Usefulness of endoscopic ultrasonography in determining the depth of invasion and indication for endoscopic treatment of early gastric cancer

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Abstract

Introduction: Endoscopic ultrasonography (EUS) is a useful method for visualizing features of gastric cancer. However, a previously reported classification system tended to result in overstaging. We investigated the usefulness of EUS for evaluation of the depth of gastric cancer invasion and indications for endoscopic treatment.

Methods: Accuracy of EUS for determining the depth of invasion and incidences of a positive basal margin were assessed in 235 patients who underwent endoscopic treatment or surgery for gastric cancer. The EUS-determined depth of invasion was classified as follows: EUS-M (lesion confined to sonographic layers 1 and 2); EUS-M/SM border (lesion with changes in sonographic layer 3 but no deeper than 1 mm); EUS-SM (lesion with changes in sonographic layer 3 deeper than 1 mm); or EUS-AD (lesion with changes in sonographic layer 4 or 5).

Results: Accuracy of EUS for determining the depth of invasion was as follows: EUS-M, 99% were M and SM1 lesions; EUS-M/SM border, 87% were M and SM1 lesions; EUS-SM, 91% were SM2 lesions; EUS-AD, 100% were MP or deeper lesions. There was no EUS-M or EUS-M/SM border lesion for which endoscopic treatment

resulted in a positive basal margin.

Conclusions: EUS is useful for accurately determining the depth of invasion of gastric cancer. When there are no endoscopically determined ulcerous changes, endoscopic treatment should be considered for EUS-M and EUS-M/SM border lesions, and EUS-SM lesions should be treated surgically.

Keywords: early gastric cancer, endoscopic ultrasound, endoscopic treatment

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INTRODUCTION

Advances in gastrointestinal endoscopy have resulted in endoscopic treatment becoming the main therapy in Japan for many early gastric cancers (EGCs) confined to the mucosa.[1] Endoscopic mucosal resection (EMR) is indicated for lesions with a diameter of less than 20 mm, differentiated adenocarcinoma (pap, tub1, tub2), and mucosal penetration without ulcerous change.[2] Endoscopic submucosal dissection (ESD) has come into widespread use. It can be used for en bloc resection of lesions larger than 30 mm in diameter that cannot be resected collectively by EMR.[3] In our institution, no well-differentiated adenocarcinoma has been associated with lymph node metastasis, provided that invasion has been less than 400 μm into the submucosa.[4] Gotoda et al. reported that lesions of less than 30 mm that were well-differentiated and showed lack of lymphatic-vascular invasion and submucosal penetration of less than 500 μm were entirely free of nodal metastasis.[5] Therefore, preoperative determination of the depth of invasion has become important.

Endoscopic ultrasonography (EUS) is useful for visualizing features of the cancer and determining the depth of invasion.[6-12] However, the previous classification system

tended to result in overstaging because of benign ulcerous change, fibrosis, benign cystic glands in the submucosal layer, inflammatory change, or an anomaly of the muscularis mucosae.[12-14] Therefore the problem may lead to surgical treatment of mucosal cancers actually indicated for endoscopic treatment.

We conducted a prospective study to determine whether we could solve this classification problem. We compared the results of EUS and histologic study to clarify the usefulness of EUS in determining the depth of invasion and the strategy for treatment of gastric cancer.

MATERIALS

During the period January 2002 through July 2005, we enrolled 343 consecutive patients from the Department of Endoscopy of Hiroshima University Hospital, all of whom had gastric cancer. We performed EUS for all lesions, and we excluded lesions with endoscopically determined ulcerous changes (94 lesions) according to the indications for endoscopic treatment given by the Japanese Gastric Cancer Association (JGCA),[2] lesions that were not treated endoscopically or surgically, and lesions for

which EUS was not sufficient for evaluation (14 lesions). EUS findings were compared with histologic findings in 235 patients who were made accurate diagnosis of depth of invasion (174 men, 61 women; mean age 66.0 years).

For the 179 patients who underwent endoscopic treatment (87 EMRs, 92 ESDs), we analyzed whether carcinoma was present in the basal margin of the resected specimen (positive basal margin).

Informed consent was obtained from patients and/or their families for participation in the study.

METHODS

EUS was performed with 12- and 20-MHz miniprobes (Fujinon, Saitama, Japan) and a GF-UM200 echoendoscope (Olympus, Tokyo, Japan). We used the highest frequency possible. If accurate diagnosis could not be achieved because of attenuation of the ultrasound beam, we lowered the frequency. Instillation of non-aerated water was performed to improve transmission of the ultrasound beam.

Lesions were classified according to a modification of the system proposed by

Yanai et al.[15] The EUS-determined depth of invasion was classified as follows: EUS-M (lesion confined to sonographic layers 1 and 2) (**Figure 1**); EUS-M/SM border (lesion with changes in sonographic layer 3 but no deeper than 1 mm) (**Figure 2**); EUS-SM (lesion with changes in sonographic layer 3 deeper than 1 mm) (**Figure 3**); or EUS-AD (lesion with changes in sonographic layer 4 or 5) (**Figure 4**).

Histologic examination of the entire resected cancerous lesion was carried out in parallel 2-mm-thick sections stained with hematoxylin and eosin.[16] The depth of invasion and histologic type of gastric cancer were determined by examination of the resected specimens and based on the Japanese Classification of Gastric Carcinoma of the JGCA.[17] 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 (SMl) or penetration of 500 μm or deeper (SM2).[16] When a neoplastic cell was faced with a vertical margin of specimen, we have defined as vertical margin positive.

The data were evaluated by Fisher's exact test. $P < 0.05$ was considered significant.

RESULTS

EUS findings are shown in relation to histopathologic findings in **Table 1**. There were 160 EUS-M lesions, with the following pathologically determined depths of invasion: M (147 lesions, 92%), SM1 (12 lesions, 7%), and SM2 (1 lesion, 1%). There were 31 EUS-M/SM border lesions, with the following pathologically determined depths of invasion: M with lymphoid follicles (11 lesions, 35%) or without detection of an echo source in the submucosa (7 lesions, 23%); SM1 (9 lesions, 29%); and SM2 (4 lesions, 13%). There were 32 EUS-SM lesions: M (1 lesion, 3%); SM1 (1 lesion, 3%); SM2 (29 lesions, 91%); and muscularis propria (MP) or deeper (1 lesion, 3%). There were 12 EUS-AD lesions: MP or deeper (12 lesions, 100%). Two lesions treated by ESD and shown to have a positive basal margin were excluded because whether invasion should be classified as SM2 or as MP or deeper could not be determined. There was no significant difference in accuracy between differentiated adenocarcinoma and undifferentiated adenocarcinoma (**Table 2**).

Endoscopic treatment was performed for 146 EUS-M lesions and 22 EUS-M/SM

border lesions (**Table 3**). The 146 EUS-M lesions had the following pathologically determined depths of invasion: M (134 lesions, 92%), SM1 (11 lesions, 7%), and SM2 (1 lesion, 1%). The 22 EUS-M/SM border lesions had the following pathologically determined depths of invasion: M (12 lesions, 55%), SM1 (6 lesions, 27%), and SM2 (4 lesions, 18%). There was no EUS-M or EUS-M/SM border lesion with a positive basal margin (accurate histologic diagnosis could be made even in cases of SM invasion). In EUS-M and EUS-M/SM border lesions, there were 7 patients with SM invasion in whom surgery was performed after endoscopic treatment. But, there was no lesion with lymph node metastasis in the 7 lesions (**Table 4**). Endoscopic treatment was also performed for 11 EUS-SM lesions in patients with complications and a poor performance status, which were considered surgical risk factors. The basal margin of the endoscopically resected specimen was positive in 2 cases (18%). There was no case of residual tumor or lymph node metastasis for which additional surgery was performed after endoscopic treatment, including the 2 cases. During the 56 surgeries, 12 lesions with lymph node metastasis were found (EUS-M: 0/14, EUS-M/SM: 0/9, EUS-SM: 6/21, EUS-AD: 6/12). There were 15 complications (bleeding that was difficult to

control, 7 lesions; perforation, 8 lesions) that resulted from the endoscopic procedures (EUS-M: 10, EUS-M/SM: 2, EUS-SM: 3). There were no complications associated with the surgical procedures.

DISCUSSION

Endoscopic treatment is widely used as radical therapy for EGC and is considered minimally invasive. Tada et al. developed an EMR technique in 1984 known as strip biopsy,[18] and Ono et al. recently developed an ESD technique for lesions larger than 30 mm in diameter that cannot be resected collectively by EMR.[3] This technique has been improved and come into widespread use. In Japan, indications for endoscopic treatment include a lesion with a diameter of less than 20 mm, differentiated adenocarcinoma (pap, tub1, tub2), and mucosal penetration without ulcerous change.[2] Because of the association between differentiated gastric adenocarcinoma and lymph node metastasis, the indications for endoscopic resection are being expanded to include such adenocarcinoma if submucosal invasion is minimal.[4,5] Recently, histochemistry examination revealed an association between gastric cancer and lymph node metastasis,

endoscopically en bloc resection of submucosal gastric cancer become important.[19,20] So the role of EUS becomes not only accurate determination of depth but also prediction of whether en bloc resection should be performed endoscopically.

EUS was developed in 1979.[21] Rapid advances ensued, and use of the miniprobe, which can be passed through the instrument channel of a conventional diagnostic endoscope, was reported in 1989.[22] Because EUS provides an image of the layers of the gastric wall, it is considered useful for assessment of the depth of invasion of EGC. The reported accuracy of EUS-based staging is approximately 70%-80% for EGCs.[12-15,23] However, it is difficult to diagnose minimal submucosal invasion preoperatively, and overstaging is common.

In this study, accuracy of EUS-M staging was better than or equal to that in previously reported studies.[12] The accuracy of EUS staging in our study was equivalent to that in the retrospective study of Yanai et al.,[15] upon which we based our classification system. There appears to be no risk of lymph node metastasis from many M lesions and from some SM1 lesions.[4,5] Ninety-nine percent (159/160) of EUS-M lesions corresponded to histologic M lesions and SM1 lesions. Fifty-eight percent

(18/31) of EUS-M/SM border lesions were M lesions histologically. In EUS images of M lesions, lymphoid follicles around the muscularis mucosae appeared to be pathologic lesions (11 lesions, 35%). It is difficult to distinguish a lymphoid follicle from a tumor on EUS images because a lymphoid follicle is depicted as a hypoechoic or anechoic structure of the same echo level as a tumor. Histologically, 29% (9/31) of EUS-M/SM border lesions were shown to be SM1 lesions histologically. Therefore, endoscopic treatment was considered in 87% (27/31) of cases of EUS–M/SM border lesion. Ninety-four percent of EUS-SM lesions were shown to be deeper than SM2, for which endoscopic treatment is never indicated according to the JGCA guidelines.[2]

There was no significant difference in the accuracy of EUS diagnosis between differentiated adenocarcinoma and undifferentiated adenocarcinoma. The differentiated type gastric cancer tends to be characterized by expansion of the tumor nodule or mass, and the undifferentiated type tends to be characterized by diffuse infiltration of tumor cells individually or in small nests.[24,25] However, according to our data, the accuracy of EUS in diagnosing undifferentiated EGC did not differ significantly from the accuracy in diagnosing differentiated EGC, possibly because, even in undifferentiated EGC, the

entire cancer does not consist of infiltration of tumor cells.

The basal margins of all EUS-M lesions treated endoscopically were shown to be negative. Pathologic examination showed that the depths of invasion had been accurately diagnosed by EUS. The basal margins of all EUS-M/SM border lesions treated endoscopically were also shown to be negative. The depth of cancer invasion was accurately detected, even with the inclusion of SM2 lesions. There were 11 EUS-SM lesions for which local resection was performed endoscopically because conventional surgery was considered risky. In 2 cases, it was not possible to determine the deepest part of the cancer pathologically. It was previously reported that exposure to heat, such as from electrocautery, stimulates rapid growth of residual tumor after incomplete resection.[26] In endoscopic treatment of EUS-SM, there is some possibility of diagnosing the depth of invasion insufficiently, the risk of recurrence was considered higher than the risk associated with surgery.

We conclude that EUS is useful for accurately determining the depth of invasion of gastric cancer, and endoscopic treatment should be considered for EUS-M and EUS-M/SM border lesions when there are no endoscopically determined ulcerous

changes. EUS-SM lesions should be treated surgically.

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Figure Legends

Figure 1 EUS and histologic images of a mucosal cancer. **a** A lesion confined to sonographic layers 1 and 2. Cancer invasion is to the EUS-M. **b** Histologic specimen confirms the diagnosis of mucosal cancer. Hematoxylin and eosin stain, original magnification x4.

Figure 2 EUS and histologic images of a mucosal cancer with lymphoid follicles. **a** A lesion with a change in sonographic layer 3 but no deeper than 1 mm. Cancer invasion is to the EUS-M/SM border. **b** Histologic specimen shows mucosal cancer and lymphoid follicles. Hematoxylin and eosin stain, original magnification x4.

Figure 3 EUS and histologic images of a submucosal cancer. **a** A lesion with a change in sonographic layer 3 deeper than 1 mm. Cancer invasion is to the EUS-SM. **b** Histologic specimen shows submucosal cancer. Hematoxylin and eosin stain, original magnification x4.

Figure 4 EUS and histologic images of a cancer in the muscularis propria. **a** A lesion with a change in sonographic layer 4 or 5. Cancer invasion is to the EUS-AD. **b** Histologic specimen shows cancer in the muscularis propria. Hematoxylin and eosin

stain, original magnification x4.

Table 1. Accuracy of EUS for determining the depth of gastric cancer

EUS diagnosis	Pathologic diagnosis				Total
	M	SM1	SM2	MP ~	
EUS-M	147 (92)	12 (7)	1 (1)		160 (100)
EUS-M/SM	18 (58)	9 (29)	4 (13)		31 (100)
EUS-SM	1 (3)	1 (3)	29 (91)	1 (3)	32 (100)
EUS-AD				12 (100)	12 (100)
Total	166 (71)	22 (10)	34 (15)	13 (6)	235 (100)

The number (and percentage) of lesions are shown.
Two cases of EUS-SM were excluded because of a positive vertical margin.

Table 2. Accuracy of EUS for determining the depth of gastric cancer according to histologic type

EUS diagnosis	Differentiated	Undifferentiated	Total
EUS-M[a]	129/130 (99)	30/30 (100)	159/160 (99)
EUS-M/SM[a]	21/23 (91)	6/8 (75)	27/31 (87)
EUS-SM[b]	17/19 (89)	12/13 (92)	29/32 (91)
EUS-AD	6/6 (100)	6/6 (100)	12/12 (100)
Total	173/178 (97)	54/57 (95)	227/235 (97)

The number (and percentage) of lesions are shown. *P <0.01, **P <0.05

[a]EUS-M and EUS-M/SM lesions were compared with M and SM1 lesions (indications for endoscopic treatment).

[b]EUS-SM lesions were compared with SM2 lesions.

Table 3. Incidences of a positive vertical margin classified by EUS and pathologic diagnosis

EUS diagnosis	Pathologic diagnosis			Total	
	M	SM1	SM2 ~		
EUS-M	0/134 (0)	0/11 (0)	0/1 (0)	0/146 (0)	*
EUS-M/SM	0/12 (0)	0/6 (0)	0/4 (0)	0/22 (0)	
EUS-SM	0/0 (0)	0/0 (0)	2/11 (18)	2/11 (18)	
Total	0/146 (0)	0/17 (0)	2/16 (13)	2/179 (1)	

The number (and percentage) of lesions are shown.

*P <0.01

Table 4. Clinical characteristics of the 7 patients in whom surgery was performed after endoscopic treatment

Sex	Age (years)	Macro	Size (mm)	EUS diagnosis	Pathology				
					Histologic type	Depth of invasion	Basal margin	N	Residual tumor
F	34	IIc	15	EUS-M	Differentiated	SM1	-	0	-
M	57	IIc	25	EUS-M	Differentiated	SM1	-	0	-
M	68	IIa	15	EUS-M/SM	Differentiated	SM1	-	0	-
M	58	IIc	5	EUS-M/SM	Differentiated	SM1	-	0	-
F	63	IIc	15	EUS-M/SM	Undifferentiated	SM2	-	0	-
M	70	IIa	20	EUS-M/SM	Differentiated	SM2	-	0	-
F	74	IIc	10	EUS-M/SM	Undifferentiated	SM2	-	0	-

Macro: Macroscopic type, N: Extent of lymph node metastasis

Figure 1

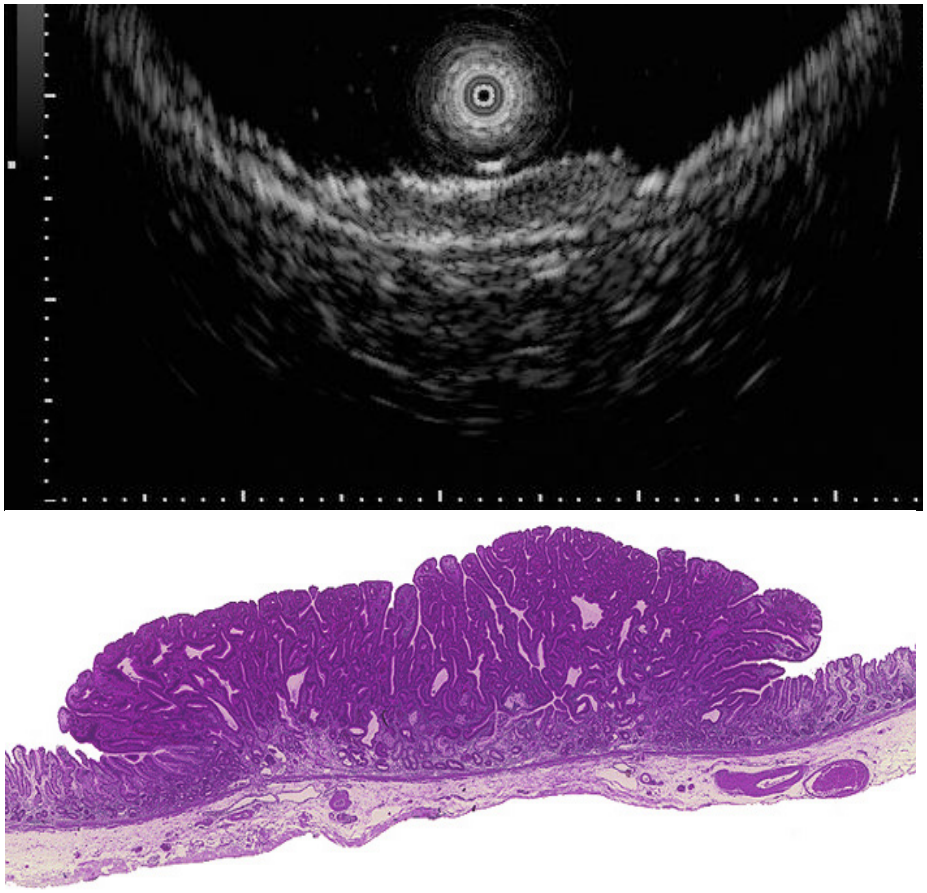

Figure 2

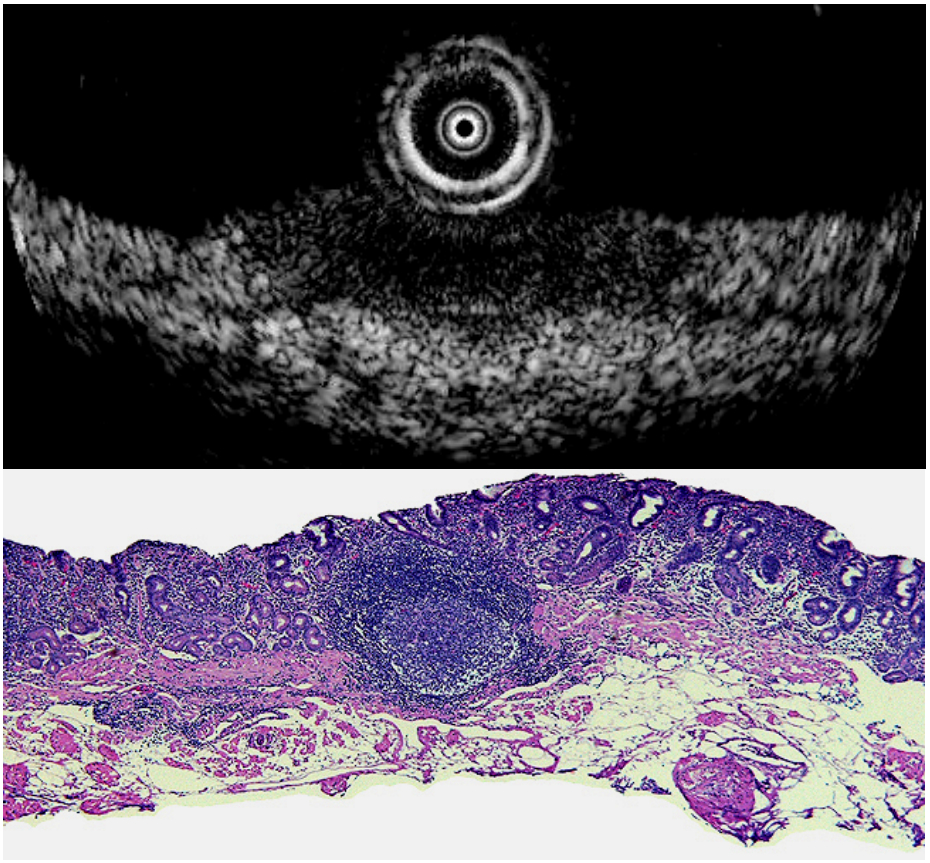

Figure 3

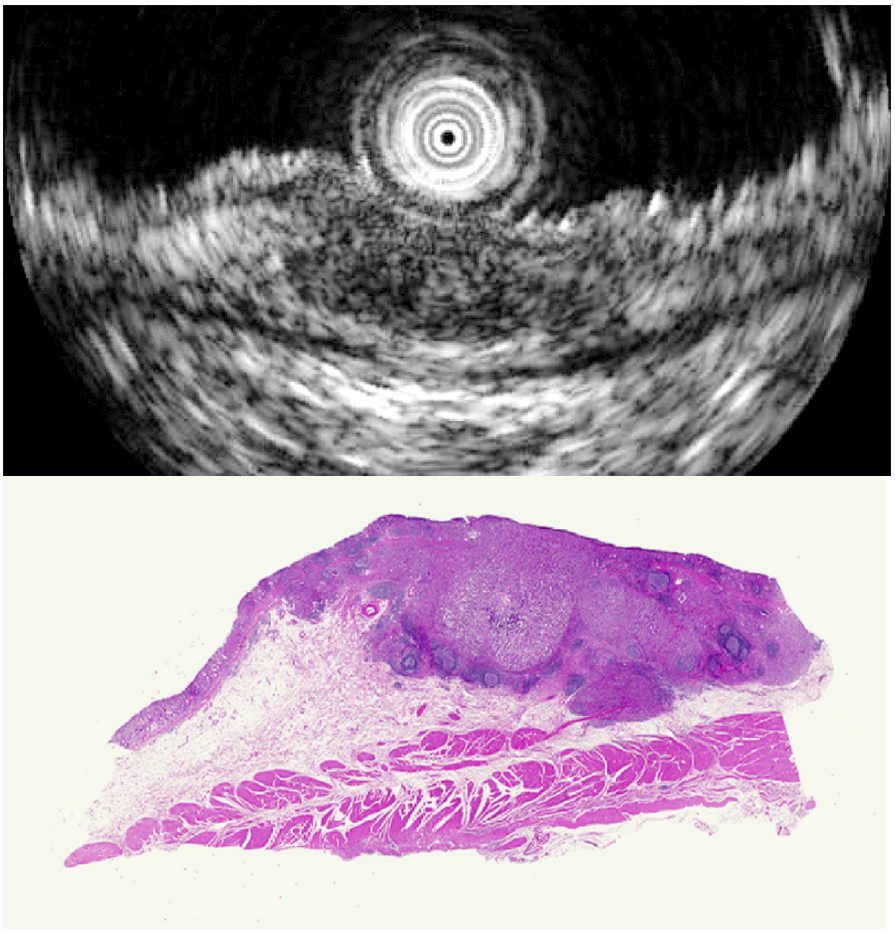

Figure 4