Transabdominal Ultrasonography for Assessing the Depth of Tumor Invasion in Gastric Cancer

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ABSTRACT

Background Although endoscopy and endoscopic ultrasonography are generally used to diagnose the depth of gastric tumor invasion, endoscopy is invasive and frequently results in patient discomfort. Transabdominal ultrasonography (TUS) is noninvasive and may be useful in determining this depth. We investigated the usefulness of TUS in determining the depth of tumor invasion in patients with gastric cancer.

Methods This retrospective study included 190 patients with gastric cancer and 200 lesions who underwent curative resection at the Department of Gastrointestinal Surgery of Tottori University Hospital from July 2007 to July 2015. The results of conventional diagnostic imaging and TUS were compared with those of pathological analysis obtained after surgery. Furthermore, the ruptured form of the third layer on TUS imaging was reviewed and investigated to differentiate between the SM2 and MP lesions.

Results The accuracy of TUS was similar to that of conventional diagnostic imaging for all depths of tumor invasion. Eight lesions could not be assessed by TUS, including four that could not be identified and four in which TUS was unable to diagnose the depth. In cases where the ruptured form of the third layer could be determined in MP lesions, the forms were observed toward the inside of the gastric lumen.

Conclusion The results of this study suggested that the accuracy of TUS was equivalent to that of conventional diagnostic imaging in determining the depth of tumor invasion. TUS assessment criteria may be useful to classify this depth. Furthermore, the ruptured form of the third layer is believed to be important in distinguishing between early and advanced gastric cancer.

Key words depth of tumor invasion; endoscopic ultrasonography; gastric cancer; ruptured form of the third layer; transabdominal ultrasonography

Determining the staging of gastric cancer is important when selecting treatment methods. In particular, preoperative assessment of the depth of tumor invasion within the gastric wall is necessary to determine whether patients with gastric cancer require endoscopic therapy, modified surgery, or standard gastrectomy.[1] Conventional diagnostic imaging methods, including endoscopy, endoscopic ultrasonography (EUS), upper gastrointestinal series, computed tomography (CT) and magnetic resonance imaging (MRI), have been considered as useful modalities for the preoperative staging of gastric cancer.[2–4] EUS is currently regarded as the most reliable method for assessing the depth of tumor invasion within the gastric wall, with a high rate of accuracy in staging early gastric cancer.[5] However, it is invasive and causes patient discomfort, preventing repeat endoscopic examinations.

Transabdominal ultrasonography (TUS) is a noninvasive procedure that can be frequently performed. Recently, TUS has been recognized as a diagnostic modality for patients with gastrointestinal disorders[6–8] and has been used to assess gastric wall thickness and for the preoperative staging of gastric cancer.[9–12] Ishigami et al.[13] reported the usefulness of TUS in early gastric cancer but not in advanced gastric cancer and did not demonstrated the details of TUS imaging. Although the use of TUS to preoperatively diagnose the depth of tumor invasion may benefit patients, few reports have investigated its ability of determining the depth in detail in patients with gastric cancer. Therefore, this study was designed to investigate the details of TUS imaging and its usefulness in preoperatively determining the depth of tumor invasion in all stages of gastric cancers.

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Received 2017 May 31
Accepted 2017 July 12

Abbreviations: CT, computed tomography; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; M, mucosa; MP, muscularis propria; MRI, magnetic resonance imaging; SE, serosa; SM1, tumor invasion within 0.5 mm of the muscularis mucosae; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; SS, subserosa; TUS, transabdominal ultrasonography

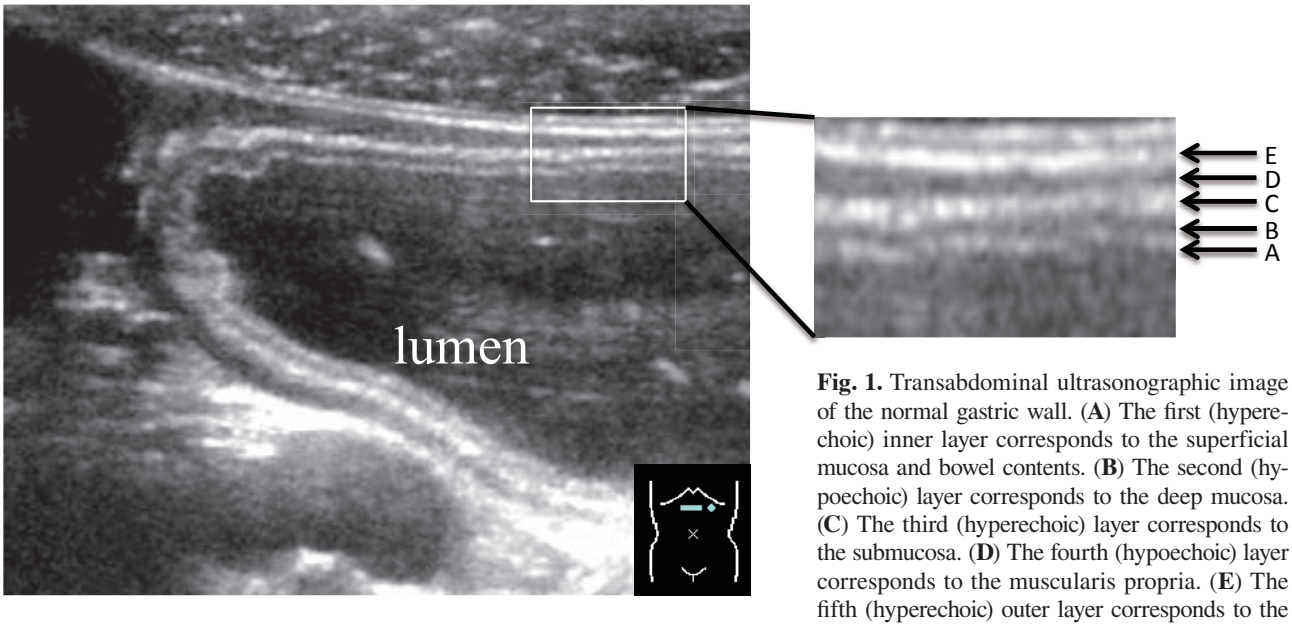

Fig. 1. Transabdominal ultrasonographic image of the normal gastric wall. (**A**) The first (hyperechoic) inner layer corresponds to the superficial mucosa and bowel contents. (**B**) The second (hypoechoic) layer corresponds to the deep mucosa. (**C**) The third (hyperechoic) layer corresponds to the submucosa. (**D**) The fourth (hypoechoic) layer corresponds to the muscularis propria. (**E**) The fifth (hyperechoic) outer layer corresponds to the subserosal fat and serosa.

SUBJECTS AND METHODS

Patients

This retrospective study included 190 patients with gastric cancer and 200 lesions who underwent curative resection at the Department of Gastrointestinal Surgery of Tottori University Hospital from July 2007 to July 2015. Of the 190 patients, 15 (12 male, 3 female) had epigastric operation scar. Patients with transverse colon at the front of the stomach were excluded from this study because the stomach could not be detected by TUS examination. All patients underwent conventional preoperative diagnostic imaging, including endoscopy, EUS, upper gastrointestinal series, CT and/or MRI, for the staging of gastric cancer. EUS analysis of the depth of tumor invasion within the gastric wall was performed in all patients with early gastric cancer but in only some of those with advanced gastric cancer. The depth of tumor invasion in all other patients with advanced gastric cancer was evaluated by other conventional diagnostic imaging methods.

TUS

TUS was performed by one examiner who had over 25 years of experience in ultrasonographic examinations. Most patients underwent TUS after information about the characteristics of gastric cancer, including the location and size, was obtained. When possible, patients underwent TUS in a fasted state. They were seated and administered 150–200 mL of boiled water before undergoing TUS using an SSA-790A and a TUS-A500 ultrasound unit (Toshiba Medical Systems, Tochigi, Japan) with a 3.75-MHz center frequency convex (PVT-375BT) or a 7.5-MHz center frequency linear (PLT-704SBT) transducer or using an EUB-7500 ultrasound unit (Hitachi Aloka Medical, Tokyo, Japan) with a 3.0-MHz convex (EUP-C715) or a 6.5-MHz linear (EUP-L73S) transducer.

Based on TUS imaging, the normal structure of the gastric wall comprises five layers.[14–17] The first (hyperechoic) inner layer corresponds to the superficial mucosa and the bowel contents, the second (hypoechoic) layer corresponds to the deep mucosa, the third (hyperechoic) layer corresponds to the submucosa, the fourth (hypoechoic) layer corresponds to the muscularis propria and the fifth (hyperechoic) outer layer corresponds to the subserosal fat and serosa (Fig. 1).

EUS and TUS categorizations of tumor depth have been previously described.[4, 5, 10–12, 18] Referring to our experience and previous studies, the TUS assessment in the present study was performed for lesions in each layer based on the following characteristics: M, tumors located in the first and second layers, with an intact third layer (Fig. 2); SM1, tumors that reached the third layer, causing thinning and a lack of distinct borders (Fig. 3); SM2, tumors that occupied the third layer or caused depressions of depth ≥ 1 mm to the third layer (Fig. 4); MP, tumors that reached the fourth layer, with an intact fifth layer (Fig. 5); SS, tumors that reached the fifth layer, which showed irregularities inside (Fig. 6); and SE, tumors that reached the fifth layer, which showed irregularities throughout (Fig. 7).

Preoperative assessments of the depth of tumor

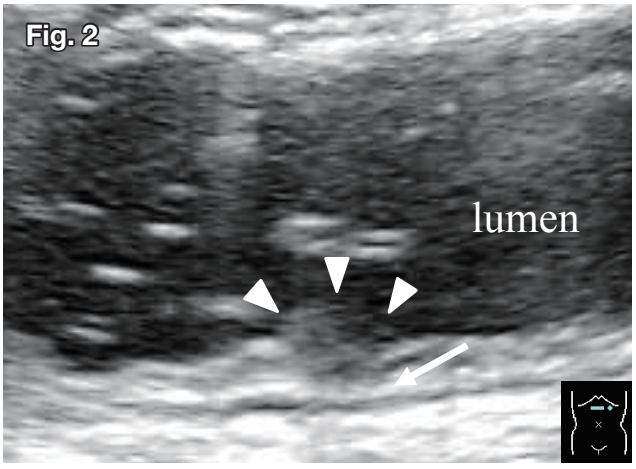

Fig. 2. Tumor (*arrowheads*) located in the first and second layers. The third layer (*arrow*) was intact. These findings suggested that the depth of tumor invasion was M. M, mucosa.

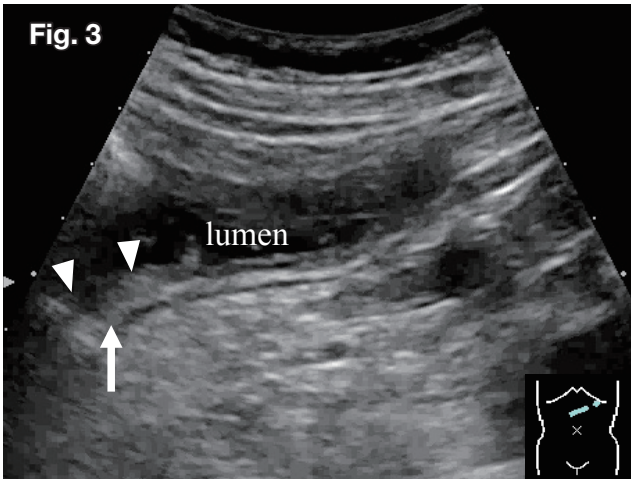

Fig. 3. Tumor (*arrowheads*) reaching the third layer and causing thinning and a lack of distinct borders (*arrow*). These findings suggested that the depth of tumor invasion was SM1. SM1, tumor invasion within 0.5 mm of the muscularis mucosae.

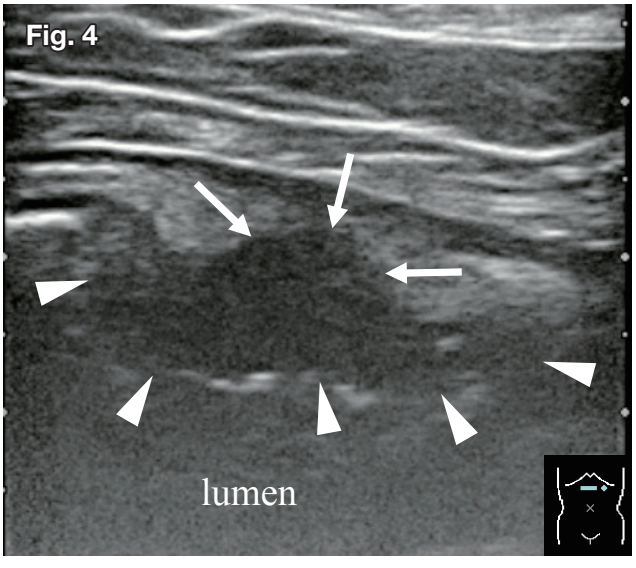

Fig. 4. Tumor (*arrowheads*) occupying the third layer or causing depressions ≥ 1 mm to the third layer (*arrow*). These findings suggested that the depth of tumor invasion was SM2. SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae.

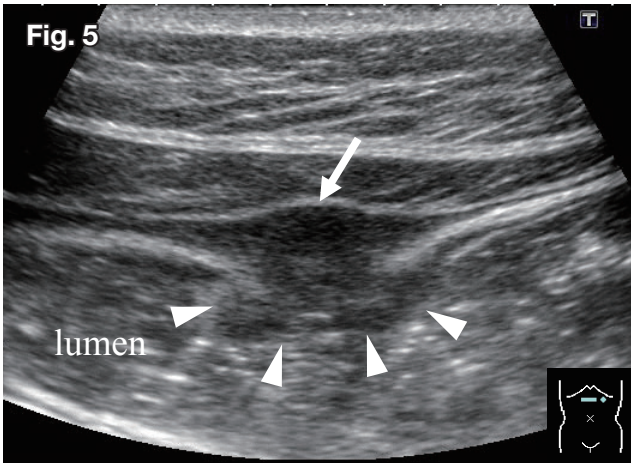

Fig. 5. Tumor (*arrowheads*) occupying the fourth layer, whereas the fifth layer (*arrow*) was intact. These findings suggested that the depth of tumor invasion was MP. MP, muscularis propria.

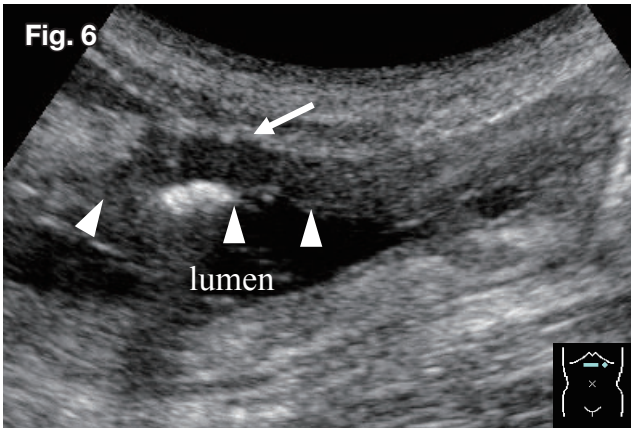

Fig. 6. Tumor (*arrowheads*) reaching the fifth layer and becoming irregular inside the fifth layer (*arrow*). These findings suggested that the depth of tumor invasion was SS. SS, subserosa.

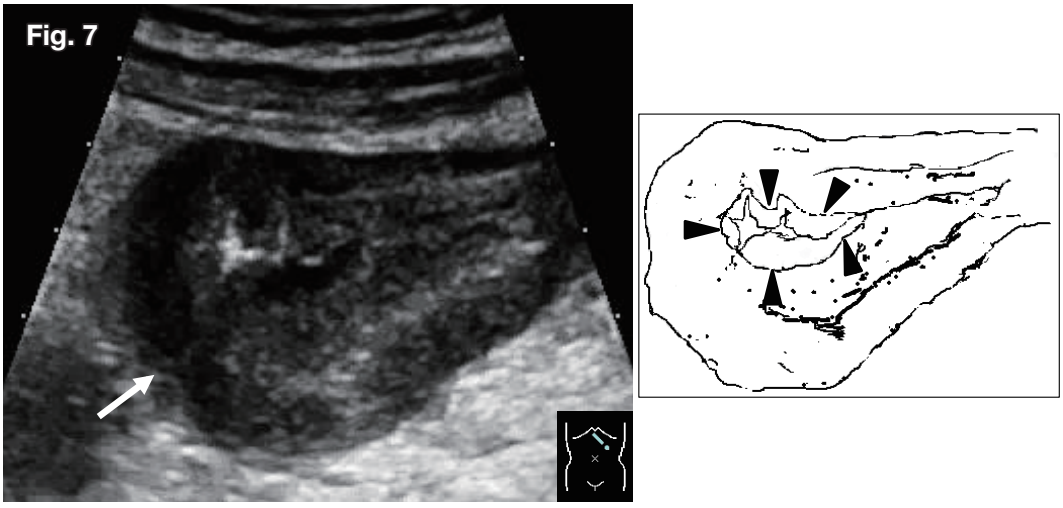

Fig. 7. Tumor reaching the fifth layer and becoming unclear throughout the entire fifth layer (*arrow*). *Arrowheads* indicated the range of the lumen. These findings suggested that the depth of tumor invasion was SE. SE, serosa.

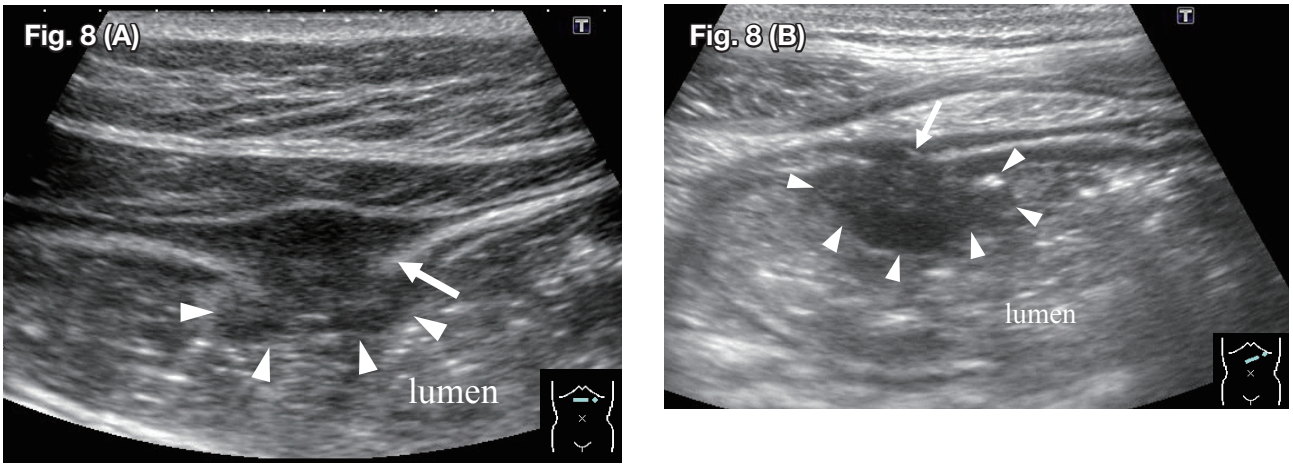

Fig. 8. (**A**) The ruptured form of the third layer was observed toward the inside of the gastric lumen (*arrow*). This finding suggested that the depth of tumor invasion was MP. (**B**) The ruptured form of the third layer was observed toward the outside of the lumen (*arrow*). This finding suggested that the depth of tumor invasion was SM2. *Arrowheads* indicated the range of the tumor. MP, muscularis propria. SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae.

invasion by conventional diagnostic imaging and TUS were compared with the results of pathological examinations, as classified according to the TNM criteria of the Japanese Classification of Gastric Carcinoma.[19] According to this pathological criteria, M is defined as tumor invasion confined to the mucosa, SM1 as tumor invasion ≤ 0.5 mm into the muscularis mucosae, SM2 as tumor invasion > 0.5 mm into the muscularis mucosae, MP as tumor invasion of the muscularis propria, SS as tumor invasion of the subserosa, and SE as tumor invasion contiguous to or penetrating the serosa and exposed to the peritoneal cavity.

Ruptured forms of the third layer based on TUS

Furthermore, we reviewed and investigated the ruptured forms of the third layer and established new diagnostic criteria for these layers based on TUS imaging. The ruptured form of the third layer was referred to as SM2 when observed to be toward the outside of the gastric lumen and as MP when observed toward the inside (Fig. 8). Based on these criteria, all 78 cases diagnosed pathologically with SM2 and MP lesions were reviewed and examined.

Statistical analysis

Based on pathologic results, the sensitivity, specificity, and accuracy of conventional imaging and TUS were calculated. Statistical analysis was performed using the SPSS Statistics 23 software (IBM, Tokyo, Japan). The correlation between the diagnostic accuracy of TUS and

location of the tumors was analyzed using the χ^2 test. P values of < 0.05 were considered statistically significant.

This study was approved by the Ethics Committee of the Tottori University Faculty of Medicine (approval number 1509A041).

RESULTS

Table 1 shows the characteristics of the enrolled patients. The median age of these patients was 69 years (mean, 68.1 ± 10.4 years; range, 35–86 years). Of the 190 patients, 134 (70.5%) were male and 56 (29.5%) were female, with a male:female ratio of 2.4:1 (134:56). Of the 200 lesions evaluated, 39 (19.5%) were located in the upper third of the stomach, 94 (47%) in the middle third and 62 (31%) in the lower third (Table 2). Cross-sectional assessment showed that 86 lesions (43%) were located in the lesser curvature, 25 (12.5%) in the greater curvature, 45 (22.5%) in the anterior wall, 25 (12.5%) in the posterior wall and 19 (9.5%) had circumferential involvement.

On pathologic assessment, the depth of tumor invasion was classified as M for 49 lesions (24.5%), SM1 for 6 (3%), SM2 for 52 (26%), MP for 28 (14%), SS for 41 (20.5%) and SE for 24 (12%). The correlation between the diagnostic accuracy of TUS and longitudinal and cross-sectional locations was not statistically significant ($P = 0.72$, $P = 0.45$, respectively).

Conventional diagnostic imaging showed a sensitivity, specificity and accuracy in diagnosing the depth of tumor invasion within the gastric wall of 40.8%, 96.7% and 83.0%, respectively, for M; 50.0%, 85.1% and 84.0%, respectively, for SM1; 59.6%, 84.5% and 78.0%, respectively, for SM2; 50.0%, 83.1% and 78.5%, respectively, for MP; 12.2%, 95.6% and 78.5%, respectively, for SS; and 54.2%, 86.9% and 83.0%, respectively, for SE lesions (Table 3).

TUS imaging showed a sensitivity, specificity and accuracy in diagnosing the depth of tumor invasion of 26.5%, 96.0% and 79.0%, respectively, for M; 50.0%, 80.9% and 80.0%, respectively, for SM1; 57.7%, 79.7% and 74.0%, respectively, for SM2; 46.4%, 83.7% and 78.5%, respectively, for MP; 36.6%, 87.4% and 77.0%, respectively, for SS; and 41.7%, 85.2% and 80.0%, respectively, for SE lesions (Table 4).

These results suggested that the accuracy of TUS was equivalent to that of conventional diagnostic imaging in determining the depth of tumor invasion. However, of eight lesions diagnosed unclear by TUS, four lesions could not be identified because they were small and present within mucosal lesions. Furthermore, TUS could not diagnose the depth of tumor invasion of four lesions: three because food residue prevented clear visualization and one because the tumor was located in the posterior wall of the upper stomach.

In addition, we examined the ruptured form of the third layer for 78 lesions diagnosed pathologically as SM2 and MP. The ruptured form had a sensitivity, specificity and accuracy in diagnosing the depth of tumor invasion of 52.9%, 100% and 69.2%, respectively, for SM2 and 66.7%, 96.1% and 85.9%, respectively, for MP lesions (Table 5). In cases where the ruptured form of the third layer could be determined in MP lesions, the forms were observed toward the inside of the gastric lumen. As a result, the accuracy rate of MP lesions was considered to be better when the ruptured form of the third layer was added to the TUS diagnostic criteria.

Table 1. Patient characteristics

N	190
Age (years)	
Mean ± SD	68.1 ± 10.1
Median (range)	69.0 (35-86)
Sex, *n* (%)	
Male: n	134 (70.5)
Female: *n*	56 (29.5)
Epigastric operation scar	
Present: *n* (%)	15 (7.9)
Absent: *n* (%)	175 (92.1)

Table 2. Characteristics of gastric cancer lesions

N	200
Tumor size (mm)	
Mean ± SD	28.3 ± 19.9
Median (range)	21.0 (3.5–104)
Longitudinal location, *n* (%)	
Upper third	39 (19.5)
Middle third	94 (47.0)
Lower third	62 (31.0)
Cross-sectional location, *n* (%)	
Lesser curvature	86 (43.0)
Greater curvature	25 (12.5)
Anterior wall	45 (22.5)
Posterior wall	25 (12.5)
Circumferential involvement	19 (9.5)
Pathological depth, *n* (%)	
M	49 (24.5)
SM1	6 (3.0)
SM2	52 (26.0)
MP	28 (14.0)
SS	41 (20.5)
SE	24 (12.0)

M, mucosa; MP, muscularis propria; SE, serosa; SM1, tumor invasion within 0.5 mm of the muscularis mucosae; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; SS, subserosa.

Table 3. Preoperative diagnosis by conventional diagnostic imaging and pathological results

Conventional imaging		Pathological depth					
		M	SM1	SM2	MP	SS	SE
EUS	M	20	0	3	1	0	0
	SM1	17	3	10	1	0	0
	SM2	9	3	31	6	4	0
Other imaging	MP	2	0	7	14	13	6
	SS	0	0	0	4	5	3
	SE	1	0	1	2	19	13
	SI	0	0	0	0	0	2

	Sensitivity (%)	Specificity (%)	Accuracy (%)
M	40.8	96.7	83.0
SM1	50.0	85.1	84.0
SM2	59.6	84.5	78.0
MP	50.0	83.1	78.5
SS	12.2	95.6	78.5
SE	54.2	86.9	83.0

EUS, endoscopic ultrasonography; M, mucosa; MP, muscularis propria; SE, serosa; SI, tumor invades adjacent structures; SM1, tumor invasion within 0.5 mm of the muscularis mucosae; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; SS, subserosa.

Table 4. Preoperative diagnosis by TUS and pathological results

TUS imaging		Pathological depth					
		M	SM1	SM2	MP	SS	SE
TUS	M	13	0	3	1	0	0
	SM1	16	3	9	3	1	0
	SM2	12	3	30	4	3	1
	MP	0	0	8	13	7	6
	SS	1	0	1	4	15	6
	SE	1	0	0	2	15	10
	SI	0	0	0	0	0	1
	Unclear	6	0	1	1	0	0

	Sensitivity (%)	Specificity (%)	Accuracy (%)
M	26.5	96.0	79.0
SM1	50.0	80.9	80.0
SM2	57.7	79.7	74.0
MP	46.4	83.7	78.5
SS	36.6	87.4	77.0
SE	41.7	85.2	80.0

M, mucosa; MP, muscularis propria; SE, serosa; SI, tumor invades adjacent structures; SM1, tumor invasion within 0.5 mm of the muscularis mucosae; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; SS, subserosa; TUS, transabdominal ultrasonography.

Table 5. Ruptured form of the third layer by TUS and pathological results

Ruptured form of the third layer	Pathological depth	
	SM2	MP
Outside	27	0
Inside	2	18
Unclear	22	9
Sensitivity (%)	52.9	66.7
Specificity (%)	100	96.1
Accuracy (%)	69.2	85.9

MP, muscularis propria; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; TUS, transabdominal ultrasonography.

Table 6. Diagnostic accuracy for the ulcer lesions by TUS

TUS diagnosis		Sensitivity (%)	Specificity (%)	Accuracy (%)
Ul (+)	M (n = 4)	25.0	100	95.1
	SM1 (n = 1)	100	95.0	95.1
	SM2 (n = 6)	33.3	98.2	91.8
	MP (n = 11)	54.5	78.0	73.8
	SS (n = 26)	34.6	82.9	62.3
	SE (n = 13)	38.5	68.8	62.3
Ul (–)	M (n = 45)	26.7	94.7	72.7
	SM1 (n = 5)	40.0	74.6	73.4
	SM2 (n = 46)	63.0	68.8	66.9
	MP (n = 17)	41.2	86.1	80.6
	SS (n = 15)	40.0	88.7	83.5
	SE (n = 11)	45.5	91.4	87.8

M, mucosa; MP, muscularis propria; SE, serosa; SM1, tumor invasion within 0.5 mm of the muscularis mucosae; SM2, tumor invasion of depth ≥ 0.5 mm into the muscularis mucosae; SS, subserosa; TUS, transabdominal ultrasonography; Ul (+), presence of ulcer lesions; Ul (–), absence of ulcer lesions.

Table 6 shows the diagnostic accuracy of the TUS for presence or absence of ulcer lesions. The correlation between the diagnostic accuracy of TUS for the presence of ulcer lesions and all lesions and the correlation between the diagnostic accuracy of TUS for the presence of ulcer legions and absence of ulcer lesions were not statistically significant (P = 0.78, P = 0.70, respectively).

DISCUSSION

Japanese treatment guidelines[1] for some patients with gastric cancer having an invasion depth of T1 recommend endoscopic resection for some mucosal lesions and modified surgery for all submucosal lesions. Therefore, accurate preoperative assessment of the depth of tumor invasion is required when planning treatment. Currently, endoscopy and EUS are used for preoperative assess-

ment, but these methods are invasive and cause patient discomfort. Therefore, this study evaluated the usefulness of TUS in assessing the depth of tumor invasion in gastric cancers. We found that the sensitivity, specificity and accuracy of TUS were equivalent to those of conventional diagnostic imaging in determining the depth of tumor invasion within the gastric wall.

TUS was previously reported to have accuracies of 55.6%[10] and 66.7%[11] in evaluating T1 lesions. In our study, TUS had accuracies of 79%, 80% and 74% in evaluating M, SM1 and SM2 lesions, respectively. Although these results could not be directly compared, accuracy in the present study seemed to be higher. Similarly, our accuracy rate for M lesions (79%) was higher than that in a previous study (67%).[12] Furthermore, the cases without clearly observed on TUS were included in this study, whereas these cases were not included in a previous study.[12] The higher accuracy rates observed in this study may have been due to further developments in ultrasonography equipment and our higher experience with TUS.

Gastric cancer patients with T2, T3 or T4 tumor should be treated with the standard gastrectomy with D2 lymphadenectomy, and some patients with T4 tumor are subjected to pre-operative staging laparoscopy.[1] Therefore, preoperative assessments of the depth of tumor invasion within the gastric wall are also necessary in patients with advanced gastric cancer. The accuracy of CT for T2, T3 and T4 advanced gastric cancer lesions ranged from 81% to 100%, whereas that of MRI ranged from 69% to 100%.[20] Another study reported that the accuracy of CT for stage T2 to T4 lesions ranged from 74% to 96%,[21] suggesting that several imaging modalities were necessary to determine the depth of tumor invasion in patients with advanced gastric cancer. CT and MRI, however, are costly, time-consuming and require large instruments, indicating the need for an easier examination method. Although EUS is regarded as the gold standard in assessing the depth of tumor invasion in patients with early gastric cancer,[2–5] it is much less accurate in patients with advanced gastric cancer,[22, 23] especially in those with tumors larger than 3 cm or located in the upper third of the stomach.[4, 5, 22, 24] However, TUS was shown to be useful in the preoperative determination of tumor depth in advanced gastric cancer[18] and to have accuracies of 75% and 87.3% for MP + SS and SE lesions, respectively.[10] Furthermore, TUS could assess larger tumors compared with EUS.[25] Similar to previous studies, we found that TUS had accuracies of 79%, 77% and 80% for MP, SS and SE lesions, respectively, and could easily differentiate MP from SS lesions. These results showed that TUS was equivalent in accuracy to conventional diagnostic imaging and suggested that our TUS assessment criteria pertaining to the depth of tumor invasion may become widely used in routine examination of patients with gastric cancer.

In the present study, in cases where the ruptured form of the third layer could be determined in MP lesions, the forms were observed toward the inside of the gastric lumen. Therefore, we considered that if the ruptured form of the third layer was observed toward the gastric lumen, the patient was highly likely to have advanced gastric cancer. This TUS criterion is a new finding, and it seemed that the ruptured forms of the third layer are useful for distinguishing early and advanced gastric cancer.

Four lesions in the present study were difficult to identify by TUS because all were small and contained within mucosal lesions. Previous studies have also suggested that small lesions are more difficult to visualize on TUS than on EUS.[9, 12] In addition, TUS was unable to diagnose the depth of tumor invasion of four other lesions in this study. In three of the four lesions, food residue prevented clear visualization on TUS, whereas the fourth was located in the posterior wall of the upper gastric body. Technically, there are difficulties in evaluating tumors located in the gastric cardia, fundus, and greater curvature of the upper gastric body by TUS.[7–9, 12, 26] Thus, some lesions are not evaluable by TUS, making it necessary to design noninvasive methods for detecting these lesions.

The ulcer in gastric cancer may cause gastric wall fibrosis and scar, which lead to wall thickening and loss of wall layers.[4, 5, 10, 11] Therefore, the lesion with ulcerous change may be associated with incorrected depth determinations by EUS and TUS. However, in this study, no significant difference was observed between the diagnostic accuracy of TUS and presence of ulcer lesions. It was thought that our new TUS criteria can diagnose the correct depth of the gastric lesions even with ulcerous change.

This study had several limitations, including its retrospective design and evaluation of patients over 8 years. In many cases, information about the characteristics of gastric cancer lesions had previously been obtained by conventional diagnostic imaging. Previous information and our clear TUS assessment criteria may have increased the accuracy of TUS in evaluating the depth of tumor invasion.

In conclusion, the results of this study suggested that the accuracy of TUS was equivalent to that of conventional diagnostic imaging in determining the depth of tumor invasion. Our new TUS criteria may be useful in detecting gastric cancers during abdominal screen-

ing. Furthermore, the ruptured forms of the third layer seemed to be useful for distinguishing between early and advanced gastric cancer.

The authors declare no conflict of interest.

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