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Original Article

Usefulness and Problems of Endoscopic Ultrasonography in Prediction of the Depth of Tumor Invasion in Early Gastric Cancer

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The objectives of this study were to evaluate the accuracy of endoscopic ultrasonography (EUS) in local and regional staging of early gastric cancer, to analyze the factors influencing the accuracy of EUS, and to reveal the usefulness and problems of EUS in pre-treatment staging of gastric cancer. We examined 105 lesions in 104 patients with histologically confirmed gastric cancer and retrospectively evaluated them with EUS. The diagnostic accuracy, sensitivity, and specificity of EUS were determined by comparing the pre-treatment EUS with the postoperative histopathological findings. The overall diagnostic accuracy of EUS for the depth of cancer invasion was 86%. The overall sensitivity and specificity were 60% and 96%, respectively. The accuracy significantly declined in lesions located in the upper-third of the stomach (70%). Type 0-I lesions tended to be over-staged (12%), and the upper-third lesions tended to be under-staged (23%). The accuracy significantly declined in differentiated adenocarcinoma with massive submucosal invasion (56.5%). EUS is useful for evaluating the depth of gastric cancer invasion which determines the feasibility of endoscopic treatment. However, it is noteworthy that the diagnostic accuracy of the invasion depth diminished for lesions in the upper third of the stomach.

Key words: endoscopic ultrasonography, early gastric cancer, accuracy, sensitivity, specificity

Early gastric cancer (EGC) is defined as gastric cancer that is confined to the mucosal or submucosal layers, 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 accepted in Japan as a standard strategy for a subgroup of patients with EGC without any risk of lymph node metastasis [2–5] because it is minimally invasive, safe, and convenient. In addition, a large-scale study has revealed that its long-term efficacy is excellent [6]. The Japanese Gastric Cancer Association (JGCA) has established the accepted indications for endoscopic resection of early gastric carcinoma as follows: (i) differentiated-type adenocarcinoma; (ii) tumor less than 20 mm in diameter; and (iii) tumor

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invasion limited to the mucosa without any ulcerous changes and no expected lymph node metastasis [7]. Gotoda *et al.* have reported that differentiated adenocarcinoma lesions 30 mm in diameter or larger were entirely free of nodal metastasis if they showed a lack of lymphatic-vascular capillary involvement and if the submucosal penetration was 500 μm or less [3]. Hirasawa *et al.* have reported that intramucosal undifferentiated adenocarcinoma 20 mm in diameter or smaller without lymphatic-vascular capillary involvement or ulcerous findings present a negligible risk of lymph node metastasis [8]. Therefore, the extended indications for endoscopic resection have been proposed as follows: (i) intramucosal cancer, differentiated-type adenocarcinoma, no lymphatic-vascular invasion, with no ulceration and irrespective of the 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 ($\leq$ 500 μm 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 [7]. With the increasingly expanded indications of endoscopic resection for EGC, it has become more important in the pre-treatment planning to accurately determine the depth of invasion.

Endoscopic ultrasonography (EUS) is considered the best diagnostic modality for local and regional staging, and is commonly used for differentiating mucosal lesions from submucosal lesions for endoscopic resection [9, 10]. Nonetheless, previous reports have suggested that the accuracy of EUS is influenced by several factors: endoscopic findings, the location of the lesion, the stage of the gastric cancer, tumor size, and study design [9, 11–13].

The objectives of this study were to evaluate the accuracy of EUS in local and regional staging of early gastric cancer, to analyze clinicopathological factors influencing the diagnostic accuracy of EUS in predicting the depth of tumor invasion, and to reveal the usefulness and problems of EUS in pre-treatment staging of gastric cancer.

Materials and Methods

Patients. We performed EUS before treatment for gastric cancer when the depth of tumor invasion was difficult to assess by conventional endoscopy. Between September 2003 and October 2009, 105 lesions in 104 patients (75 men and 29 women) with gastric cancer diagnosed by conventional endoscopic examination and confirmed with a biopsy specimen, underwent EUS examination to determine the depth of tumor invasion prior to endoscopic resection or surgery at our institution. Of these 105 lesions investigated in the present study, 78 underwent ESD and 27 underwent surgery. EUS was performed for these lesions due to difficulties in diagnosing the depth of the tumor invasions.

EUS equipment and examination procedures. The instrument used for the EUS examinations was a miniature sonoprobe system (UM-3R, with an ultrasound frequency of 20 MHz, Olympus, Tokyo, Japan). Prior to EUS, examination was performed by conventional endoscopy with biopsy to confirm gastric cancer. After pre-medication with local pharyngeal anesthesia and diazepam (2.5–5 mg intravenously) or flunitrazepam (0.5–1 mg intravenously), if needed, the patients were examined in the left lateral decubitus position. Under direct vision, the echoendoscope was advanced beyond the tumor. Acoustic coupling with the gastrointestinal (GI) wall was obtained by instilling 200–500 ml of deaerated water into the gastric lumen. EUS imaging was performed by the same group of endosonographers under the supervision of the leading endoscopist at out institution (R. T., H. O, or Y. K.). We obtained written informed consent from all the patients before the endoscopic procedures.

Definition and identification of cancer invasion depth. On endoscopy, submucosal or deeper invasion by the lesions was assessed by the presence of an uneven nodular surface without flexibility, a marked depression in the elevated lesion, fold convergence with bulging, or consistent submucosal elevation around the lesion [14].

On EUS, the gastric wall was assessed based on the standard five-layer sonographic structure [9, 15]. On the EUS image, the first hyperechoic and second hypoechoic layers (layers 1 and 2) represent the mucosa (M), the third hyperechoic layer (layer 3) represents the submucosa (SM), the fourth

hypoechoic layer (layer 4) corresponds to the muscularis propria (MP), and the fifth hyperechoic layer (layer 5) reflects the subserosa and serosa (SS). Cancer depth was evaluated as M if the hypoechoic mass disrupted the sonographic layers 1 to 2; and as SM or deeper if it disrupted layers 1 to 3 or deeper.

Data analysis. Detailed information regarding the endoscopic images and the results of the histopathological examination were obtained from the medical records.

The tumor locations were categorized by the longitudinal axis of the stomach, divided into three sections (upper third containing the fundus, cardia, and upper body; middle third containing the middle body, lower body, and angle; and lower third containing the antrum and pylorus). The endoscopic findings related to the tumor were categorized according to the JGCA classification [2]. 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), or combined type (0-IIa + IIc or III).

All resected specimens were sectioned into 2- to 5-mm slices and evaluated histopathologically based on the JGCA classification [2]. Undifferentiated adenocarcinoma in this classification lacks gland formation and includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma as in the World Health Organization classification [16].

The depth of submucosal invasion was sub-classified histologically into one of 2 grades: penetration into the submucosal layer less than 500 μm from the muscularis mucosa (SM1) or penetration of 500 μm or deeper (SM2) [2]. The 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 the lesions met the expanded-indication criteria for ESD in the patients with EGC, and investigated the clinicopathological factors affecting the diagnostic accuracy of EUS in measuring the invasion depth of EGC. In this study, M and SM1 were combined into the same category in calculating the accuracy rate because EUS has difficulty in distinguishing M from SM1 [17].

Statistical analysis. The accuracy, sensitivity, and specificity of EUS in detecting tumor invasion beyond SM1 were calculated manually. The accuracy of EUS in relation to the clinicopathological features was assessed using the chi-square test and Fisher's exact test. 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).

Results

Demographic, endoscopic, and histological characteristics. Table 1 shows the baseline characteristics of the study population and the clinicopathological features of the enrolled patients' lesions. The median age of the patients was 70 years (range: 52–91 years), and the male: female ratio was 2.59 : 1 (75 : 29). Thirty lesions (29%) were located in the upper third of the stomach, 36 (34%) in the middle third, and 39 (37%) in the lower third. The median tumor diameter was 20 mm (range: 5–60 mm). There were 8 lesions (8%) with type 0-I tumors, 33 (31%) with type 0-IIa or IIa+IIc (mainly superficial elevated type), and 64 (61%) with type 0-IIc or 0-IIc + IIa (mainly superficial depressed type). The pathological depth was M-SM1 for 77 lesions (73%), SM2 for 25 (24%), and MP or deeper for 3 (3%). The histological examination showed that 96 lesions (91.4%) were differentiated adenocarcinoma and the others were undifferentiated adenocarcinoma. Seventeen lesions (16%) had concomitant ulcerous findings histologically.

Diagnostic accuracy of EUS in assessing the tumor invasion depth. The overall accuracy of EUS in predicting the depth of tumor invasion was 86%. As shown in Table 2, the accuracy tended to decline in lesions located in the upper third of the stomach (70%), lesions with a diameter between 11 and 20 mm (80%), and those of the mainly superficial elevated type (82%). However, there were significant differences in the accuracy among each category only in the upper third lesions ($p = 0.01$). On the whole, we tended to under-stage by EUS more frequently than over-stage (11% vs. 3%). On the contrary, we tended to over-stage more frequently than under-stage in the lower third lesions (8% vs. 2%), O-I lesions (12% vs. 0%), and lesions with ulcers (6% vs. 0%). However, there were significant differences in over-

Table 1 The clinical background of our study subjects

Patients' characteristics (n=104)	
Age (years) Median (range)	70 (52–91)
Gender Male / Female (%)	75 (72%) / 29 (28%)
Lesion characteristics (n=105)	
Location U / M / L	30 (29%) / 36 (34%) / 39 (37%)
Tumor diameter (histologically)	
Median (range)	20mm (5–60mm)
≤10mm	23 (22%)
11–20mm	35 (33%)
≥21mm	37 (35%)
Macroscopic type	
0-I	8 (8%)
0-IIa, 0-IIa+IIc	33 (31%)
0-IIc, 0-IIc+IIa	64 (61%)
Pathologic depth	
M-SM1 (<500μm)	77 (73%)
SM2	25 (24%)
MP or deeper	3 (3%)
Histology	
Differentiated	97 (92%)
tub1 / tub2 /pap	73 (69%) / 22 (21%) /2 (2%)
Undifferentiated	8 (8%)
por / sig	5 (5%) / 3(3 %)
Ulcerous (UI) findings histologically	
UI+ / UI−	17 (16%) / 88 (84%)

U, upper their; M, middle third; L, lower third; 0-I, protruding type; 0-IIa, superficial elevated type; 0-IIc, superficial depressed type; M, mucosal; SM1, submucosal layer less than 500μm from the muscularis mucosa; SM2, submucosal layer penetration of 500μm or deeper; MP, muscularis propria; UI (−), lesions without ulcerous findings; UI (+), lesions with ulcerous findings; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma.

staging among each category only in 0-I lesions ($p=0.05$). There were no significant differences in accuracy, over-staging, or under-staging between differentiated and undifferentiated adenocarcinoma. Similarly, there were no significant differences in more detailed histological assessments, namely well-, moderately, papillary, poorly differentiated adenocarcinoma and signet ring cell.

Table 3 shows the sensitivity and specificity of EUS in detecting tumor invasion beyond SM1. Overall, EUS showed both a low sensitivity (60%) and a high specificity (96%). Two parameters had a high sensitivity, namely, a macroscopic type 0-I and a lesion with ulcer.

The accuracy of EUS was reevaluated according to the accepted and extended indications for endoscopic resection (Table 4). The levels of accuracy of EUS for the lesions with accepted indications and with extended indications were 94.1% (32 of 34 lesions) and 95.4% (42 of 44 lesions), respectively (Table 4-b). For the lesions beyond the extended indications for ESD, the accuracy of EUS was 59.3% (16 of 27 lesions) (Table 4-b). Of the 11 lesions that were incorrectly diagnosed, 7 were located in the upper third of the stomach. (Data not shown.)

Discussion

Currently, EUS is the most reliable diagnostic modality used to predict the depth of gastric cancer with high accuracy [18]. The accuracy of EUS for local and regional staging of gastric cancer ranges from 65% to 92% [10]. In the present study, we retrospectively investigated the accuracy of EUS in

Table 2 Summary of the accuracy, over-staging, and under-staging of local and regional staging

Lesion characteristics	n	Accuracy (p value)	Over-staging (p value)	Under-staging (p value)
Overall	105	86%	3%	11%
Location				
Upper third	30	70% (0.02)*	7% (0.62)	23% (0.03)*
Middle third	36	89% (0.40)	0% (0.16)	11% (0.99)
Lower third	39	90% (0.27)	8% (0.35)	2% (0.03)*
Tumor diameter (histologically)				
≤ 10 mm	23	91% (0.35)	0% (0.58)	9% (0.99)
11–20 mm	35	80% (0.26)	9% (0.33)	11% (0.52)
≥ 21 mm	37	90% (0.79)	2% (0.99)	11% (0.99)
Macroscopic type				
0-I	8	88% (0.61)	12% (0.05)*	0% (0.59)
0-IIa, 0-IIa + IIc	33	82% (0.77)	6% (0.64)	12% (0.99)
0-IIc, 0-IIc + IIa	64	86% (0.58)	2% (0.07)	12% (0.76)
Histology				
Differentiated	97	86% (0.99)	3% (0.99)	11% (0.99)
tub1	73	85% (0.77)	7% (0.31)	8% (0.17)
tub2	22	82% (0.75)	0% (0.58)	18% (0.27)
pap	2	50% (0.29)	0% (0.99)	50% (0.21)
Undifferentiated	8	87.5% (0.99)	0% (0.99)	12.5% (0.99)
por	5	80% (0.99)	0% (0.99)	12.5% (0.99)
sig	3	100% (0.99)	0% (0.99)	25% (0.46)
Ulcerous (UI) findings histologically				
UI +	17	94% (0.29)	6% (0.99)	0% (0.20)
UI −	88	84% (0.29)	2% (0.99)	14% (0.20)

P values are calculated by the Fisher's exact test. O-I, protruding type; O-IIa, superficial elevated type; O-IIc, superficial depressed type; UI −, lesions without ulcerous findings; UI +, lesions with ulcerous findings; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma. *$p \leq 0.05$

EGC by using a 20-MHz catheter probe. We performed EUS only for difficult cases such as those with suspected submucosal invasion or concomitant ulcerous changes or relatively large lesions. However, the accuracy of the EUS in assessing the tumor invasion depth was 86%, which is compatible with previous studies [10]. One of the reasons for its fine accuracy is that M and SM1 are combined into one category when calculating the accuracy rate in considering the resolution of EUS [19] and the criteria for indications for ESD [3]. When calculated for distinguishing M from SM1, the accuracy rate of EUS in predicting the tumor invasion depth was 70% in the present study (data not shown).

To evaluate the invasion depth of EGC, clinicopathological factors, including location, macroscopic type, size, histology, and ulcerative change, have been established as important factors that influence the local and regional staging accuracy of EUS [11, 20, 21]. With regard to the lesion location in this study, the accuracy significantly declined in the upper third lesions as compared with the other locations (Table 2), which is consistent with previous study results [11]. In this location, the staging rate was significantly higher than that in the other locations. Lesions in the upper third of the stomach, where adequate filling with deaerated water is not possible, are difficult to access by EUS [14]. In the upper third of the stomach, the submucosal layer is relatively thin and tends to have fibrosis and many vessels [22], which may make the signs of submucosal invasion difficult to detect, thus leading to under-staging.

In the present study, we calculated not only the accuracy but also the sensitivity and specificity for the detection of SM2 or deeper invasion to categorically evaluate the usefulness of EUS (Table 3). Overall,

Table 3 Summary of the accuracy, sensitivity, and specificity of EUS for diagnosing SM2 or deeper cancer

Lesion characteristics	n	Accuracy (%)	Sensitivity (%)	Specificity (%)
Overall	105	86	60	96
Location				
Upper third	30	70	30	90
Middle third	36	89	64	100
Lower third	39	90	80	97
Tumor diameter (histologically)				
≤ 10 mm	23	91	50	100
11–20 mm	35	80	50	89
≥ 21 mm	37	90	67	97
Macroscopic type				
0-I	8	88	100	86
0-IIa, 0-IIa + IIc	33	82	50	92
0-IIc, 0-IIc + IIa	64	86	58	98
Histology				
Differentiated	97	86	60	96
Undifferentiated	8	87.5	75	100
Ulcerous (UI) findings histologically				
UI +	17	94	100	89
UI −	88	84	30	90

0-I, protruding type; 0-IIa, superficial elevated type; 0-IIc, superficial depressed type; UI −, lesions without ulcerous findings; UI +, lesions with ulcerous findings.

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

4-a

Histology	Mucosal cancer				Submucosal cancer		
	Ulcer (−)		Ulcer (+)		SM1		≥ SM2
	≤ 20 mm	> 20 mm	≤ 30 mm	> 30 mm	≤ 30 mm	> 30 mm	any size
Differentiated	32/34	20/20	7/8	0	10/10	1/1	13/23
	94.1%	100%	87.5%	−	100.0%	100%	56.5%*
Undifferentiated	5/6	1/1	0	0	1/1		0/1
	83.3%	100%			100%		0%

4-b

	n	Accuracy	Over-staging	Under-staging
Accepted indications for endoscopic resection	34	94.1%	5.9%	0%
Extended indication for endoscopic submucosal dissection (ESD)	44	95.4%	2.3%	2.3%
Beyond the extended indication for ESD	27	59.3%*	0%	40.7%

*$p < 0.0001$

M, mucosal; SM1, submucosal layer less than 500 μm from the muscularis mucosa; SM2, submucosal layer penetration of 500 μm or deeper.

Accepted indications for endoscopic resection; Extended indication for endoscopic submucosal dissection (ESD); Beyond the extended indication for ESD.

EUS showed both a low sensitivity (60%) and a high specificity (96%). This statistically means that EUS is in general useful to confirm the diagnosis of SM2 or deeper invasion, but not to rule out SM2 or deeper invasion, namely to confirm the diagnosis of M or SM1 tumor, and it is inadequate for the screening of SM2 or deeper tumors.

In our study, type 0-I lesions and UL + lesions had relatively good accuracy, high specificity (100%), and relatively good sensitivity. It is generally reported that these lesions often make the diagnosis of invasion depth of gastric cancer difficult because 0-I lesions are sometimes too thick to visualize the submucosal layer using a 20-MHz probe, and ulcerous lesions commonly have fibrosis and inflammatory cells that might be misinterpreted as tumor invasion [21]. In the present study, EUS was performed just after conventional endoscopic examination, which may influence the diagnosis by EUS. However, type 0-I lesions and UL + lesions are considered to be highly indicative of sm invasion in conventional endoscopic diagnosis [14, 23]. It is therefore difficult to exclude the possibility that these lesions were diagnosed as greater than SM2 due to the endoscopic findings when the EUS diagnosis of depth of invasion was difficult. This result may explain why these lesions had good results and were not under-staged in our study (Table 2).

Concerning the histological findings, there were no statistical differences between the differentiated and undifferentiated types in the present study. This result cannot be adequately relied upon because we had only a few cases of the undifferentiated type.

The diagnostic accuracy of EUS was significantly lower in the cases requiring surgical intervention as compared to those indicated for endoscopic resection (Table 4). These results are consistent with the study of Kim *et al.* [24] In the present study, most of the misdiagnosed lesions (7 of 11 cases) were located in the upper third of the stomach. As described earlier, we believe that the presence of thin and fibrotic submucosal layers in this region [22] contributed to the decreased diagnostic accuracy.

As already stated, there were several methodological limitations to the present study. First, this was a retrospective study and, for the cases that were difficult to diagnosis with EUS, it is possible that the diagnosis with conventional endoscopy performed immediately before EUS affected the EUS diagnostic results. Second, the number of cases investigated in the present study was relatively small. Further prospective studies that include larger numbers of patients with EGC are required to obtain more accurate results.

In conclusion, EUS is useful to confirm whether the depth of early gastric cancer is included in the accepted or extended indications of ESD. Nonetheless, the lesions in the upper third of the stomach were associated with an incorrect diagnosis. It is important to perform EUS to compensate for the diagnosis by conventional endoscopy when considering the clinicopathological factors of the tumor.

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