Int J Gastrointest Canc (2006) 37:133–138
DOI 10.1007/s12029-007-9004-9

Ulcerous Change Decreases the Accuracy of Endoscopic Ultrasonography Diagnosis for the Invasive Depth of Early Gastric Cancer

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Published online: 15 December 2007

Abstract
Background With the development of endoscopic submucosal dissection, an expansion of the criteria for local treatment was suggested for lesions with ulcerous changes or undifferentiated-type adenocarcinoma.
Aim of the Study To determine the efficacy of endoscopic ultrasonography for such lesions, we retrospectively analyzed factors that influenced accurate diagnosis by endoscopic ultrasonography of the depth of tumor invasion.
Methods We investigated 267 gastric adenocarcinomas for which histopathological results were obtained by endoscopic mucosal resection or gastrectomy. The lesions were divided into four groups by histological type and the presence of ulcerous changes. Five clinicopathological factors were assessed for their possible associations with incorrect diagnosis.
Results The positive predictive value (PPV) for cancer limited within the mucosa (endoscopic ultrasonography, EUS-M) and cancer invaded into the submucosal layer (EUS-SM) were 88.0% (125 of 142 lesions) and 60.0% (30 of 50 lesions), respectively. The lesions diagnosed as EUS-M/SM borderline (37 lesions) included 19 lesions (51.4%) of M cancer and 17 lesions (45.9%) of SM cancer. In logistic analysis, ulcerous changes ($p<0.0001$) and macroscopic classification ($p=0.0284$) were factors that caused incorrect diagnosis by endoscopic ultrasonography. In the group having differentiated-type adenocarcinoma with ulcerous changes, the PPV of EUS-SM was 25% (3 of 12), and there was a significant difference ($p<0.05$) between the EUS-SM of this group and that of the differentiated-type adenocarcinoma without ulcerous changes.
Conclusion The accuracy of endoscopic ultrasonography tumor staging was not sufficient for the lesions with ulcerous changes in our study. Therefore, we should be careful to perform endoscopic submucosal dissection for lesions with ulcerous changes.

Keywords gastric cancer · endoscopic ultrasonography (EUS) · endoscopic mucosal resection (EMR) · endoscopic submucosal dissection (ESD) · ulcerous change

Abbreviations

EGC	early gastric cancer
EMR	endoscopic mucosal resection
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasonography
PPV	positive predictive value

Introduction

Gastric cancer is a common malignancy and the second leading cause of cancer mortality worldwide [1]. Endoscopic mucosal resection (EMR) has been widely employed as a radical therapy for some early gastric cancers (EGC) since Tada et al. [2, 3] developed the strip biopsy in 1984

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[4]. For EMR, it is necessary to select indicative lesions that have no metastasis to lymph nodes or any other organs because it is a local therapy in the stomach. The Japanese Gastric Cancer Association established the criteria of curative EMR for early gastric carcinomas: differentiated-type adenocarcinoma, less than 20 mm in diameter, and tumor invasion limited to the mucosa without any ulcerous change for which no lymph node metastasis is expected [5]. Thus, it is important to investigate the invasive depth of the tumor before EMR. Endoscopic ultrasonography (EUS) is thought to be a reliable method to determine the depth of invasion for gastric cancers, and T staging accuracy has been reported to be about 80–90% [6].

Endoscopic submucosal dissection (ESD), a newly modified EMR method, has been developed for en bloc resection regardless of tumor size. This method could be useful for the treatment of lesions with ulcerous changes [7–14]. Gotoda et al. recently reviewed a large number of gastrectomy cases and showed the possibility of the expansion of the criteria for local treatment. In their study, differentiated-type adenocarcinoma less than 3 cm in diameter with ulcer findings and undifferentiated-type adenocarcinomas less than 2 cm in diameter limited to within the mucosa without ulcerous findings were considered to have a minimal risk of lymph node metastasis [15]. Therefore, such lesions are expected to be included in the expanded indication for ESD.

However, the accuracy of EUS is not fully established for lesions with ulcerous changes and undifferentiated-type histology. To determine the efficacy of EUS for such lesions to be subjected to endoscopic therapy, we retrospectively analyzed factors that influenced accurate diagnosis of the depth of tumor invasion by EUS.

Materials and Methods

Two hundred sixty-seven consecutive gastric adenocarcinomas of 260 patients for which histopathological results were obtained by EMR or gastrectomy between January 1999 and December 2003 at Yamaguchi University Hospital were enrolled in this retrospective study. The classification of gastric carcinoma of the Japanese Research Society for Gastric Cancer was used for tumor description [16]. The lesions were histologically classified as the differentiated-type and undifferentiated-type using forceps biopsy specimens and endoscopically classified as lesions with ulcerous changes and lesions without ulcerous changes from endoscopic findings of ulceration or fold convergency. To examine the influence of the tumor differentiation and ulcerous changes on EUS diagnosis of the depth of tumor invasion, lesions were divided into four groups. The first group included 172 differentiated-type adenocarcinomas without ulcerous changes, the second 29 differentiated-type adenocarcinomas with ulcerous changes, the third 37 undifferentiated-type adenocarcinomas without ulcerous changes, and the fourth 29 undifferentiated-type adenocarcinomas with ulcerous changes. The diagnostic accuracy of the depth of tumor invasion was retrospectively studied in each of the four groups that underwent EUS. This retrospective study was approved by our institutional review board.

Histologically, tumors that remained within the mucosa were classified as M cancer, those invading the submucosa were SM cancer, and those invading the muscularis propria or deeper were MP or deeper cancer [16].

An EUS catheter probe system (Sonoprobe System, SP-701, 20/15/12 MHz, Fujinon, Saitama, Japan) was used for EUS diagnosis of the depth of tumor invasion. The probes were passed through the instrument channel of a two-channel endoscope (GIF2T-200 or 2T-240, Olympus, Tokyo Japan). The gastric wall was assessed with reference to the standard five-layer sonographic structure. On EUS, the mucosal layer is visualized as a combination of the first hyperechoic and second hypoechoic layers, and the submucosal layer corresponds to the third hyperechoic layer. The layer of the muscularis propria is visualized as the fourth hypoechoic layer, and the fifth hyperechoic layer is the serosa, including the subserosa [17–22]. As in a previous report, EUS findings on the depth of tumor invasion were classified as follows: lesions confined to the first and second sonographic layers, EUS-M carcinoma; lesions with changes in the third sonographic layer but no deeper than 1 mm, EUS-M/SM borderline; and lesions with changes seen in the third sonographic layer at a depth of 1 mm or greater than 1 mm, EUS-SM carcinoma; and lesions with changes in the fourth sonographic layer or deeper as EUS-MP or deeper [23, 24]. For lesions with ulcerous changes, a benign ulcer scar pattern such as smooth tapering of the third layer was considered the standard layer structure. H.Y. and J.N. were the interpreters of the EUS images. EUS was interpreted in a blind fashion to histopathological findings. EMR or gastrectomy was performed within 2 weeks after EUS. Data were analyzed using the χ^2 test. A p value of less than 0.05 was considered significant.

In the lesions diagnosed as EUS-M or EUS-SM, logistic regression analysis stepwise selection was performed to determine what variables were relevant to incorrect diagnosis. The following factors were used for the analysis: the location of the tumor (five categories: cardia, body, angle, antrum, and prepylorus), the endoscopic form of the tumor (elevated or depressed type), the size of the tumor ($\leq$2 or >2 cm), the presence of ulcerous changes (positive or negative), and tumor differentiation (differentiated or undifferentiated type).

Results

In the 267 lesions, the positive predictive value (PPV) for EUS-M (142 lesions) and EUS-SM (50 lesions) were 88.0% (125 of 142 lesions) and 60.0% (30 of 50 lesions), respectively. The lesions diagnosed as EUS-M/SM borderline (37 lesions) included 19 (51.4%) of M cancer and 17 (45.9%) of SM cancer. The PPV for EUS-MP or deeper (38 lesions) was 63.2% (24 of 38 lesions) (Table 1). The overall PPV for staging of EGC (M, SM) was 97.4% (223 of 229).

Table 2 shows the results of the logistic regression analysis of 192 EUS-M and EUS-SM lesions. Tumor differentiation and size were deselected by stepwise selection. Ulcerous changes ($p<0.0001$) and depressed-type morphology ($p=0.0284$) were factors that caused incorrect diagnosis by EUS. For depressed-type lesions accompanied by ulcereous changes, the PPV of EUS was decreased.

We investigated the PPV of the EUS diagnosis of tumor depth in the four individual groups. The PPV of EUS in the lesions classified as differentiated-type adenocarcinoma without ulcerous changes is shown in Table 3. The PPV of EUS-M and EUS-SM were 90.1% (109 of 121) and 83.3% (15 of 18), respectively. The lesions classified as EUS-M/SM borderline included 12 of 26 (57.7%) M cancers and 11 of 26 (42.3%) SM cancers.

For differentiated-type adenocarcinoma with ulcerous changes, the PPV of the EUS-M was 75.0% (3 of 4). The PPV for EUS-SM was 25% (3 of 12), and there was a significant difference ($p<0.05$) between the EUS-SM of this group and that for the differentiated-type adenocarcinoma without ulcerous changes. The nine lesions of EUS-SM were overstaged, and no lesion was understaged by EUS (Figs. 1, 2, and 3).

For undifferentiated-type adenocarcinoma without ulcerous changes, the PPV of EUS-M and EUS-SM were comparatively high, 76.9% (10 of 13) and 81.8% (9 of 11), respectively (Table 4). There was no significant difference between undifferentiated-type adenocarcinoma without ulcerous changes and differentiated-type adenocarcinoma without ulcerous changes. For the undifferentiated type of cancer, the PPV of EUS was not low in our experience.

In the group having undifferentiated adenocarcinoma with ulcerous changes, the PPV of EUS-M was 75.0% (3 of 4). The PPV of EUS-SM was 33.3% (3 of 9), and there was no significant difference ($p>0.05$) between the groups having undifferentiated adenocarcinoma with ulcerous changes and differentiated adenocarcinoma without ulcerous changes. We tended to overstage by EUS in these lesions (Table 4).

Table 1 Positive Predictive Value of Staging the Depth of Invasion of All Endoscopic EGC Lesions

Endoscopic ultrasonography	Histopathological invasive depth			
	Total	M	SM	MP or deeper
EUS-M	142	125 (88.0%)	15	2
EUS-M/SM	37	19	17	1
EUS-SM	50	17	30 (60.0%)	3
EUS-MP or deeper	38	3	11	24
Total	267	164	73	30

M Cancer limited to within mucosa, *SM* cancer invading the submucosal layer, *MP* cancer invading the proper muscle layer

Table 2 Analysis of the Influence of Macroscopic Features of Gastric Cancer Lesions on EUS Depth Staging

		Odds ratio (95% CI)	*p* Value
Macroscopic classification	Elevated type		
	Depressed type	3.279 (0.106–0.882)	0.0284*
UL	Negative		
	Positive	9.903 (3.842–28.167)	<0.0001*
Location	Antrum		
	Angulus	0.562 (0.135–2.34)	0.4287
	Prepylorus	2.817 (0.453–17.513)	0.2666
	Body	1.982 (0.694–5.66)	0.2015
	Cardia	3.301 (0.772–14.117)	0.1072

The tumor differentiation and the size of tumor were deselected by stepwise selection.
UL Ulcerous change

Table 3 Positive Predictive Value of Endoscopic Staging of the Depth of Invasion of Differentiated-Type EGC Lesions

Endoscopic ultrasonography	Histopathological invasive depth			
	Total	M	SM	MP or deeper
Differentiated-type adenocarcinoma without ulcerous changes				
EUS-M	121	109 (90.1%)	12	0
EUS-M/SM	26	15	11	0
EUS-SM	18	2	15 (83.3%)	1
EUS-MP or deeper	7	2	3	2
Total	172	128	41	3
Differentiated-type adenocarcinoma with ulcerous changes				
	Total	M	SM	MP or deeper
EUS-M	4	3 (75.0%)	0	1
EUS-M/SM	4	2	2	0
EUS-SM	12	9	3 (25.0%)[a]	0
EUS-MP or deeper	9	0	5	4
Total	29	14	10	5

The PPV of EUS for differentiated-type gastric cancer lesions.
*In the differentiated-type adenocarcinoma with ulcerous change group, the PPV of EUS-SM was 25%, and there was a significant difference between EUS-SM of differentiated-type adenocarcinoma with ulcerous changes and that of differentiated-type adenocarcinoma without ulcerous changes ($p<0.05$).

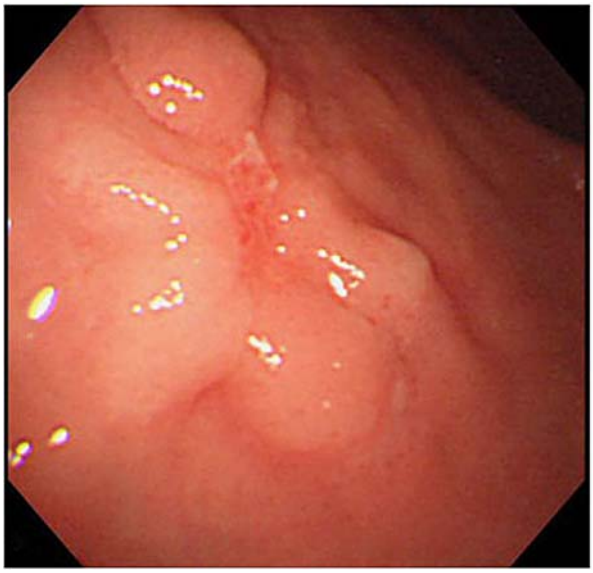

Fig. 1 Endoscopic image of a superficial depressed (0 IIc)-type EGC with ulcerous change in the gastric body

Discussion

We have shown the efficacy of EUS for evaluating the depth of tumor invasion before EMR [23, 24]. The first group, differentiated-type adenocarcinoma without ulcerous changes, is generally within the clinical indication for curative EMR. In such lesions, our EUS diagnosis results were favorable; therefore, we recommend curative EMR for patients who are diagnosed with EUS-M and surgical treatment for those cases diagnosed as EUS-SM. We also recommend diagnostic EMR for those diagnosed as EUS-M/SM borderline to prevent oversurgery because half of the EUS-M/SM borderline lesions were finally diagnosed as mucosal cancer after EMR or gastrectomy.

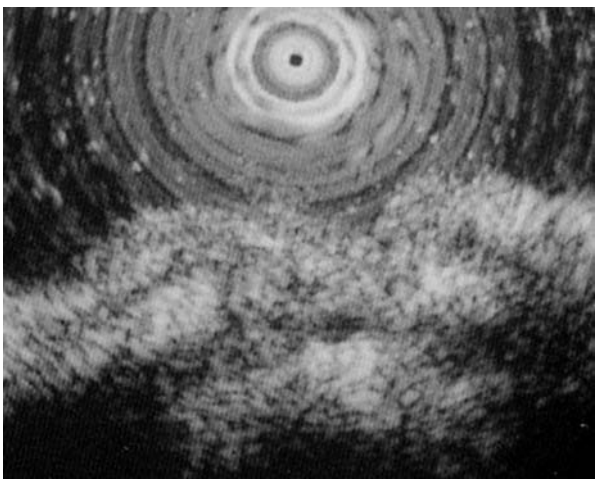

Fig. 2 EUS image of a representative gastric tumor. Hyperechoic layer 3 (submucosa) was disrupted over 1 mm. The tumor invasion depth is thought to be limited to the submucosa (EUS-SM)

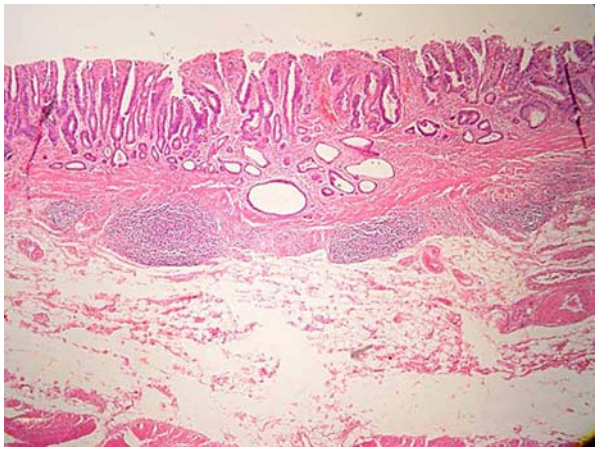

Fig. 3 Photomicrograph of the resected specimen. The differentiated-type adenocarcinoma cell is limited to the mucosa. Fibrosis of the submucosa is present, corresponding to the disruption of the third layer of the EUS picture

ESD was developed for en bloc resection regardless of tumor size and has made it possible to obtain an accurate histopathologic diagnosis [7–14]. Gotoda et al. [15] suggested an expansion of the criteria for local treatment of lesions. It is as follows: (1) intramucosal cancer, differentiated adenocarcinoma, no lymphatic-vascular invasion, irrespective of ulcer findings, and tumor less than 3 cm in size; (2) intramucosal cancer, differentiated adenocarcinoma, no lymphatic-vascular invasion, without ulcer findings, and irrespective of tumor size; (3) undifferentiated intramucosal cancer no lymphatic-vascular invasion, without ulcer findings, and tumor less than 3 cm in size.

In this study, lesions with ulcerous changes that were diagnosed as EUS-SM tended to include many intramucosal cancers. The PPV for EUS-SM of differentiated-type adenocarcinoma with ulcerous changes was significantly lower than that for differentiated-type adenocarcinoma without

Table 4 Positive Predictive Value of Endoscopic Staging of the Depth of Invasion of Undifferentiated-Type EGC Lesions

Endoscopic ultrasonography	Histopathological invasive depth			
	Total	M	SM	MP or deeper
Undifferentiated-type aenocarcinoma without ulcerous changes				
EUS-M	13	10 (76.9%)	3	0
EUS-M/SM	5	2	3	0
EUS-SM	11	2	9 (81.8%)	0
EUS-MP or deeper	8	1	0	7
Total	37	15	15	7
Undifferentiated-type adenocarcinoma with ulcerous changes				
EUS-M	4	3 (75.0%)	0	1
EUS-M/SM	2	0	1	1
EUS-SM	9	4	3 (33.3%)	2
EUS-MP or deeper	14	0	3	11
Total	29	7	7	15

ulcerous changes, and logistic regression analysis revealed that ulcerous changes and macroscopic classification were factors that caused incorrect diagnosis by EUS. It was difficult to distinguish tumor invasion and benign ulcers or fibrosis in the submucosal layer. Therefore, two MP cancers were diagnosed as EUS-M in the lesions with ulcerous changes. We must perform ESD carefully when lesions exhibit ulcereous changes, as it is sometimes difficult to distinguish MP cancer from M cancer.

Logistic regression analysis also showed that the depressed-type morphology was a factor in incorrect diagnosis of tumor invasion. This result was understandable because ulcerous changes usually accompanied the depressed-type gastric carcinomas.

The difficulty of EUS diagnosis for lesions with ulcerous changes has been reported. Chonan [25] suggested that, in depressed-type EGCs, interruption of the third layer was shown in massive SM cancer when fibrosis was not visible, and there was both inward and outward growth of the gastric wall when it was accompanied by fibrosis. Kida et al. [26] also suggested that spread to the submucosa was a finding of SM cancer, when there was fibrosis of a coexisting ulcer in the cancer. Ohashi et al. [27] suggested that a diffuse and low echogenicity region in the third layer was a finding of SM cancer. Contrast-enhanced EUS was reported to improve the accuracy of diagnosis of the invasive depth of gastric carcinomas [28]. If the area of carcinoma cells is selectively enhanced, it might contribute to distinguishing tumor invasion from fibrosis and lead to accurate diagnosis for lesions with ulceration.

There was one case report about a patient with poorly differentiated adenocarcinoma of the stomach who died as a result of local recurrence after EMR because of the unclear extent of invasion and the rapid progression of disease [29]. We expected that the accuracy of EUS diagnosis would not be favorable in undifferentiated-type carcinomas. However, the result for undifferentiated-type adenocarcinomas without ulcerous changes was comparable to that for differentiated-type adenocarcinomas without ulcerous changes in this study. As one of the expanded indicative criteria for ESD, undifferentiated-type adenocarcinoma without any ulcerous change, EUS could be useful to examine tumor invasion before ESD.

We included only patients in which EUS and EMR or gastrectomy was performed, which might have introduced some bias.

Ulcerous changes and the macroscopic type were associated with incorrect diagnosis of EUS by logistic regression analysis. Especially in differentiated adenocarcinoma with ulcerous changes, the PPV of EUS-SM was significantly lower than for lesions without such changes. EUS tend to overstage in the lesions with ulcerous changes. The accuracy of EUS tumor staging was not sufficient for the lesions with ulcerous changes in our study. Therefore, we should be careful to perform ESD for lesions with such changes.

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