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Clinical efficacy of endoscopic ultrasonography for decision of treatment strategy of gastric cancer

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Abstract

Background Accurate preoperative tumor staging of gastric cancer is indispensable with expansion of indications for laparoscopic surgery and endoscopic resection. It is important to distinguish mucosal cancer (T1a) in smaller lesion and differentiate early gastric cancer (EGC) in larger lesion considering endoscopic resection indication and laparoscopic surgery indication. We evaluated the clinical outcomes of endoscopic ultrasonography (EUS) for the decision of treatment strategy of gastric cancer compared with pathological staging.

Methods The patients who underwent EUS and surgical or endoscopic resection for gastric cancer were retrospectively reviewed between September 2005 and February 2016. The depth of tumor invasion (T staging) by EUS was compared with the pathological staging after endoscopic or surgical resection.

Results A total of 6084 patients were finally analyzed. The accuracy rates for T1a and EGC were 75.0 and 89.4%, respectively. The overall accuracy of T staging by EUS was 66.3% when divided by T1a, T1b, and over T2. The accuracy of EUS prior to endoscopic resection was 75.1% in absolute indication and 73.1% in expanded criteria, respectively. The accuracy rates for T1a with lesion ≤ 2 cm in miniprobe EUS and EGC with lesion > 2 cm in conventional EUS were 84.6 and 83.2%, respectively. In multivariate analysis, presence of ulcer, large tumor size, and radial EUS were associated with overestimation, and small tumor size and miniprobe were associated with underestimation in T staging.

Conclusions EUS showed the high accuracy of 84.6% for T1a in lesion ≤ 2 cm in miniprobe EUS and 83.2% for EGC in lesion > 2 cm in conventional EUS, respectively. EUS can be a complementary diagnostic method to determine endoscopic or surgical treatment modality.

Keywords Endoscopic ultrasonography · Gastric cancer · Tumor staging

It has been demonstrated that the depth of invasion (T stage) of gastric cancer is a predictor of not only prognosis but also lymph node metastasis, and plays an important role in determining the treatment strategy [1, 2]. With the national cancer screening program, early detection of gastric cancer has been increasing in Korea [3]. In addition, the quality of life [4] and long term outcome of endoscopic treatment have been known to be not inferior to surgical treatment for gastric cancer [5]. Therefore, the indications for endoscopic treatment have been gradually expanded [1] and the prediction of T stage has been more important. As the indications for laparoscopic gastrectomy have been also expanded [6] with the progression of surgical technique, the preoperative evaluation of T stage has been important in determining the treatment strategy of gastric cancer.

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Endoscopic ultrasonography (EUS) has been accepted as a useful diagnostic modality for the evaluation of gastrointestinal tract and the structures around it. Conventional EUS has a deep penetration depth but has a disadvantage of reinserting EUS scope with an outer diameter of 12.5–14.5 mm separately from the conventional endoscope for examination. Miniprobe with a smaller diameter, smaller penetration depth of 2–3 cm, and higher frequency (7.5–30 MHz) than conventional EUS is limited to obtain images of large tumors. However, it provides high resolution and smaller diameter makes it possible to observe the narrowed zone with stenosis. Because it is inserted into the working channel of the endoscope, the conventional endoscopy and miniprobe EUS can be performed as a single examination. Miniprobe EUS has been known to assess tumor invasion depth precisely in small and superficial tumors compared to conventional EUS [7–9].

EUS has been also used for the staging of gastric cancer with high accuracy around 90% and sensitivity and specificity of 80–90% [10–13]. However, several other studies have reported the opposite results, in which EUS was not superior to conventional esophagogastroduodenoscopy (EGD) in the prediction of T staging of early gastric cancer (EGC) [9, 14–17]. Moreover, previous studies have evaluated the efficacy of EUS to differentiate mucosal cancer from submucosa-invasive cancer [9, 14–19] and few studies have conducted to determine T1a, T1b, and advanced gastric cancer (AGC). The aim of the present study was to evaluate the accuracy of T staging and the effect on the decision of treatment strategy of all types of gastric cancer of EUS by comparison with pathological staging, and to elucidate the factors associated with the accuracy of EUS staging.

Materials and methods

Patients

We retrospectively analyzed the patients who were diagnosed with biopsy-proven adenocarcinoma and underwent EUS for gastric cancer from September 2005 to February 2016 at Seoul National University Hospital.

The treatment strategy was decided by the results of conventional endoscopy, pathology, EUS, and computerized tomography (CT). Endoscopic resection was performed by the method of endoscopic submucosal dissection (ESD), and the indications were as follows: well- or moderately differentiated histology, ≤ 2 cm in diameter without ulcer, and no evidence of lymph node and distant metastases [20]. For the cases of EGC beyond the indication of ESD in the results of endoscopy, pathology, EUS, and CT, laparoscopic or robot-assisted surgery was performed. Open surgery was performed for the cases with diagnosis of AGC in EUS or CT. The institutional review board of Seoul National University Hospital approved the present study (IRB no. 1603-006-745) (Fig. 1).

EUS staging

We used a radial array echoendoscope (GF-UM-2000, GF-EU-260; Olympus, Tokyo, Japan) or a miniature ultrasound probe (miniprobe, Olympus UM-2R, 12 MHz; Olympus, Japan). Miniprobe EUS was used mainly for the lesions ≤ 2 cm and considered as mucosal cancer in conventional endoscopy, and radial EUS for beyond the lesions. The procedure was as previously described [14]. After aspiration of air inside the stomach, deaerated water (300–800 mL) was filled in the stomach. The T stage was evaluated at 12 MHz. Miniprobe was inserted through the working channel of the endoscope and evaluated with endoscopic examination. On EUS, the normal gastric wall appears as the mucosa (combination of the first hyperechoic and second hypoechoic layers), the submucosa (third, hyperechoic layer), the muscularis propria (fourth, hypoechoic layer), and the subserosa and serosa (fifth, hyperechoic layer). If the layer was thick or irregular, and the integrity between the layers was interrupted, the layer was considered as the tumor invasion. The stage was determined according to AJCC 7th edition TNM staging system. In EUS, T1a was defined as tumor confined to first and second mucosal layer, T1b as tumor invasion to third submucosal layer, T2 as tumor invasion to muscularis propria in fourth layer, T3 as tumor invasion to subserosa without interruption of serosa, T4a as tumor invasion to serosa in fifth layer, and T4b as tumor invasion to adjacent organ.

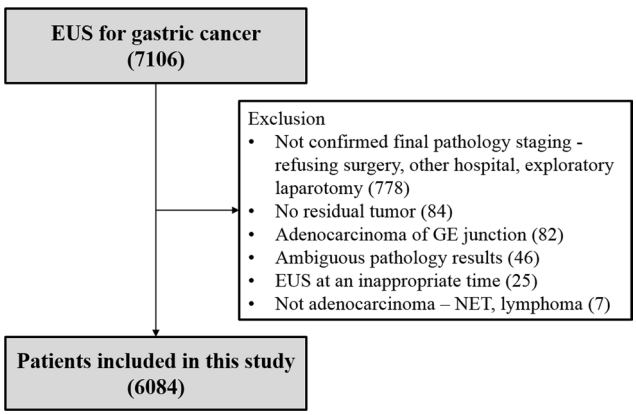

Fig. 1 Flow diagram of the study. *EUS* endoscopic ultrasonography, *GE* gastroesophageal, *NET* neuroendocrine tumor

Histopathology

Histopathological evaluation was performed by sections of 2 mm thickness for endoscopic resection, and 4 mm thickness for surgical resection stained with hematoxylin and eosin. Well- or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma was classified as differentiated type, whereas poorly cohesive carcinoma, poorly differentiated tubular adenocarcinoma, or mucinous adenocarcinoma was categorized as undifferentiated type. T1b was divided into sm1, which was submucosal layer < 500 μm from the muscularis mucosa, and sm2 over 500 μm. Final histopathological result was categorized into three groups after ESD: within absolute indication, within expanded criteria, and beyond expanded criteria [20] (Figs. 2, 3, 4).

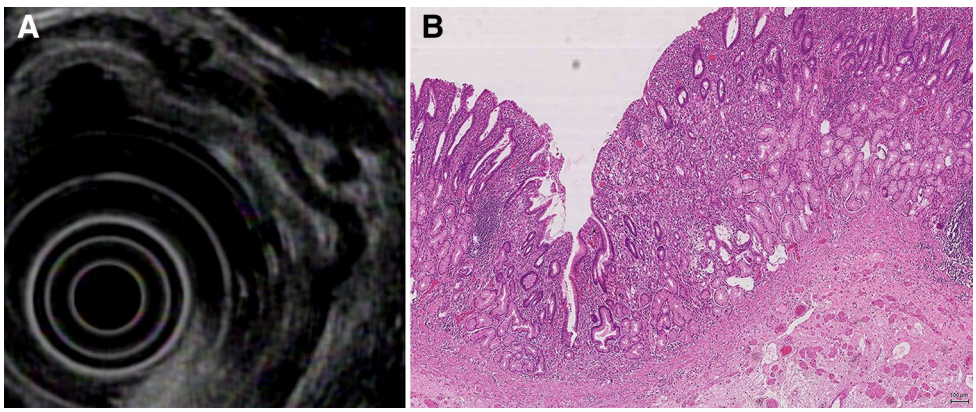

Fig. 2 Gastric cancer, mucosal invasion. **A** Radial echoendoscope reveals thickening of the 1st and 2nd layer, whereas there is no change in the thickness of the third layer. **B** Histological examination after surgical resection shows a poorly cohesive carcinoma confined to the mucosa; scale bar = 100 μm

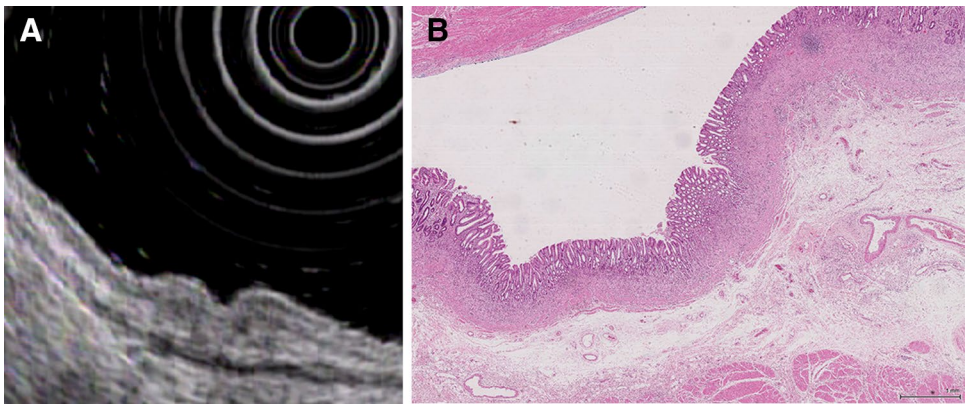

Fig. 3 Gastric cancer, submucosal invasion. **A** Radial echoendoscope reveals irregular, diffuse thickening of the 2nd layer and the interruption of the submucosa due to cancer invasion. **B** Histological examination after surgical resection shows that the tumor had invaded the submucosal layer; scale bar = 1 mm

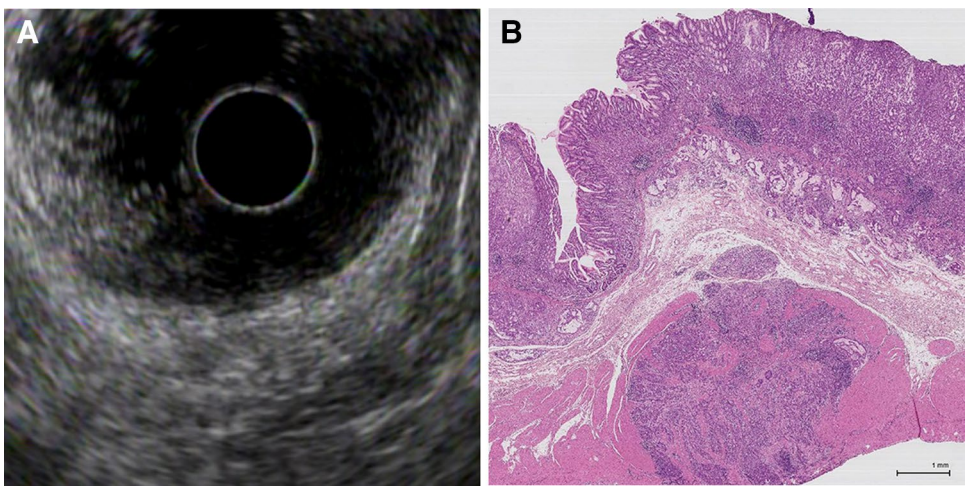

Fig. 4 Gastric cancer, invasion up to muscularis propria. **A** Radial echoendoscope reveals complete destruction of the submucosa, and the distinction between the mucosa, submucosa, and muscularis propria is obscured. **B** Histological examination after surgical resection shows that the tumor had invaded the muscularis propria; scale bar = 1 mm

Statistical analysis

EUS T stage was compared with histopathological T stage as a gold standard. The diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for T1a and EGC were calculated using standard definitions. We also evaluated the accuracy of EUS according to ESD indications. The absolute indications were mucosal cancer, differentiated-type adenocarcinoma, ulcer (−), and ≤ 2 cm in diameter. The expanded criteria were (1) mucosal cancer, differentiated-type adenocarcinoma, ulcer (−), and any tumor size; (2) mucosal cancer, differentiated-type adenocarcinoma, ulcer (+), and ≤ 3 cm in size. The χ^2 test was used to compare the accuracy of miniprobe EUS with conventional EUS, and multivariable logistic regression was used to evaluate the factors affecting EUS accuracy. The factors affecting overestimation and underestimation of T staging were evaluated. The correctly identified group was compared with the overestimated group, and the correctly identified group with the underestimated group. We calculated the odds ratio (OR) and associated 95% CI. All tests for significance were two-tailed, and *P* values below 0.05 denoted statistical significance. Analyses were performed using the Statistical Package for the Social Sciences, version 23.0 (SPSS 23.0K for windows SPSS Korea, Seoul, Korea).

Results

Baseline characteristics

A total of 6084 patients were finally analyzed. The mean age of the patients was 60.7 year (mean, 60.7 ± 11.5), and the proportion of male was 66.7%. The mean tumor diameter was 2.9 cm (mean, 2.9 ± 2.2), and ulcer was accompanied in 22.9%. In final pathological diagnosis, EGC was diagnosed in 79.2% and AGC in 20.8%, and differentiated histology in 58.6% and undifferentiated histology in 41.4%. ESD was initially performed in 27.4% of the patients, in whom 7.3% of the patients had undergone additional surgery by beyond expanded criteria of ESD in pathological result (Table 1).

Table 1 Clinical characteristics of 6084 patients with gastric cancer

	N	%
Sex		
M	4059	66.7
F	2025	33.3
Age, mean (SD) (years)	60.7 (11.5)	
BMI, mean (SD) (kg/m^2)	24.0 (3.0)	
Location		
Upper third	633	10.4
Middle third	1562	25.7
Lower third	3395	55.8
Size, mean (SD) (cm)	2.9 (2.2)	
≤ 2.0 cm	2601	42.8
> 2.0 cm	3483	57.2
Gross type		
I	127	2.1
IIa	617	10.1
IIb	752	12.4
IIc	3264	53.6
III	58	1.0
AGC	1266	20.8
Ulcer		
No ulcer	4688	77.1
Ulcer present	1396	22.9
Differentiation		
Differentiated	3563	58.6
Undifferentiated	2521	41.4
Treatment		
ESD	1545	25.4
Surgery	4418	72.6
Surgery after ESD	121	2.0
EUS type		
Radial echoendoscope	4760	78.2
Miniprobe	1324	21.8

SD standard deviation, *ESD* endoscopic submucosal dissection, *AGC* advanced gastric cancer

Accuracy rates of EUS for T staging of gastric cancer

The accuracy, sensitivity, specificity, PPV, and NPV for T1a were 75.0, 67.4, 82.5, 79.4, and 71.7%, respectively. The accuracy, sensitivity, specificity, PPV, and NPV for EGC were 89.4, 94.0, 72.0, 92.8, and 75.9%, respectively. The overall accuracy of T staging by EUS was 66.3% (4032/6084) when divided by T1a, T1b, and over T2 (Table 2). The accuracy of T1a was 75.1% in differentiated lesion ≤ 2 cm without ulcer and 73.1% in differentiated lesion any size without ulcer or differentiated lesion ≤ 3 cm with ulcer, respectively (Table 3).

In the patients of T1a who were overestimated as T1b or more by EUS ($n = 991$), 215 patients showed the final pathological result within the absolute ESD indication, accounting for 7.0% (215/3043) of pathologic T1a. In the patients of T1b or more who were underestimated as T1a by with EUS ($n = 532$), 57.0% ($n = 303$) of the patients had received ESD, in whom 33.7% ($n = 102$) of the patients had additional surgical resection.

Table 2 Accuracy rates for T staging by endoscopic ultrasonography

	T stage by EUS			T stage by EUS	
	T1a	T1b-T4b		EGC	AGC
Pathologic stage			Pathologic stage		
T1a	2052	991	EGC	4529	289
T1b-T4b	532	2509	AGC	354	912
Overall accuracy	75.0%		Overall accuracy	89.4%	
T1a sensitivity	67.4 (65.7–69.1)		EGC sensitivity	94.0 (93.3–94.7)	
T1a specificity	82.5 (81.1–83.8)		EGC specificity	72.0 (69.5–74.5)	
T1a PPV	79.4 (78.1–80.7)		EGC PPV	92.8 (92.1–93.3)	
T1a NPV	71.7 (70.6–72.8)		EGC NPV	75.9 (73.7–78.0)	

EUS endoscopic ultrasonography, *EGC* early gastric cancer, *AGC* advanced gastric cancer, *PPV* positive predictive value, *NPV* negative predictive value

Table 3 Subgroup analysis: accuracy rates for T staging according to ESD indication

Histology	Ulcer (−)				Ulcer (+)			
	≤ 20 mm		> 20 mm		≤ 30 mm		> 30 mm	
Differentiated	T stage by EUS		T stage by EUS		T stage by EUS		T stage by EUS	
Pathologic stage	T1a	T1b-T4	T1a	T1b-T4	T1a	T1b-T4	T1a	T1b-T4
T1a	1052	215	368	278	48	23	7	10
T1b-T4	203	206	127	527	24	161	2	312
Accuracy	75.1% (1258/1676)		68.8% (895/1300)		81.6% (209/256)		96.4% (319/331)	
Undifferentiated	T stage by EUS		T stage by EUS		T stage by EUS		T stage by EUS	
Pathologic stage	T1a	T1b-T4	T1a	T1b-T4	T1a	T1b-T4	T1a	T1b-T4
T1a	334	149	225	250	15	34	3	32
T1b-T4	69	159	76	450	21	220	10	474
Accuracy	69.3% (493/711)		67.4% (675/1001)		81.0% (235/290)		91.9% (477/519)	

ESD, endoscopic submucosal dissection, *EUS* endoscopic ultrasonography

Accuracy rates for T staging by miniprobe and conventional EUS

The overall accuracy was significantly higher in miniprobe EUS than conventional EUS (81.0 vs. 62.2%, $p < 0.001$) when divided by T1a, T1b, and over T2. The overall accuracy was significantly higher in miniprobe EUS than conventional EUS for lesion ≤ 2 cm (84.5 vs. 61.6%, $p < 0.001$), or 2 cm < lesion ≤ 3 cm (74. 6 vs. 59.0%, $p < 0.001$). There was no significant difference in accuracy between miniprobe EUS and conventional EUS for lesions > 3 cm (69.6 vs. 64.4%, $p = 0.189$) (Table 4). The accuracy EGC with lesion > 2 cm in conventional EUS was 83.2%.

Associated factors affecting the accuracy of T staging by EUS

The characteristics of the overestimated and the underestimated group were compared with those of the correctly predicted group. In multivariate logistic regression analysis, the overestimation in pathologic T1a was significantly associated with presence of ulcer, location at upper third, elevated or depressed type, large tumor size, and radial EUS (Table 5). In pathologic T1b, presence of ulcer, tumor size > 3 cm, and radial EUS were significantly associated with overestimation, and flat type, tumor size ≤ 2 cm, and miniprobe EUS with underestimation (Table 6). In AGC, tumor size ≤ 2 cm and miniprobe EUS were significantly associated with underestimation in T staging (Table 7).

Discussion

Prediction of T stage has been more important with increased early detection of gastric cancer by national cancer screening program and the expansion of the indication of endoscopic resection and minimally invasive surgery in Korea. As the indication of endoscopic resection and minimally invasive surgery is usually decided by T stage, depth of tumor invasion has been the key to determine the treatment modality. Although CT scan has been conventionally used for TNM staging of gastric cancer, CT has showed

Table 4 Accuracy rates for T staging by miniprobe EUS and conventional EUS

	Miniprobe EUS			Conventional EUS			*p* Value
	T1a	T1b	T2-T4b	T1a	T1b	T2-T4b	
≤ 2.0 cm							
Pathologic stage							
T1a	776	11	0	651	367	17	
T1b	133	14	0	157	339	32	
T2-T4b	0	1	0	10	56	37	
Overall accuracy	84.5%			61.6%			< 0.001
2.0–3.0 cm							
Pathologic stage							
T1a	165	3	0	210	241	17	
T1b	51	5	0	58	284	50	
T2-T4b	2	2	0	10	82	166	
Overall accuracy	74.6%			59.0%			< 0.001
> 3.0 cm							
Pathologic stage							
T1a	104	9	0	146	279	47	
T1b	36	7	0	64	420	126	
T2-T4b	2	2	1	9	178	708	
Overall accuracy	69.6%			64.4%			0.189

EUS endoscopic ultrasonography

Table 5 Associated factors for overestimation of T staging in pathologic T1a

Variables	Multivariate OR	95% CI	*p* Value
Ulcer			
Ulcer −	1 (reference)		
Ulcer +	2.116	1.409–3.177	0.000
Location			0.001
Upper	1 (reference)		
Middle	0.462	0.309–0.691	0.000
Lower	0.520	0.355–0.763	0.001
Gross type			0.000
IIb	1 (reference)		
IIa	2.030	1.376–2.995	0.000
IIc	2.306	1.760–3.023	0.000
I	7.583	3.323–17.304	0.000
III	5.094	1.281–20.263	0.021
Tumor size			0.000
≤ 2.0 cm	1 (reference)		
2.0–3.0 cm	1.923	1.530–2.417	0.000
> 3.0	4.003	3.112–5.148	0.000
EUS type			
Conventional	1 (reference)		0.000
Miniprobe	0.024	0.016–0.038	

EUS endoscopic ultrasonography

low diagnostic accuracy in T staging [21]. Moreover, CT cannot discriminate the depth of tumor invasion between mucosa and submucosa, or submucosa and muscularis propria, which is indispensable for the decision of treatment modality for gastric cancer.

EUS has been used for the staging of gastric cancer, especially T staging. Although previous studies have shown the clinical efficacy of EUS in T staging of gastric cancer, the results have been conflicting. In this study, the overall accuracy was 66.3% when divided into T1a, T1b, and over T2. However, the accuracy rates of T1a and EGC including T1a and T1b were 75.0% and 89.4%, respectively. The accuracy rates for T1a with lesion ≤ 2 cm in miniprobe EUS and EGC with lesion > 2 cm in conventional EUS were 84.6 and 83.2%, respectively. Also, the accuracy of T1a was 75.1% in differentiated lesion ≤ 2 cm without ulcer and 73.1% in differentiated lesion any size without ulcer or differentiated lesion ≤ 3 cm with ulcer. However, most patients with pathological T1a who were overestimated as T1b or more by EUS escaped the absolute indication of ESD. The patients accounted for only 7.0% ($n = 215$) in pathologic T1a who were expected to have a treatment plan changed from ESD to surgery due to overestimation of EUS in mucosal cancer. In addition, the proportion of additional surgery was minimal after ESD by underestimation of EUS in the patients with pathological T1b or more, which showed that EUS was helpful in determining the treatment modality with the high accuracy

Table 6 Associated factors for overestimation and underestimation of T staging in pathologic T1b

Variables	Overestimation multivariate OR	95% CI	*p* Value	Underestimation multivariate OR	95% CI	*p* Value
Ulcer						
Ulcer −	1 (reference)			1 (reference)		
Ulcer +	3.356	2.110–5.340	0.000	0.797	0.436–1.458	0.462
Gross type			0.000			0.000
IIb	1 (reference)			1 (reference)		
IIa	1.657	0.806–3.408	0.170	0.293	0.176–0.489	0.000
IIc	1.408	0.734–2.702	0.303	0.420	0.284–0.621	0.000
I	4.738	2.149–10.447	0.000	0.138	0.046–0.415	0.000
III	3.360	1.329–8.492	0.010	0.000	0.000	0.998
Tumor size			0.002			0.000
≤2.0 cm	1 (reference)			1 (reference)		
2.0–3.0 cm	1.621	0.997–2.634	0.051	0.522	0.372–0.723	0.000
> 3.0	2.979	1.947–4.558	0.000	0.360	0.262–0.495	0.000
EUS type						
Conventional	1 (reference)			1 (reference)		
Miniprobe	0.000	–	0.000	31.204	20.022–48.632	0.000

EUS endoscopic ultrasonography

Table 7 Associated factors for underestimation of T staging in pathologic AGC

Variables	Multivariate OR	95% CI	*p* Value
Ulcer			
Ulcer −	1 (reference)		
Ulcer +	0.712	0.489–1.036	0.076
Tumor size			0.000
≤2.0 cm	1 (reference)		
2.0–3.0 cm	0.313	0.194–0.504	0.000
> 3.0	0.141	0.091–0.219	0.000
EUS type			
Conventional	1 (reference)		
Miniprobe	22.174	2.736–179.730	0.004

EUS endoscopic ultrasonography, *AGC* advanced gastric cancer

of 84.6% for T1a in lesion ≤2 cm in miniprobe EUS and 83.2% for EGC in lesion > 2 cm in conventional EUS.

The accuracy was 66.3% when divided by T1a, T1b, and over T2, which was lower than 67–82% reported in previous studies [9, 14–19]. However, the accuracy in the previous studies was not the results between T1a and T1b, but mucosa/sm1 and sm2, and the results of EUS were retrospectively reviewed by still images [16, 17]. Moreover, most of the studies were conducted only on EGC with small sample size. In other studies in which real-time diagnosis was performed like our study, the accuracy of EUS was 45–67% [15, 22, 23], which was similar to the accuracy of this study.

It has been reported that the accuracy of EUS tended to decline for the lesions with ulcer [9, 14, 17, 19], location in the upper third [9], large tumor size [9, 14, 19], and radial EUS [14]. In this study as well, these factors also affected the overestimation of pathologic T1a. It is difficult to differentiate whether ulcer is invaded by tumor or thickened by fibrosis. Thin submucosal layer and prominent vasculature can be the factors by which it is difficult to evaluate submucosal tumor invasion in the upper third [17]. In addition, it is difficult to fill the deaerated water and locate the EUS probe close to the lesion because of the angulation of the EUS scope [22].

Several studies have suggested that EUS was not helpful because the accuracy of EUS was not superior to that of EGD in predicting T stage [9, 14–17]. In the studies which compared EGD with EUS in the accuracy of T stage focusing on the distinction between T1a and T1b, the criteria for T stage in EUS were relatively objective, but were rarely presented objectively in EGD. There was an attempt to distinguish between T1a and T1b with endoscopic objective criteria. The results showed that irregular surface, submucosal tumor-like marginal elevation [16], tumor size more than 30 mm, remarkable redness, uneven surface, margin elevation [24], irregular/nodular surface fusion, abrupt cutting, and clubbing of converging fold [25] were associated with T1b rather than T1a. However, the endoscopic findings that can distinguish between T1b and T2 or T2 and T3 have not been yet fully elucidated. As the indications for laparoscopic and robot-assisted surgery have been expanded, preoperative T staging has been important for decision of treatment strategy. EUS may present more accurate T staging based on objective criteria.

In the case of underestimation, additional surgery after ESD is indispensable. However, unnecessary surgical resection may be an overtreatment in the case of overestimation. As the accuracy of T1b has been reported to be lower than that of T1a in EGD [25, 26], further study comparing EGD and EUS focusing on T1b will be helpful to confirm the role of EUS in determining the treatment strategy of EGC.

This study has several advantages. First, all cases with the diagnosis of gastric cancer were included during the study period irrespective of staging and tumor differentiation. Second, large sample size was enrolled in our study. Last, the factors affecting overestimation and underestimation were analyzed among T1a, T1b, and T2 or more.

The limitation of this study was that EGD findings might affect EUS results because the endoscopists were not blinded to the EGD findings. However, EUS result was not affected by EGD finding in the case over T1b because EGD could not differentiate the stage of tumor over T1b.

In conclusion, EUS was useful in determining treatment strategy of gastric cancer by differentiating T1a from T1b with the accuracy of 84.6% in lesion ≤ 2 cm in miniprobe EUS and T1 from T2 or more with the accuracy of 83.2% in lesion > 2 cm in conventional EUS, respectively. Overestimation or underestimation should be carefully considered in the case with ulcer, large tumor size, and the location of upper third.

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Compliance with ethical standards

Disclosures Jung Kim, Sang Gyun Kim, Hyunsoo Chung, Joo Hyun Lim, Ji Min Choi, Jae Yong Park, Hyo-Joon Yang, Seung Jun Han, Sooyeon Oh, Min Seong Kim, Hyun Ju Kim, Hyoungju Hong, Hee Jong Lee, Jue Lie Kim, Eunwoo Lee, and Hyun Chae Jung have no conflicts of interest or financial ties to disclose.

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