.3% (81 of 95 cases), the specificity was 75.7% (28 of 37), the positive predictive value (PPV) was 90.0% (81 of 90), and the negative predictive value (NPV) was 66.7% (28 of 42). The diagnostic accuracy of EUS was not significantly different among the three macroscopic types or the three tumor locations, or between the histological types, *i.e.*, the differentiated type and the undifferentiated type.

However, UL(+) and the non-indication criteria for ER were significantly associated with the incorrect diagnosis of tumor invasion depth by EUS (P < 0.0001 and P = 0.0004, respectively). In addition, UL(+) (OR = 4.49; 95%CI: 1.68-11.97; P = 0.003) and the non-indication criteria for ER (OR = 3.02; 95%CI: 1.14-8.00; P = 0.03) were significant and independent risk factors affecting misdiagnosis by EUS in our multivariate logistic regression analysis.

There were no significant differences in the accuracy or other parameters between EUS and CE; the sensitivity of CE diagnosis for M/SM1 was 88.2% (97 of 110 cases), the specificity was 58.1% (25 of 43), the PPV was 84.3% (97 of 115), and the NPV was 65.8% (25 of 38). As shown in Table 3, the accuracy rate obtained for the absolute-indication criteria lesions was very high for both modalities, and was significantly higher than that of the non-indication criteria lesions (P < 0.0001 in EUS and P = 0.01 in CE). There were also significant differences in the accuracy between the lesions with the expanded-indication criteria and those with the non-indication criteria for ER (P = 0.02 in both EUS and CE). However, no significant differences in diagnostic accuracy between the two modalities were observed within the expanded-indication criteria group or the

Table 3 Comparison of the invasion depth diagnosis between endoscopic ultrasonography and conventional endoscopy

	Clinical diagnosis	Histologic diagnosis		EUS diagnosis		P^2	Histologic diagnosis		Accuracy	P (*vs* EUS)
		M/SM1	SM2	Overall accuracy	Accuracy[1]		M/SM1	SM2		
Diagnosis	M/SM1	81	9	71.2	82.6		97	18	79.7	0.54
	SM2	14	28				13	25		
Macroscopic type						0.30				
I	M/SM1	-	-	-	-		5	1	88.9	-
	SM2	-	-				0	3		
IIa/IIb	M/SM1	26	4	67.3	77.8		32	5	78.8	0.90
	SM2	6	9				6	9		
IIc	M/SM1	55	5	80.4	85.1		60	12	79.3	0.32
	SM2	8	19				7	13		
Location						0.55				
Upper	M/SM1	21	2	74.4	80		24	4	80.0	> 0.99
	SM2	6	11				5	12		
Middle	M/SM1	40	7	69.9	78.5		44	11	78.3	0.98
	SM2	7	11				4	10		
Lower	M/SM1	19	2	62.2	85.2		29	3	82.1	> 0.99
	SM2	2	4				4	3		
Histology						0.79				
Diff.	M/SM1	71	10	70.4	83		77	12	80.5	0.63
	SM2	8	17				11	18		
Undiff.	M/SM1	9	1	75.0	84		20	6	77.1	> 0.99
	SM2	4	12				2	7		
Ulcer scar						< 0.0001				
Positive	M/SM1	3	2	46.7	50		7	4	58.6	0.51
	SM2	12	11				8	10		
Negative	M/SM1	77	7	75.6	89.4		90	14	84.7	0.29
	SM2	4	16				5	15		
Indication for ER						< 0.0001				
Absolute	M/SM1	37	-	80.4	97.4[b]		43	-	84.3[f]	0.07
	SM2	1	-				8	-		
Expanded	M/SM1	28	-	75.7	87.5[d]		33	-	86.8[h]	> 0.99
	SM2	4	-				5	-		
Non-indication	M/SM1	12	13	56.1	62.7[b,d]		16	18	64.1[f,h]	> 0.99
	SM2	9	25				5	25		

Accuracy[1] was calculated with the exception of 21 inconclusive cases of EUS; P^2 indicates a significant difference in Accuracy[1]. [b]$P < 0.0001$; [d]$P = 0.02$; [f]$P = 0.02$; [h]$P = 0.01$. EUS: Endoscopic ultrasonography; CE: conventional endoscopy; Diff: Differentiated-type; Undiff: Undifferentiated-type; ER: Endoscopic resection.

non-indication criteria group (Table 3).

Diagnostic concordance between EUS and CE

As shown in Table 4, the number of lesions that showed a correct diagnosis by CE and an incorrect diagnosis by EUS was almost the same as the number of lesions that showed an incorrect diagnosis by CE and a correct diagnosis by EUS in both the expanded-indication criteria group and the non-indication criteria group, irrespective of histology. This result may indicate that there is no additive effect of EUS in the diagnosis of invasion depth.

In the subgroup analysis of a total of 13 differentiated-type cancers without UL and with SM2 invasion diagnosed by CE, three (23.1%) cases that were misdiagnosed by CE were correctly diagnosed as M/SM1 lesions by EUS (Table 5 and Figure 1). We identified two cases (20.0%, 2 of 10) lesions that were ⩽ 2 cm and three cases (25.0%, 3 of 12) that were 3 cm in size. These cases were subsequently treated with ESD, avoiding surgery. The reverse phenomenon, *i.e.*, cases misdiagnosed by EUS but correctly diagnosed by CE - was not seen.

Similarly, in our subgroup analysis of 13 undifferentiated-type cases that met the expanded-indication criteria for ER, which were judged endoscopically as M/SM1 lesions, UL(-) and ⩽ 2 cm in size, three cases (23.1%) were correctly diagnosed by EUS as having SM2 invasion (Table 6 and Figure 2). These three cases were thus adequately treated with surgery.

DISCUSSION

Although there have been many investigations comparing the efficacy of EUS and CE for the pretreatment staging of EGCs, much controversy remains. In our present study, the overall accuracy of EUS for diagnosing invasion depth was lower than that of CE, but not significantly so. The accuracy of EUS was 82.6% (71.1% in overall accuracy), which was similar to the values reported in previous studies[13,14,19,22-25,27] but higher than the values obtained in other studies[9,11,12,15,20,21,26]. In recent meta-analyses, most of the cited studies showed that EUS has only a limited effect on determining the

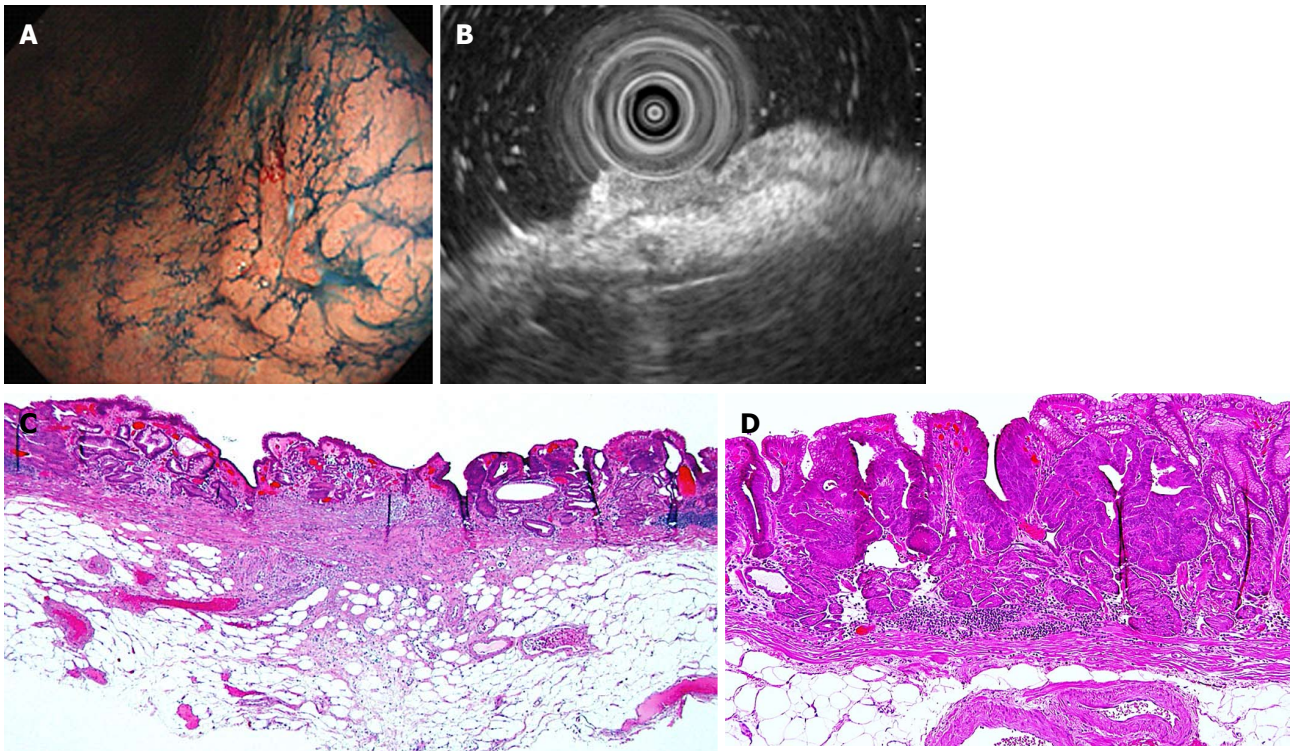

Figure 1 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows an irregular surface in a depressed lesion diagnosed as SM2; B: On this EUS image, irregular narrowing of sonographic layer 3 was not observed, and thus this lesion was considered an M/SM1 lesion; C: The histology by endoscopic submucosal dissection showed a differentiated-type intramucosal cancer with slightly fibrosis by biopsy; D: Histologic specimen of the lesion shows well differentiated-type adenocarcinoma limited to the mucosae (× 200). EUS: Endoscopic ultrasonography.

Table 4 Diagnostic concordance between endoscopic ultrasonography and conventional endoscopy

Diagnosis		Indication for endoscopic resection		
		Absolute criteria	Expanded criteria	Non-indication
Differentiated-type cancer (n = 99)				
EUS	CE	(n = 42) (%)	(n = 25) (%)	(n = 32) (%)
Correct	Correct	39 (92.9)	19 (76)	20 (62.5)
Incorrect	Incorrect	0 (0)	3 (12)	11 (34.4)
Correct	Incorrect	1 (4.8)	1 (4)	1 (3.1)
Incorrect	Correct	1 (2.4)	2 (8)	0 (0)
Undifferentiated-type cancer (n = 33)				
EUS	CE		(n = 8) (%)	(n = 25) (%)
Correct	Correct	-	8 (100)	15 (60)
Incorrect	Incorrect	-	0 (0)	1 (4)
Correct	Incorrect	-	0 (0)	5 (20)
Incorrect	Correct	-	0 (0)	4 (16)

EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

optimal therapeutic strategy[15,18-20,25]. Our present findings clearly demonstrated the limitations of EUS and the characteristics of EGCs that make them suitable for analysis by EUS.

In the present study, all nine of the 0-I-type cancers (protruded-type) yielded low-quality EUS images and were thus judged as inconclusive cases, as mentioned above[11,22]. The main cause of inconclusiveness was ultrasound attenuation due to the use of a high-frequency ultrasound probe (20 MHz); the submucosal layer could not be clearly visualized. If a low-frequency EUS or probe had been used, the number of inconclusive cases among those types of cancers might have been lower. However, in 0-I-type cancer the mucosa is thick and the muscularis mucosae elevates toward the mucosa from the submucosa, and it may thus be difficult to make an accurate diagnosis even if low-frequency EUS is performed.

In addition, the accuracy rate of EUS in the UL(+) lesions was extremely low (≤ 50%), and significantly lower than that in the UL(-) lesions (P < 0.0001). Regarding the reason for this finding, most of the lesions (80%, 12 of 15) of M/SM1 cancers with UL were over-diagnosed due to submucosal fibrosis,

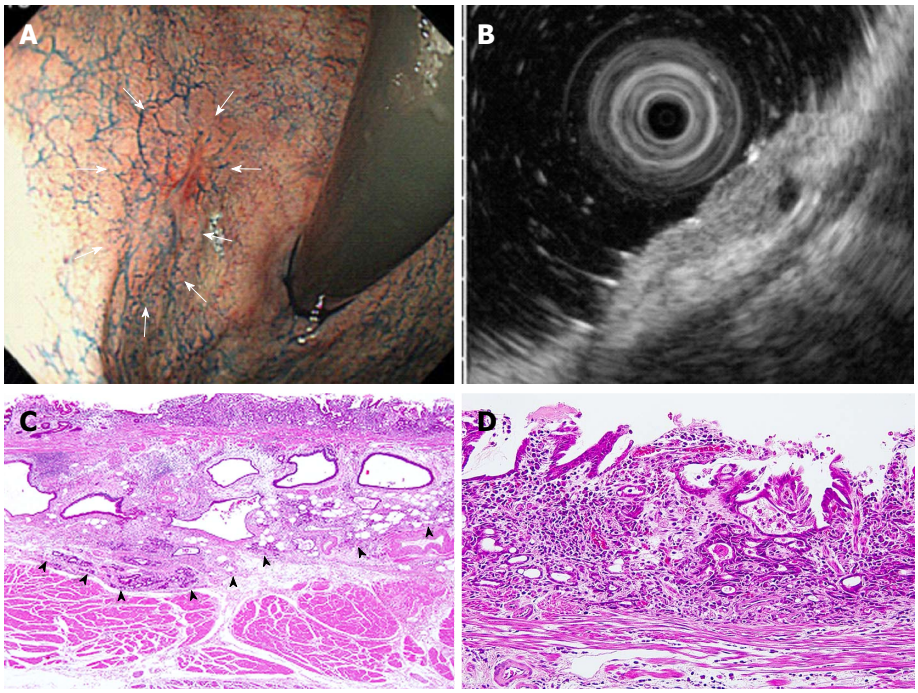

Figure 2 Case diagnosed correctly by endoscopic ultrasonography but misdiagnosed by endoscopy. A: Chromoendoscopy shows a reddish and smooth surface in a shallow depressed lesion diagnosed as M/SM1 (arrows). Histologically, the biopsy sample indicated a moderately to poorly differentiated adenocarcinoma; B: EUS image showing that a hypoechoic mass invaded the submucosal layer (sonographic layer 3). This lesion was diagnosed as SM2; C: Histology revealed that undifferentiated type adenocarcinoma massively invaded the submucosal layer (arrowheads); D: Moderately to poorly differentiated adenocarcinoma cells were observed in the gastric mucosae (× 200). EUS: Endoscopic ultrasonography.

Table 5 Subgroup analysis of 13 differentiated-type cancers without UL and with SM2 diagnosed by conventional endoscopy[1]

EUS	CE	*n* (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

SM2 indicates invasion ⩾ 500 μm into the submucosal layer. [1]The lesions with an ulcer scar or 0-I macroscopic type were excluded from this analysis because the diagnostic capability for those lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

Table 6 Subgroup analysis of 13 undifferentiated-type cancers diagnosed as meeting the expanded criteria for endoscopic treatment by conventional endoscopy[1]

EUS	CE	*n* (%)
Correct	Correct	10 (76.9)
Correct	Incorrect	3 (23.1)
Incorrect	Correct	0 (0)
Incorrect	Incorrect	0 (0)

[1]One 0-I macroscopic type lesion was excluded from this analysis because the diagnostic capability of this type of lesions was extremely low. EUS: Endoscopic ultrasonography; CE: Conventional endoscopy.

which is in agreement with previous reports[12,15,19,21,23]. In the report by Mandai *et al*[21], the accuracy rate of EUS decreased from 86.5% to 28.9% in the UL(-) lesions. Although a few studies have introduced a method that distinguishes cancer invasion from ulcer fibrosis[13,27], it may be difficult in practice to differentiate between those two conditions. In our multivariate logistic regression analysis, UL was a significant and independent risk factor affecting misdiagnosis by EUS, and thus it may be futile to perform EUS for UL(+) lesions.

There was no significant difference in the accuracy rate of EUS among the three tumor locations of the stomach, but inconclusive cases were observed significantly more frequently in the lower third of the stomach than in the other portions (P = 0.03). Several studies showed that the diagnostic accuracy of the invasion depth was diminished for lesions in the upper portion of the stomach[8,12,14,15,19,23]. Tsuzuki *et al*[25] reported that the submucosal layer in the upper third of the stomach is relatively thin and tends to have fibrosis and many vessels, making signs of submucosal invasion difficult to diagnosis and leading to incorrect staging. For other reasons, it is considered that it is difficult to fill this region with deaerated water[8,19,25]. However, this problem can be overcome by adjusting the volumes of air and deaerated water. In our patient population, it was often difficult to achieve the necessary pool of deaerated water in the lower third of the stomach, and there were technical problems with scanning this portion.

The diagnostic accuracy of EUS has been reported to be low for undifferentiated-type lesions[10-12,14,18,22] and

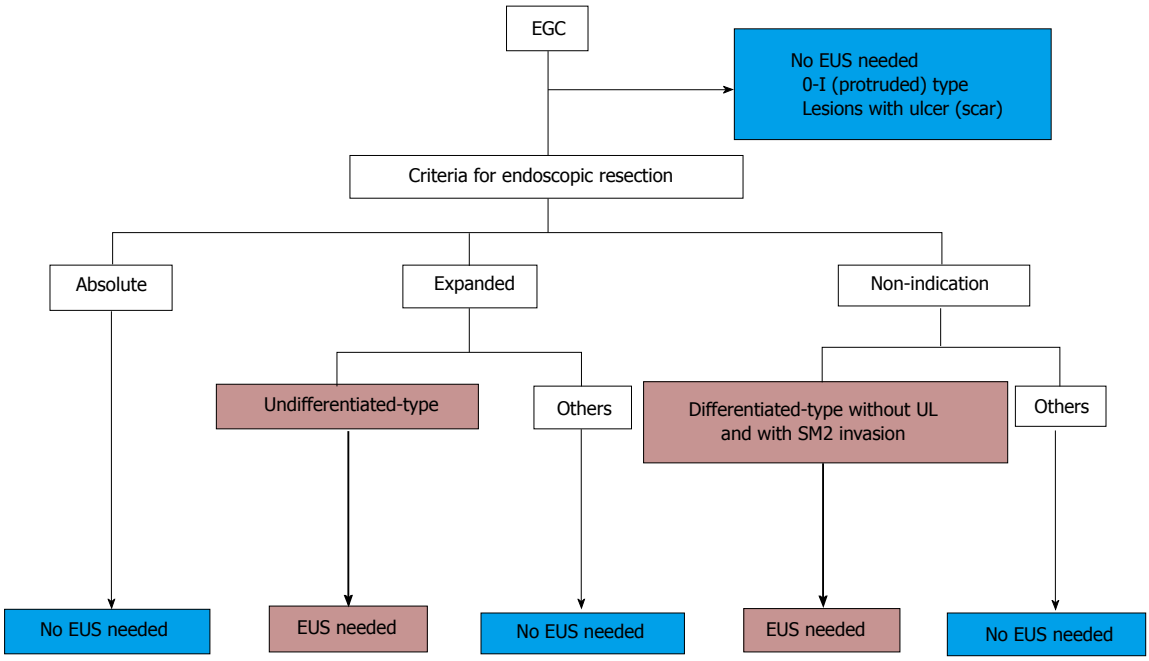

Figure 3 Flowchart of endoscopic ultrasonography diagnostic strategy for early gastric cancer. EUS should be considered performing the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by conventional endoscopy as meeting the expanded-indication criteria for endoscopic resection. In cases rather than those lesions, however, EUS may not be needed for the preoperative determination of the depth of EGCs. SM2 indicates invasion ⩾ 500 μm into the submucosal layer. EGC: Early gastric cancer; EUS: Endoscopic ultrasonography.

larger-size lesions[11,12,18,19,21], which were categorized mainly as meeting the expanded-indication criteria or non-indication criteria for ER. In the present study, the diagnostic accuracy for the lesions meeting the absolute-indication criteria for ER was very high for both EUS (97.4%) and CE (84.3%) as expected, whereas the accuracy rates of EUS and CE were significantly lower for the lesions that met the non-indication criteria for ER compared to those that met other criteria for ER.

If EUS is going to be performed for many lesions meeting the absolute-indication criteria for ER, the overall accuracy of EUS may naturally increase, but not to a clinically significant degree. It has been reported that magnifying endoscopy with narrow-band imaging (ME-NBI) is useful for determining the invasion depth diagnosis of EGC[29,30]; however the diagnostic criteria for SM2 are complex[29] and the diagnostic specificity of ME-NBI may be relatively low[30]. Actually, when the staging of an EGC is doubtful by CE, EUS is likely to provide helpful information to stage the EGC, *i.e.*, to determine the M/SM1 or SM2 status[16]. In such cases EUS may correct a misdiagnosis by CE, especially with respect to the expanded-indication and non-indication criteria for ER.

Taking past findings into consideration along with our present results, we propose that EUS may be considered for the following lesions: (1) differentiated-type cancers without UL diagnosed as invading to SM2; and (2) undifferentiated-type cancers diagnosed by CE as meeting the expanded-indication criteria for ER. When EUS is performed for these lesions, the additive effect of EUS will increase the accuracy by 23.1%. It should be noted, however, that we studied only a small number of either type of lesions, *i.e.*, three lesions of type (1) and three lesions of type (2). In contrast, it should also be emphasized that there were no lesions of either type which were correctly diagnosed by CE and incorrectly diagnosed by EUS. Based on our conclusion, we have summarized the indications of EUS for the pretreatment diagnosis of EGCs in Figure 3.

Our study has several potential limitations. First, it was a retrospective study at a single institution. Second, the sample size was relatively small. However, we did not perform EUS for most of the lesions that met the absolute-indication criteria, which could be definitely diagnosed as mucosal cancer by CE as mentioned above. Indeed, of the 186 EGCs that met the absolute-indication criteria for ER and that were treated with ER during this study period, only 50 lesions (26.9%) underwent EUS. This result may thus have resulted in a selection bias because there were no eligibility criteria for performing EUS in this study. Third, only the patients with histologically confirmed EGC who underwent EUS and ESD or surgery were evaluated, which might also have introduced a potential selection bias. Fourth, since EUS was performed under CE by an endosonographer, the construction of EUS images may have been affected by the endoscopic appearance of the lesions and the experience of the endosonographer[31]. In addition, one observer might have been involved in both of the examinations, *i.e.*, CE and EUS, in some cases. In general, the observer who validates the criteria should not have been involved in the evaluation of the EUS and CE images[24].

In conclusion, our analyses revealed that: (1) EUS may not be necessary to determine the pretreatment staging of 0-I type and UL(+) or absolute-indication criteria lesions; and (2) EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

COMMENTS

Background

It is sometimes difficult to establish diagnostic criteria for differentiating mucosal cancer from submucosal invasive cancer by conventional endoscopy (CE) alone. Although endoscopic ultrasonography (EUS) permits a more objective assessment by providing a tomographic image, recent meta-analyses showed that EUS has relatively low accuracy for staging the depth of early gastric cancer (EGC) invasion.

Research frontiers

According to the previous studies, some of these reports clearly demonstrated the superiority of EUS for diagnosing EGC invasion depth whereas others did not. The authors retrospectively investigated the application of EUS in the pre-treatment staging of EGD.

Innovations and breakthrough

All protruded-type EGCs were "inconclusive" cases with low-quality EUS images. There was no significant difference in the diagnostic accuracy between CE and EUS. The lesions with ulcer scar (UL) and non-indication criteria for endoscopic resection (ER) were significant independent risk factors for misdiagnosis by EUS. In the subgroup analysis, however, the additive effect of EUS was found in the lesions with the differentiated-type cancers exhibiting SM2 invasion (submucosal invasion $\geqslant$ 500 μm) by CE and the undifferentiated-type EGCs meeting the expanded-indication criteria for ER.

Applications

EUS may not be necessary to determine the pretreatment staging of protruded (0-I)-type and the lesions with UL or absolute-indication criteria for ER; and EUS may be considered for the following lesions: (1) differentiated-type cancers diagnosed without UL and with invasion to SM2; and (2) undifferentiated-type cancers diagnosed as meeting the expanded-indication criteria for ER by CE.

Terminology

EUS is a reliable method for predicting the invasion depth diagnosis of EGC. However, there is no need to perform EUS for the EGCs with the absolute-indication criteria, UL(+) or 0-I-type. The modality should be considered performing the limited lesions.

Peer-review

This is a good article to describe the indications for EUS staging of invasion depth in EGCs.

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