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Morphologic pattern analysis of submucosal deformities identified by endoscopic ultrasonography for predicting the depth of invasion in early gastric cancer

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Abstract

Background The aims of this study are to evaluate the usefulness of submucosal deformity pattern analysis with endoscopic ultrasonography (EUS) for predicting the depth of invasion in early gastric cancer (EGC) and the treatment results of endoscopic submucosal dissection (ESD).

Methods The endoscopic and EUS parameters of 345 patients with endoscopically suspected EGC who underwent endoscopic or surgical resection between July 2012 and May 2017 were retrospectively reviewed. All patients were classified into three categories as follows according to the morphologic type of submucosal deformity identified by EUS: (1) no submucosal deformity, (2) wedge-shaped deformity, and (3) arch-shaped deformity. The presence of an arch-shaped submucosal deformity on EUS and an active endoscopic ulcer or surrounding mucosal fold convergence/clubbing on conventional endoscopy were defined as suggestive of deep submucosal cancer invasion (SCI).

Results Upper location ($p = 0.034$) and the presence of an arch-shaped submucosal deformity on EUS ($p < 0.001$) were significant predictors of deep submucosal invasion, with the presence of an arch-shaped submucosal deformity showing the highest predictive value (odds ratio of 26.27). The overall diagnostic accuracy of EUS for predicting deep SCI was 83.5%, with a sensitivity of 84.0% and a specificity of 83.3%, which were significantly higher than those of conventional endoscopy. A larger lesion size and the presence of an arch-shaped submucosal deformity were significant factors associated with noncurative resection after ESD.

Conclusions Submucosal deformity pattern analysis with EUS can provide more accurate information than conventional endoscopy for predicting deep SCI. The presence of an arch-shaped submucosal deformity on EUS was an effective predictor of deep SCI and noncurative resection.

Keywords Endoscopic ultrasonography · Early gastric cancer · Submucosal deformity · Depth of invasion

Advanced endoscopic resection methods such as endoscopic submucosal dissection (ESD) allow endoscopists to overcome the limitations of lesion size and location as well as submucosal fibrosis/ulceration and to identify lesions with minute submucosal invasion in the endoscopic treatment of early gastric cancer (EGC). Recent long-term data reporting favorable overall and disease-free survival rates for EGC with expanded criteria have suggested that ESD can be an effective therapeutic modality for EGC with minute submucosal invasion or ulceration [1–3]. However, as ESD is a nonradical organ-preserving technique, there is concern about the possibility of recurrence with regional or distal lymph node (LN) metastases [4]. Therefore, preprocedural staging evaluations to select appropriate indications that minimize the risk of LN metastases are crucial for improving the treatment results after ESD. In particular, predicting the depth of cancer invasion is critical because of its importance in relation to the possibility of LN metastases [5, 6].

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Currently, endoscopic ultrasonography (EUS) is thought be the most accurate tool for predicting the depth of cancer invasion in EGC, although its accuracy is significantly affected by the lesion size, location, and histological differentiation [7, 8]. In particular, the accuracy of EUS is reported to be considerably reduced for EGC associated with ulceration [9–12], and overestimation of T staging due to submucosal inflammation and fibrosis may be the cause of this low accuracy.

Hence, several morphological pattern analysis systems with EUS for distinguishing submucosal fibrosis/ulceration from cancer invasion have been suggested by some Japanese endoscopists [13–15]. These systems are based on the fact that submucosal deformities caused by ulceration/fibrosis are wedge-shaped; in contrast, submucosal deformities caused by cancer invasion are mostly arch-shaped. Although these systems are simple, a certain degree of experience is needed for precise evaluation of submucosal deformity patterns, which prohibits generalization of these systems in clinical practice, even in countries where the prevalence of gastric cancer is high and ESD is commonly performed. Furthermore, subsequent large-scale studies evaluating the validity of these classification systems have been limited until recently.

Our aims are to evaluate the usefulness of submucosal deformity pattern analysis with EUS for predicting (1) the depth of invasion in EGC compared with conventional endoscopic parameters and (2) the treatment results in patients with endoscopically resected EGC.

Methods

Patients

The medical records of consecutive patients with an endoscopic diagnosis of EGC who underwent EUS and endoscopic treatment or surgical resection at Inje University Busan Paik Hospital from July 2012 and May 2017 were retrospectively reviewed.

The inclusion criteria were as follows: (1) endoscopically suspected EGC based on conventional endoscopy; (2) EUS performed with a 20-MHz miniprobe catheter; and (3) endoscopic resection or surgical resection performed within 2 months of the initial diagnosis.

The exclusion criteria were as follows: (1) cases in which the EUS images were too poor for the classification of submucosal deformity patterns, or cases in which submucosal pattern analysis was not feasible because of surrounding organ compression or prominent calcification; (2) cases of submucosal cancer invasion (SCI) or histological ulceration at more than two locations, preventing

a precise correlation between EUS findings and histology; (3) ulcerative lesions with extensive surrounding mucosal infiltration or hardness more than 3 cm in maximal diameter; (4) ulcerative cases with marked marginal elevation (tumorous bank formation); and (5) patients who underwent piecemeal resection or patients with lateral margin positive on histological evaluation after ESD.

Conventional endoscopic and EUS parameters

Conventional endoscopic parameters including location, the presence and degree of ulcer, surrounding mucosal fold convergence or fusion/clubbing, and lesion size were estimated. The longitudinal locations of the tumors were defined as being in the upper, middle, or lower thirds of the stomach; (1) Upper thirds included lesions located in upper body, cardia, and fundus, (2) middle thirds included lesions located in mid and low body, and (3) lower thirds included lesions located in antrum. EGC with ulcer or an ulcer scar was defined as EGC combined with a stage A or H endoscopic ulcers or a stage S1 ulcer scar, respectively [16]. In detail, active ulcers, which included stage A or H1 ulcers, were defined according to the following endoscopic criteria: (1) depressed lesion with an exudative base with size ≥ 1 cm; (2) sharply demarcated and raised margins; and (3) surrounding mucosal edema or fold convergence. Healing ulcers, which included stage H2 ulcers or stage S1 ulcer scars, were also defined as slightly depressed or flat lesions ≥ 1 cm in size with reddish regenerating epithelium and surrounding edematous mucosa or fold convergence, with or without an exudative base < 1 cm in size.

We defined deep SCI as lesions surrounded by mucosal fold changes such as fusion/clubbing of converging folds or active endoscopic ulcers.

EUS examinations were performed by a single experienced endoscopist (JHK) who had performed more than 800 examinations using a 20-MHz miniprobe catheter (UM3D-DP20-25R, Olympus, Tokyo, Japan).

All patients were classified into 3 categories according to the morphologic type of submucosal deformity: (1) no submucosal deformity (Fig. 1); (2) a type I deformity, which was defined as a smoothly tapering wedge-shaped submucosal deformity (Fig. 2); or a (3) type II deformity, which was defined as punched out arch-shaped submucosal deformity (Fig. 3). The presence of a type II submucosal deformity was suggestive of deep SCI.

Conventional endoscopic and EUS images from all subjects were reviewed by two experienced endoscopists (JHK and THK) who were blinded to clinical and histological information. The presence of findings of deep SCI was assessed by consensus between the two endoscopists.

Fig. 1 A patient with early gastric cancer with no submucosal deformity identified by endoscopic ultrasonography (EUS). **A** Conventional endoscopy showed an ulcerative mucosal lesion with surrounding fold elevation located along the greater curvature of the lower body. **B** EUS showed a hypoechoic thickened mucosal layer with an intact submucosal layer (dotted line). **C** Differentiated adenocarcinoma confined to mucosal layer (arrows) and an intact submucosal layer were identified on the histological examination (Hematoxylin and eosin stain, × 10)
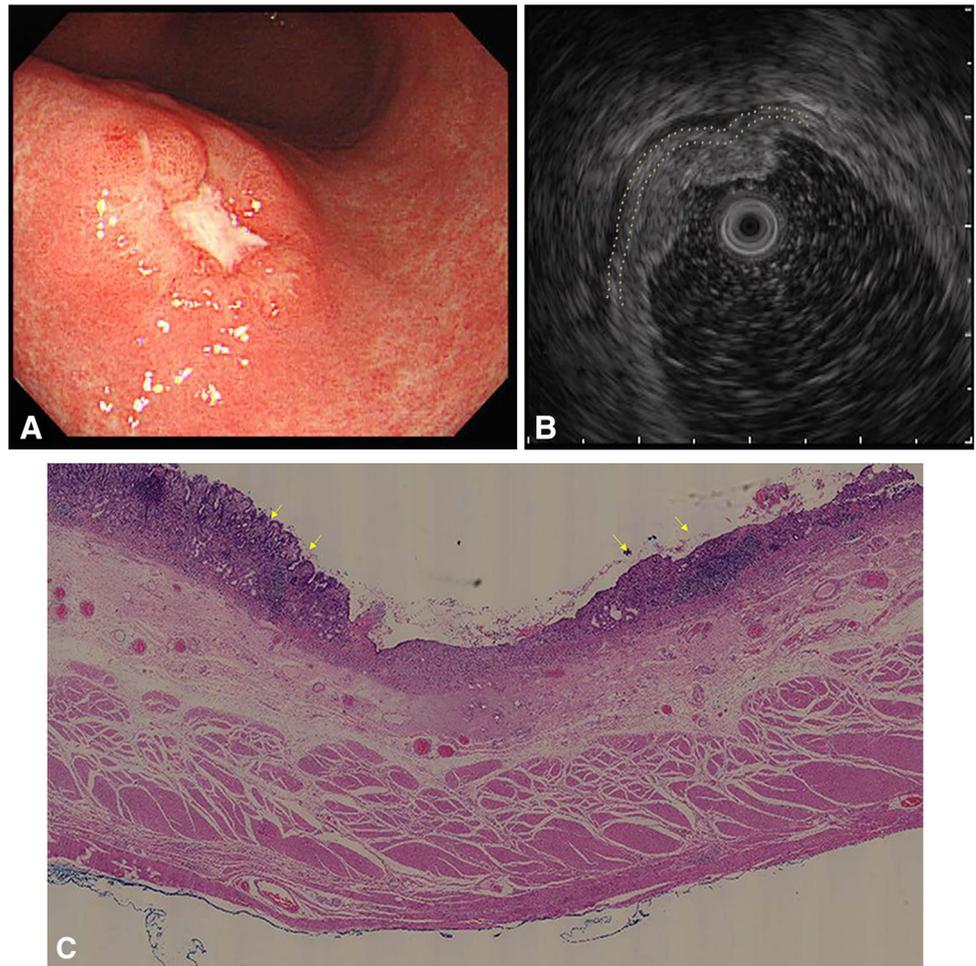

Histological analysis

Resected specimens fixed in 10% formalin were cut into sections 2 mm in width. Histological interpretations including cancer differentiation, the depth of cancer invasion, and the presence of lymphovascular invasion (LVI) were made by a single experienced pathologist (MSK). Histological ulceration was defined as mucosal defects deeper than the mucosal layer or fibrosis in the submucosal layer or deeper layers in both endoscopically and surgically resected specimens and deformities of the proper muscle layer in surgically resected specimens. The lesion size was measured, including the sizes of ulcerated areas and ulcer scars. The depth of SCI in surgically resected cases was reported in terms of three grades: SM1 (upper third of the submucosal layer), SM2 (middle third), and SM3 (lower third). In the endoscopically resected cases, the depth of invasion was reported in terms of two grades: SM1 (penetration into the submucosal layer < 500 μm from the muscularis mucosa), and SM2 (penetration ≥ 500 μm). Deep SCI was defined as SM2 submucosal invasion in endoscopically resected specimens and SM2 or deeper in surgically resected specimens.

In patients who underwent endoscopic resection, the complete resection and curative resection rates were evaluated. Complete resection was defined as a vertical margin free of a tumor and lateral margins free of a tumor for greater than 2 mm on histological examination. The resection was considered to be curative when all the following conditions were fulfilled: (1) complete resection without LVI; (2) differentiated mucosal cancer without histological ulceration regardless of tumor size; (2) differentiated mucosal cancer associated with histological ulceration with the largest tumor size with ≤ 3 cm; (3) differentiated SM1 invasive cancer with the largest tumor size ≤ 3 cm ; and (4) undifferentiated mucosal cancer without ulceration with the largest tumor size ≤ 2 cm.

Statistical analyses

The association between clinicopathologic factors (including endoscopic characteristics and EUS parameters) and the depth of cancer invasion, and the presence of histological ulceration were assessed with the Chi-square test, independent *t* test, and Fisher's exact test. Differences in the
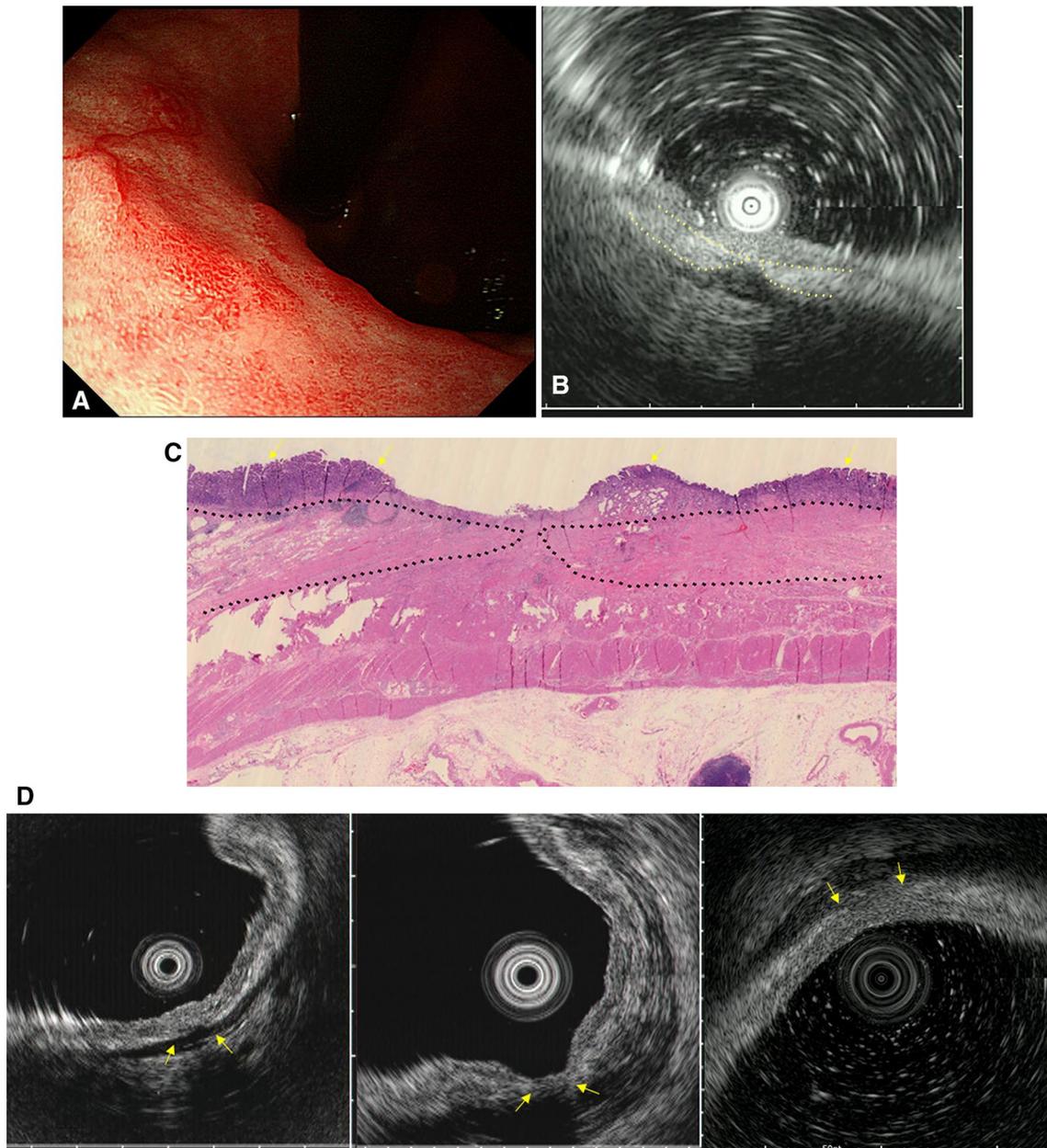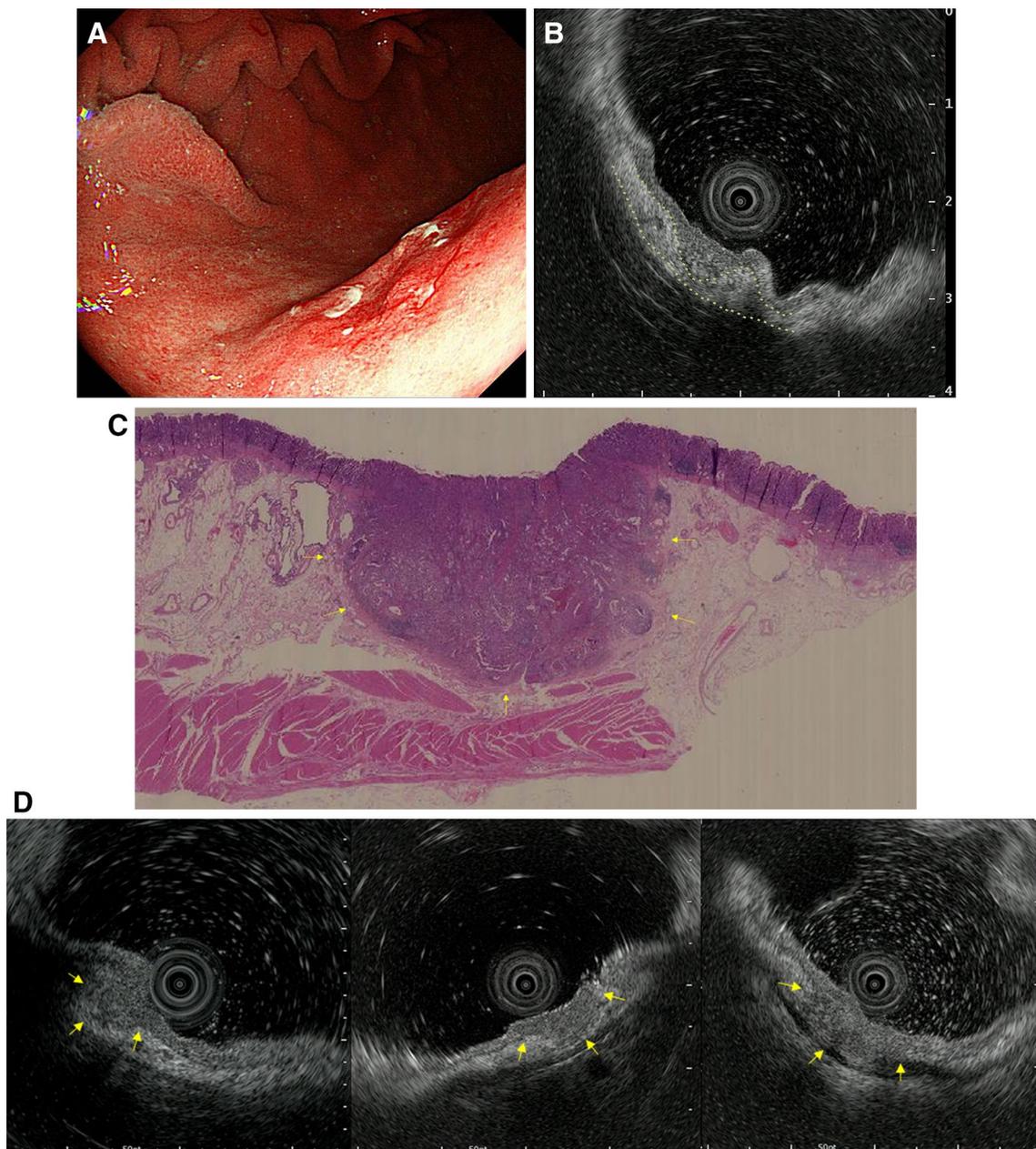
Fig. 2 A patient with early gastric cancer with a type I submucosal deformity. **A** Conventional endoscopy showed a depressed mucosal lesion without active ulceration or an ulcer scar at the posterior wall of upper body. **B** Endoscopic ultrasonography showed a symmetric wedge-shaped hypoechoic submucosal deformity (dotted line). **C** Histological evaluation revealed differentiated mucosal cancer (arrows) and prominent submucosal fibrosis with a wedge-shaped deformity (dotted line) (Hematoxylin and eosin stain, × 10). **D** Illustrated EUS images of a wedge-shaped submucosal deformity show a smoothly tapered submucosal layer with or without focal proper muscle layer deformity (arrows)

sensitivity, specificity, and accuracy between conventional endoscopic and EUS findings for predicting deep SCI were determined using McNemar's test. A multivariate analysis was conducted with a binary logistic regression test. A p value < 0.05 was considered statistically significant.

Ethical approval

This study was approved by the Institutional Review Board of Inje University Busan Paik Hospital (Approval No. 15-0280), which confirmed that the study was performed in accordance with the ethical guidelines of the Helsinki Declaration.

Fig. 3 A patient with early gastric cancer with a type II submucosal deformity. **A** Conventional endoscopy revealed a slightly depressed mucosal lesion with a stage S1 ulcer scar at the posterior wall of upper body. **B** Endoscopic ultrasonography showed an arch-shaped hypoechoic submucosal deformity (dotted line). **C** Histological exam-ination showed differentiated adenocarcinoma with deep submucosal invasion (arrows) (Hematoxylin and eosin stain, ×10). **D** Illustrated EUS images of arch-shaped submucosal deformities show well-defined or ill-defined abrupt arch-shaped submucosal defects without tapering (arrows), which are induced by cancer invasion

Results

Baseline characteristics

Among 406 endoscopically suspected EGC patients who underwent EUS examinations and endoscopic or surgical resection, 51 patients were excluded from the analysis for the following reasons: (1) classification of submucosal deformi-ties was not possible due to poor-quality EUS images, sur-rounding organ compression, or combined calcification in 12 patients; (2) SCI or histological ulcerations were found at more than two locations on histological analysis in 11 patients; (3) ulcerative lesions with extensive surround-ing mucosal infiltration or hardness affecting greater than 3 cm were present in 16 patients; (4) thirteen patients had

ulcerative EGC with tumorous bank formation; and (5) three patients underwent piecemeal resection and 6 patients were proved as lateral margin positive on histological evaluation after ESD. Ultimately, 345 lesions from 345 patients (mean age, 63.4 ± 10.09 years; 238 males, 107 females) were analyzed. Surgical resection was performed in 202 patients (58.6%) as the initial treatment modality. ESD with curative or diagnostic intent was performed in 143 patients (41.4%), and subsequent surgical resection was performed in six patients. The mean lesion size was 21.6 ± 12.9 mm. The maximal lesion diameter was less than 20 mm in 172 patients (49.9%) and greater than 30 mm in 77 patients (22.3%). Lesions were found most frequently in the middle thirds of the stomach (46.1%) with a longitudinal view or at the lesser curvature (48.1%) with a circumferential view.

Surrounding mucosal fold changes, such as fusion/clubbing of converging folds, were found in 33 patients (9.6%). Active or healing ulcers accompanied in 150 (43.5%) and 78 patients (22.6%), respectively. Type I and type II deformities identified by EUS were found in 82 (23.8%) and 112 patients (32.5%), respectively.

On histological evaluation, 62.6% and 13.9% of the total cases were identified as mucosal cancer or SM1 invasive cancer, respectively. Eight-one cases (23.4%) were graded as SM2 or deeper invasive cancers including 5 cases of T2-stage advanced cancer. Histological ulceration and LVI were found in 130 (37.7%) and 13 patients (8.1%), respectively. Undifferentiated EGC accounted for 21.2% of the total cases (Table 1).

Factors associated with deep SCI, the presence of histological ulceration, and the presence of LVI

In the univariate analysis, a larger lesion size, a location in the upper portion of the stomach, the presence of active or healing ulcers, the presence of fusion/clubbing of converging folds, and the presence of type II submucosal deformities identified by EUS were significant factors for predicting deep SCI. Among these, a location in the upper portion of the stomach and the presence of type II submucosal deformities were determined to be significant according to the multivariate analysis (p value = 0.034, < 0.001, respectively). The presence of type II submucosal deformities had the highest predictive value, with a multivariate adjusted odds ratio of 26.27 (Table 2).

Histological ulceration was found in 27.3% of mucosal cancer cases, 52.1% of SM1 invasive cancer cases, and 56.8% of SM2 or deeper invasive cancer cases. Histological ulceration was found in 49.3% of patients with active ulcers and 37.2% of patients with healing ulcers, and even in 23.1% of patients without endoscopic ulcers or ulcer scars. The presence of an active or healing ulcer

Table 1 Baseline characteristics of 345 patients with early gastric cancer

Variables	$n = 345$ (%)
Mean age (years, mean ± SD)	63.4 ± 10.09
> 65	190 (55.1)
≥ 65	155 (44.9)
Sex, n (%)	
Male	238 (69.0)
Female	107 (31.0)
Treatment, n (%)	
Surgery	202 (58.6)
ESD	143 (41.4)
H. pylori infection, n (%)	
Not infected	195 (56.5)
Infected	150 (43.5)
Macroscopic morphology, n (%)	
Elevated	54 (15.7)
Flat/depressed	291 (84.3)
Endoscopic ulcer or ulcer scar, n (%)	
Absent	117 (33.9)
Active ulcer	150 (43.5)
Healing ulcer	78 (22.6)
Location, n (%)	
Longitudinal	
Upper	34 (9.9)
Middle	159 (46.1)
Lower	152 (44.1)
Circumferential	
Anterior wall	58 (16.8)
Posterior wall	63 (18.3)
Lesser curvature	166 (48.1)
Greater curvature	58 (16.8)
Clubbing or fusion of converging folds, n (%)	
Absent	312 (90.4%)
Present	33 (9.6%)
Submucosal deformity identified by EUS, n (%)	
No deformity	151 (43.8)
Type I deformity	82 (23.8)
Type II deformity	112 (32.5)
Long-axis diameter (mm, mean ± SD)	21.6 ± 12.9
Long-axis diameter, n (%)	
< 20 mm	172 (49.9)
20 mm ≤, < 30 mm	96 (27.8)
≤ 30 mm	77 (22.3)
Depth of cancer invasion, n (%)	
Mucosa	216 (62.6)
SM1	48 (13.9)
≥ SM2	81 (23.4)
Histological ulcer, n (%)	
Absent	215 (62.3)
Present	130 (37.7)

Table 1 (continued)

Variables	$n = 345$ (%)
Lymphovascular invasion, n (%)	
Absent	147 (91.9)
Present	13 (8.1)
Histological differentiation, n (%)	
Differentiated	272 (78.8)
Undifferentiated	73 (21.2)

was significantly associated with the presence of histological ulceration in the univariate analysis, but not in the multivariate analysis ($p = 0.368$). Histological ulceration was found in 53.7% of patients with type I submucosal deformities and 52.7% of patients with type II submucosal deformities identified by EUS. Histological ulceration was found in 17.9% of patients without submucosal deformities identified by EUS. The presence of type I or II submucosal deformities was found to be a unique independent factor for predicting the presence of histological ulceration ($p < 0.001$).

In terms of the presence of LVI, a larger lesion size, the presence of an active or healing ulcer, and the presence of fusion/clubbing of converging folds were significantly associated with the presence of LVI in the univariate analysis but not in the multivariate analysis. Similar to the results regarding deep SCI, the presence of type II submucosal deformities identified by EUS was an independent predictor of the presence of LVI ($p = 0.001$) (Table 3).

Accuracy of conventional endoscopy and EUS for predicting deep SCI

Active ulcers were more frequently found in patients with type I or II submucosal deformities identified by EUS (52.4% and 67.0%, respectively) than in those without submucosal deformities (21.2%) ($p < 0.001$) (Table 4).

The overall diagnostic accuracy of conventional endoscopy for predicting deep SCI was 62.0%, and the sensitivity, specificity, positive predictive value, and negative predictive value were 69.1%, 59.8%, 27.3%, and 80.5%, respectively. The overall diagnostic accuracy of EUS for predicting deep SCI was 83.5%, with a sensitivity of 84.0%, a specificity of 83.3%, a positive predictive value of 60.7%, and a negative predictive value of 94.4%. Submucosal deformity pattern analysis with EUS had a higher diagnostic accuracy than conventional endoscopy in terms of specificity and sensitivity, as well as overall accuracy (Table 5).

The lesion size, longitudinal location, presence of active endoscopic ulcers, and surrounding mucosal fold/clubbing were not significant factors influencing the diagnostic accuracy of EUS for predicting deep SCI (Table 6).

Table 2 Relationship between clinical factors and the depth of cancer invasion

	Mucosa or SM1, $n = 264$ (%)	$\geq$ SM2, $n = 81$ (%)	p value, univariate	p value, multivariate	Multivariate adjusted OR (95% CI)
Histological long-axis diameter (mm, mean $\pm$ SD)	20.9 $\pm$ 13.23	24.1 $\pm$ 11.75	0.046	0.885	
Longitudinal location			0.007	0.034	
Upper	20 (58.8)	14 (41.2)			4.07 (1.36–12.17)
Middle	118 (74.2)	41 (25.8)			1.88 (0.90–3.94)
Lower	126 (82.9)	26 (17.1)			Ref
Endoscopic ulcer or ulcer scar			< 0.001	0.304	
Absent	106 (90.6)	11 (9.4)			
Active ulcer	97 (64.7)	53 (35.3)			
Healing ulcer	61 (78.2)	17 (21.8)			
Clubbing or fusion of converging folds			0.002	0.714	
Absent	246 (78.8)	66 (21.2)			
Present	18 (54.5)	15 (45.5)			
Submucosal deformity identified by EUS			< 0.001	< 0.001	
No deformity	145 (96.0)	6 (4.0)			Ref
Type I deformity	75 (91.5)	7 (8.5)			1.45 (0.44–4.710)
Type II deformity	44 (39.3)	68 (60.7)			26.27 (9.88–69.82)
Histological differentiation			0.936		
Differentiated	208 (76.5)	64 (23.5)			
Undifferentiated	56 (76.7)	17 (23.3)			

Table 3 Relationship between clinical factors and the presence of lymphovascular invasion

	Absence, $n=316$ (%)	Presence, $n=29$ (%)	p value, univariate	p value, multivariate	Multivariate adjusted OR (95% CI)
Histological long diameter (mm, mean ± SD)	21.0 ± 12.73	28.6 ± 13.53	0.002	0.053	
Endoscopic ulcer or ulcer scar			< 0.001	0.380	
Absent	115 (98.3)	2 (1.7)			
Active ulcer	127 (84.7)	23 (15.3)			
Healing ulcer	74 (94.9)	4 (5.1)			
Clubbing or fusion of converging folds			< 0.001	0.192	
Absent	292 (93.6)	20 (6.4)			
Present	24 (72.7)	9 (27.3)			
Submucosal deformity identified by EUS			< 0.001	0.001	
No deformity	149 (98.7)	2 (1.3)			Ref
Type I deformity	80 (97.6)	2 (2.4)			1.08 (0.14–8.40)
Type II deformity	87 (77.7)	25 (22.3)			9.54 (1.98–45.92)

Table 4 Association between the degree of endoscopic ulceration and submucosal deformity pattern identified by endoscopic ultrasonography

		Endoscopic ulcer or ulcer scar			p value
		Absent	Active ulcer	Healing ulcer	
Type of submucosal deformity identified by EUS	No deformity (%)	58.3 (88/151)	21.2 (32/151)	20.5 (31/151)	
	Type I deformity (%)	12.2 (10/82)	52.4 (43/82)	35.4 (29/82)	
	Type II deformity (%)	17.0 (19/112)	67.0 (75/112)	16.1 (18/112)	
					< 0.001

Table 5 Comparison of the accuracy of endoscopic ultrasonography and conventional endoscopy for predicting deep submucosal cancer invasion

	EUS (95% CI)	Conventional endoscopy (95% CI)	p value
Sensitivity (%)	84.0 (74.1–91.2)	69.1 (57.9–78.9)	0.023
Specificity (%)	83.3 (78.3–87.6)	59.8 (53.7–65.8)	< 0.001
Accuracy (%)	83.5 (79.1–87.2)	62.0 (59.3–70.4)	< 0.001

Factors associated with the treatment results of ESD for EGC

Among 345 patients, ESD was performed as the initial curative therapeutic modality in 143 patients (mean age, 65.1 ± 10.21 years; 97 males, 46 females; mean size: 22.4 ± 13.0 mm). Seventy-four patients (51.8%) had lesions in the upper or middle region of the stomach in a longitudinal plane. Mucosal cancer accounted for 72.0% of all cases, and SM1 and SM2 cancer accounted for 15.4% (22 cases) and 12.6% (18 cases), respectively. Complete or curative resection was performed in 121 patients (84.6%) and 106 patients (74.1%), respectively. Seventeen patients (11.9%) with undifferentiated histology were also included.

The presence of type II deformities identified by EUS was a unique predictive factor for incomplete resection. In terms of curative resection, a larger lesion size and the presence of type II submucosal deformities were significant factors associated with noncurative resection in the multivariate analysis. Type II submucosal deformities identified by EUS had the highest adjusted odds ratio of 19.09 for noncurative resection (Table 7).

Discussion

Gastric cancer is known to be accompanied by various degrees of inflammation, ulceration, and fibrosis caused not only by the desmoplastic reaction of cancer itself [17, 18] but also by gastric acid [19, 20]. In our study, the frequencies of active or healing-stage endoscopic ulcers and histological ulcerations were 43.5% and 37.7%, respectively. In addition, the frequency of histological ulceration was significantly higher in submucosal cancer (55.0%) than in mucosal cancer, which was consistent with previous results.

Traditional studies evaluating the prediction of the depth of cancer invasion in gastric cancer have focused on the importance of conventional endoscopic findings suggestive of deep SCI, such as the degree of depression, the presence

Table 6 Conventional endoscopic parameters associated with the accuracy of endoscopic ultrasonography for predicting deep submucosal cancer invasion

	Accurate, n = 288 (%)	Inaccurate, n = 57 (%)	p value, univariate	p value, multivariate
Histological long-axis diameter (mm, mean ± SD)	21.6 ± 13.59	21.9 ± 9.16	0.872	
Longitudinal location			0.103	
Upper	24 (70.6)	10 (29.4)		
Middle	135 (84.9)	24 (15.1)		
Lower	129 (84.9)	23 (15.1)		
Endoscopic ulcer or ulcer scar			0.054	0.183
Absent	102 (87.2)	15 (12.8)		
Active ulcer	117 (78.0)	33 (22.0)		
Healing ulcer	69 (88.5)	9 (11.5)		
Clubbing or fusion of converging folds			0.787	
Absent	261 (83.7)	51 (16.3)		
Present	27 (81.8)	6 (18.2)		

Table 7 Relationship between conventional endoscopic/ultrasonographic parameters and curative resection rate in patients who underwent endoscopic resection

	Curative, n = 89 (%)	Noncurative, n = 54 (%)	p value, univariate	p value, multivariate	Multivariate adjusted OR (95% CI)
Histological long-axis diameter (mm, mean ± SD)	13.1 ± 7.54	20.7 ± 12.02	< 0.001	< 0.001	
Endoscopic ulcer or ulcer scar			0.132	0.062	
Absent	49 (77.8)	14 (22.2)			
Active ulcer	30 (63.8)	17 (36.2)			
Healing ulcer	27 (81.8)	6 (18.2)			
Submucosal deformity identified by EUS			< 0.001	< 0.001	
No deformity	67 (87.0)	10 (13.0)			Ref
Type I deformity	31 (81.6)	7 (18.4)			1.28 (0.36–4.55)
Type II deformity	8 (28.6)	20 (71.4)			19.09 (5.41–67.37)

of ulceration or surrounding mucosal fold changes and convergence or clubbing [21–24]. Consistent with our results, a proximal lesion location was identified as a risk factor for deep SCI of EGC [25]. Anatomical differences, such as the thickness of the gastric wall and submucosal layer and the density of muscle bundles of smooth muscle cells and lymphatic capillaries, may have accounted for this finding [26, 27]. Among these characteristics, ulcerative EGC has been associated with submucosal or deeper invasion, and this form of EGC was regarded as unsuitable for endoscopic treatment [28]. However, the accuracy of conventional endoscopic parameters for predicting the depth of cancer invasion is likely affected by several factors, such as the degree of air inflation, the degree of surrounding mucosal inflammation/edema, and the number and intensity of previous endoscopic biopsies [29]. Considering the fact that endoscopic ulcers in EGC can be induced not only by cancer invasion but also by gastric acid and that a considerable number of EGC lesions are going through a malignant cycle [16, 19, 20], predicting the depth of invasion based on the presence of ulcerative lesions can cause overestimation.

The present study revealed a poor correlation between endoscopic and histological ulcers. Additionally, endoscopic prediction for deep SCI using parameters such as the presence of active ulcers or surrounding fold clubbing/convergence showed suboptimal overall accuracy (62.0%) and specificity (59.8%), suggesting a tendency to overestimate the depth of cancer invasion. Similar to the findings of previous studies evaluating the feasibility of ESD for ulcerative EGC [20, 30, 31], our data suggested that the EGC associated with endoscopic ulcers may not necessarily be a contraindication for ESD.

EUS, which can be used to visualize the whole gastric wall layer in an image, is known to be most accurate tool

for predicting the depth of invasion in EGC. However, the accuracy of EUS is seriously deteriorated by the presence of endoscopic or histological ulceration, with reported accuracies ranging between 30 and 70% [9–12]. Several large-scale retrospective studies reporting the limited advantages of EUS over conventional endoscopic findings for predicting the depth of invasion have raised doubts about the clinical implications of using EUS to determine treatment strategies for EGC [23, 32].

However, in previous studies, submucosal invasion identified by EUS was determined only by hypoechoic changes in the submucosal layer, which has been hypothesized to be responsible for the low diagnostic accuracy [10, 12, 23, 32]. Pattern analysis for submucosal deformities may be an effective modality for overcoming the limitations of EUS for differentiating cancer invasion from submucosal ulceration/fibrosis [13–15]. Our study is meaningful because we analyzed the validity of these systems in a large number of patients with ulcerative EGC.

In the present study, an arch-shaped submucosal deformity was identified as a significant independent predictive factor for deep SCI, with the highest odds ratio of 26.27. In contrast, 91% of patients with wedge-shaped submucosal deformities were determined to have mucosal or SM1 invasive cancers. Additionally, the diagnostic accuracy of the pattern analysis method was not affected by factors such as lesion size, longitudinal lesion location, or endoscopic ulcer, which are known to decrease the accuracy of EUS.

In terms of the diagnostic yields of EUS and conventional endoscopy, EUS showed higher sensitivity, specificity, and overall accuracy than conventional endoscopy. In particular, EUS showed a crucial diagnostic advantage over conventional endoscopy in terms of specificity (83.3% vs. 59.8%), suggesting that the considerable overestimation of deep SCI with conventional endoscopy can be corrected with EUS examination [33]. In addition to the depth of cancer invasion, an arch-shaped submucosal deformity identified by EUS was a significant independent predictor of LVI, which also had been identified as one of the most important factors for predicting LN metastasis in EGC. Based on this finding, we can assume that tumor burden can also be predicted with pattern analysis of submucosal deformities in EGC.

In addition to the depth of invasion, predicting the presence and degree of histological ulceration and fibrosis is also important for choosing a treatment method because histological ulceration is not only associated with an increased risk of LN metastasis but also with the frequency of complications and the treatment outcomes of ESD for EGC [30, 34, 35]. In our study, the presence of submucosal deformities, including both wedge- and arch-shaped deformities, was a significant predictor of the presence of histological ulceration. That is, 53.1% of patients with submucosal deformities identified by EUS were found to have histological ulceration,

whereas only 17.9% of patients without submucosal deformities were found to have histological ulceration. Similar to the depth of cancer invasion, the presence of endoscopic ulcers was not an independent predictor of the presence of histological ulceration. One interesting result of the present study was that histologic ulceration was found in 57.2% of cases with arch-shaped submucosal deformities which are thought to be formed by deep SCI. This result indicates that a significant proportion of cancers with deep SCI were associated with histological deformations, such as fibrosis and defects in the submucosal layer, which occur during the course of malignant ulcer cycle.

We also evaluated the advantages of EUS over conventional endoscopy from a therapeutic viewpoint by evaluating patients who underwent endoscopic resection and demonstrated that the presence of an arch-shaped deformity on EUS was a significant predictor of incomplete and noncurative resection for EGC. In other words, curative resection was achieved in 85.2% of patients without submucosal deformities or with wedge-shaped submucosal deformities, whereas it was achieved in only 28.6% of patients with arch-shaped deformities. Interestingly, curative resection was feasible in 81.6% of patients with wedge-shaped submucosal deformities, suggesting that patients with submucosal fibrosis without evidence of deep SCI are rational candidates for ESD. Additionally, considering the results showing that 40% of EGC cases with arch-shaped submucosal deformities were determined to be mucosal SM1 invasive cancer, ESD with diagnostic intent rather than curative intent can also be performed in select EGC cases with small-sized arch-shaped submucosal deformities. In contrast, the presence of endoscopic ulcer on conventional endoscopy was not a significant predictor for noncurative resection, as 63.8% of patients with active endoscopic ulcers achieved curative resection. Although the sample size was small (143 cases), these results suggest that pattern analysis for submucosal deformities can be effectively applied to selected patients with disease that was overestimated by conventional endoscopy and reduce the overtreatment of EGC as a result [36].

This retrospective study had several methodological limitations.

First, the number of patients with endoscopic ulcers, histological ulceration, and deep SCI were relatively higher (43.5%, 37.7%, and 23.4%, respectively) than those in previous studies [10–12, 37], which may have occurred because we performed EUS to identify depth of cancer invasion in patients with suspected deep SCI based on conventional endoscopy; thus, this may have caused selection bias, resulting in the possibility that our patients are not representative of patients with EGC seen in general clinical practice. Second, ESD was performed as a curative treatment modality in 41.4% of EGC patients in the present study. Considering that we could not evaluate the entire submucosal layer with

endoscopically resected specimens, underestimation of histological factors such as histological ulceration and LVI may have occurred in these cases. Finally, the interval between conventional endoscopic/EUS examinations and endoscopic/surgical resection was variable (3–50 days), and the use of antisecretory medication was not controlled due to the retrospective nature of the study; these factors may potentially have affected the results of the correlation between endoscopic ulcers and submucosal deformity patterns identified by EUS and histological ulceration on resected specimens.

In conclusion, this study demonstrated that submucosal pattern analysis performed with EUS can provide more accurate information than conventional endoscopy for predicting deep SCI in EGC. Arch-shaped submucosal deformity identified by EUS examinations can be an effective predictor of deep SCI and noncurative resection after ESD. We also showed that curative endoscopic resection can be recommended even for patients with EGC with wedge-shaped submucosal deformity as well as for those without submucosal deformity.

Compliance with ethical standards

Disclosures Drs. Tae Young Kim, Nam Hee Yi, Jin Won Hwang, Ji Hyun Kim, Gwang Ha Kim, and Mi Seon Kang have no conflicts of interest or financial ties to disclose.

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