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Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography

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Abstract

Background and Aim: The aim of this study was to determine the accuracy of endoscopic ultrasonography (EUS) and multidetector-row computed tomography (MDCT) for the locoregional staging of gastric cancer. EUS and computed tomography (CT) are valuable tools for the preoperative evaluation of gastric cancer. With the introduction of new therapeutic options and the recent improvements in CT technology, further evaluation of the diagnostic accuracy of EUS and MDCT is needed.

Methods: In total, 277 patients who underwent EUS and MDCT, followed by gastrectomy or endoscopic resection at Bundang Hospital, Seoul National University, from July 2006 to April 2008, were analyzed. The results from the preoperative EUS and MDCT were compared to the postoperative pathological findings.

Results: Among the 277 patients, the overall accuracy of EUS and MDCT for T staging was 74.7% and 76.9%, respectively. Among the 141 patients with visualized primary lesions on MDCT, the overall accuracy of EUS and MDCT for T staging was 61.7% and 63.8%, respectively. The overall accuracy for N staging was 66% and 62.8%, respectively. The performance of EUS and MDCT for large lesions and lesions at the cardia and angle had significantly lower accuracy than that of other groups. For EUS, the early gastric cancer lesions with ulcerative changes had significantly lower accuracy than those without ulcerative changes.

Conclusions: For the preoperative assessment of individual T and N staging in patients with gastric cancer, the accuracy of MDCT was close to that of EUS. Both EUS and MDCT are useful complementary modalities for the locoregional staging of gastric cancer.

Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of death from cancer.[1,2] Only complete resection of all gross disease with negative microscopic margins (R0 resection) provides a long-term survival benefit, and the overall 5-year relative survival rate is approximately 20%.[1,3] To improve survival and quality of life, new therapeutic approaches have been introduced. In patients with early gastric cancer (EGC), especially in cases confined to mucosa, endoscopic resection (ER) is performed to avoid unnecessary surgical procedures.[4] To achieve R0 resection for locally-advanced gastric cancer (AGC), neoadjuvant treatments have been investigated.[5] Laparoscopic surgery has been shown to improve quality of life for both early EGC and AGC.[6,7]

Previously, precise preoperative staging was not essential because the exact stage did not alter treatment plans. Endoscopic ultrasonography (EUS), which is considered to be the most precise method for locoregional staging,[8,9] was commonly used for differentiating mucosal lesions from submucosal lesions for ER. By contrast, computed tomography (CT) was used to detect the presence of distant metastasis.[10] However, recent technological advances with the helical and multidetector scanners have provided better CT performance.[11–13]

With the introduction of new therapeutic options and the recent improvements in CT, further evaluation of the diagnostic accuracy for individual staging by EUS and multidetector-row computed tomography (MDCT) is needed. The present study was conducted to compare the staging accuracy of EUS with that of MDCT in a

large series of patients and to evaluate their usefulness in association with the clinicopathological factors.

Methods

Study population

A total of 425 consecutive patients that underwent EUS and MDCT, followed by gastrectomy with lymphadenectomy or ER at the Bundang Hospital, Seoul National University, between July 2006 and April 2008, were investigated. The following patients were excluded from the analysis: (i) patients with a previous gastric resection, multiple lesions, or incomplete medical records; (ii) patients that received neoadjuvant chemotherapy or only bypass surgery; and (iii) patients with an interval from the preoperative imaging to gastrectomy greater than 14 days or from the imaging to ER greater than 31 days.

EUS

A radial scanning ultrasonic endoscope (GF-UM2000; Olympus, Tokyo, Japan) was used. Two experienced endoscopists carried out all of the procedures at 5, 7.5, 12, or 20 MHz. Prior to the procedure, 20 mg scopolamine butylbromide was intravenously administrated. After evaluation of the primary lesion, the stomach was filled with 300–600 mL water to examine the five-layered structure. The tumor infiltration depth was assessed at the time of the procedure using the standard criteria.[10] Lymph nodes equal to or larger than 8 mm were considered positive for metastasis.[14] When lymph node enlargement was found to be >3 cm from the primary lesion, stage N_2 disease was diagnosed.

MDCT

Contrast material-enhanced CT examinations were performed using 16 or 64 detector row scanners (Mx8000 IDT 16 and Brilliance 64; Philips Medical Systems, Cleveland, OH, USA). Each patient drank 500–1000 mL tap water. Intravenous non-ionic contrast material (iopromide, Ultravist 370; Schering, Berlin, Germany), 2 mL per kilogram of body weight, was administered at a rate of 3 mL/s. Transverse section data sets were reconstructed: 4-mm thick at 3-mm increments and 2-mm thick at 1-mm increments (16 detector row scanners) or 0.67-mm thick at 0.33-mm increments (64–detector row scanners). In each case, from the 2- or 0.67-mm-thick sections, we reformatted the coronal images with a section thickness of 4 mm and an increment of 3 mm (Extended Brilliance Workspace; Philips Medical Systems, USA).

Tumor invasion depth was assessed according to previously reported criteria:[15] (i) T_1, focal thickening of inner layer, which was almost well enhanced, and preservation of low-attenuation strip outer layer of gastric wall; (ii) T_2, gastric wall thickening with loss or disruption of low-attenuation strip, but with smooth outer border and clear fat plane around tumor; (iii) T_3, irregular and nodular outer border or perigastric fat infiltration; and (iv) T_4, obliteration of fat plane between tumor and adjacent organs or obvious tumor invasion of adjacent organs. Lymph nodes were considered positive for metastasis if they were equal to or larger than 8 mm in the short-axis diameter.

Operation

When ER was indicated from the preoperative imaging,[4,16] endoscopic mucosal resection or endoscopic submucosal dissection was performed by the same two endoscopists. Patients who were not candidates for ER or had residual disease after ER underwent either a total or subtotal gastrectomy by two experienced surgeons. The operative specimens were staged by one experienced pathologist according to the Japanese Classification of Gastric Cancer.[17]

Analysis

The results from the preoperative EUS and MDCT were compared with the postoperative pathological staging. The patients that had ER performed were excluded from the analysis of nodal staging because the presence of lymph node metastasis could not be accurately assessed. The cases with residual disease at the lateral resection margin after ER were also excluded from the size analysis because of the incorrect evaluation of size. For simplicity of the analysis, one of the superficial types of EGC, occupying the largest area, was selected for evaluation. In cases with mixed pathology, the pathological type that mainly accounted for the lesion was selected. Papillary and tubular adenocarcinomas were considered differentiated gastric cancers, and poorly-differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma were considered undifferentiated carcinomas.[17,18] In the analysis of T-staging accuracy in relation to the clinicopathological features, χ^2-test was used. A *P*-value of less than 0.05 was considered significant.

Results

Study group

A total of 277 patients (171 men, 106 women; mean age: 53 years; interquartile range: 49–56) were included in this analysis. Twenty-nine patients had an EUS performed earlier than an MDCT, and 103 patients had an MDCT performed earlier than an EUS. A total of 145 patients underwent an EUS and MDCT on the same day. Table 1 shows the distribution of gross features and histology.

Table 1 Gross and histological types

Gross (early gastric cancer)		Gross (advanced gastric cancer)	
0-I	6	1	3
0-IIa	21	2	11
0-IIb	17	3	69
0-IIc	136	4	10
0-III	1	Unclassifiable	3
Histology			
Well-differentiated tubular adenocarcinoma			47
Moderately-differentiated tubular adenocarcinoma			105
Poorly-differentiated adenocarcinoma			85
Signet-ring cell carcinoma			33
Mucinous adenocarcinoma			7

T-staging accuracy by EUS and MDCT

The results of T staging by EUS and MDCT are summarized in Table 2. Among the 277 patients included in this analysis, the overall accuracy of EUS for T staging was 74.7%, and the rate of overstaging (13.7%) was higher than that of understaging (11.6%). On MDCT, the primary lesions were visualized in 141 of the 277 patients, which meant an overall detection rate of 50.9%. The detection rate for EGC and AGC was 32% (58 of 181) and 86.5% (83 of 96), respectively. To minimize the underestimation of MDCT accuracy from the high proportion and low-detection rate of EGC, non-visualized primary lesions (T_0) were regarded as T_1; the overall accuracy was 76.9%, and the rate of overstaging (14.1%) was higher than that of understaging (9%). The accuracy of EUS in determining serosal invasion ($T_{1/2}$ and $T_{3/4}$) was 89.9%, and the accuracy of MDCT ($T_{0/1/2}$ and $T_{3/4}$) was 88.1%. The sensitivity and specificity were 64% and 92.5% for EUS and 96% and 87.3% for MDCT.

Among all 141 patients with visualized primary lesions on MDCT, the overall accuracy of EUS and MDCT for the determination of individual T stage was 61.7% and 63.8%, respectively. The rates of overstaging in both EUS and MDCT (21.3% and 27.7%) were higher than those of understaging (17% and 8.5%). The accuracy of MDCT for identifying serosal invasion ($T_{1/2}$ and $T_{3/4}$) was 76.6% (sensitivity: 96%; specificity: 72.4%). EUS demonstrated similar results, in which the accuracy was 80.9% (sensitivity: 64%; specificity: 84.5%). The overall performance and individual T-stage accuracy are summarized in Table 3.

Among the 136 patients with non-visualized primary lesions on MDCT, 123 patients (90.4%) were staged as pathological (p)T_1, and another 13 (9.6%) were staged as pT_2. The mean sizes of the pT_1 and pT_2 lesions were 25 mm (range 2–70) and 41 mm (range 21–80), respectively. The presence of lymph node metastasis was identified in 14 cases (10.3%), of which five patients were staged as pT_2.

Among the 277 patients, 222 patients had a 16 MDCT, and the accuracy was 75.7%. The other 55 had a 64 MDCT, and 45 patients (81.8%) were correctly diagnosed. The EUS accuracy corresponding to the 16 and 64 MDCT groups was 73.4% (163 of 222) and 80% (44 of 55), respectively.

N-staging accuracy by EUS and MDCT

The assessment of lymph node involvement by EUS and MDCT is shown in Table 4. The overall accuracy of EUS and MDCT for N staging was 66% and 62.8%, respectively. In both modalities, the rates of understaging (EUS: 31.6%; MDCT: 26.7%) were higher than those of overstaging (EUS: 2.4%; MDCT: 10.5%). When assessed according to the individual N stage, MDCT (N_1: 21.2%; N_2: 19 %; N_3: 0%) showed better sensitivity than EUS (N_1: 12.1%; $N_{2/3}$: 2%). In contrast, EUS (N_1: 19%; $N_{2/3}$: 100%) demonstrated a better positive predictive value (PPV) than MDCT (N_1: 15.9%; N_2: 53.3%; N_3: 0%). The detection of the presence of lymph node metastasis by EUS and MDCT was correctly assessed in 70.4% (sensitivity: 19.3%, specificity: 96.3%) and 71.7% (sensitivity: 44.6%, specificity: 85.4%), respectively.

Table 2 Comparison of T-staging accuracy between EUS and MDCT

Pathological stage	*n*	%	EUS				MDCT				
			T_1	T_2	T_3	T_4	T_0	T_1	T_2	T_3	T_4
T_1	181 (58)	65 (41)	162 (46)	18 (11)	1 (1)		123	47	6	5	
T_2	71 (58)	26 (41)	20 (12)	33 (29)	18 (17)		13	9	22	26	1
T_3	22 (22)	8 (16)	1 (1)	8 (8)	12 (12)	1 (1)			1	20	1
T_4	3 (3)	1 (2)			3 (3)					2	1
Total	277 (141)	100 (100)	183 (59)	59 (48)	34 (33)	1 (1)	136	56	29	53	3

Numbers in parentheses show the T-staging accuracy of endoscopic ultrasonography (EUS) in 141 patients with visualized lesions upon multidetector row computed tomography (MDCT).

Table 3 Test performance of individual T staging by EUS and MDCT

	In 277 patients				In 141 patients with visualized lesions on MDCT			
	EUS		MDCT†		EUS		MDCT	
	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)
T_1	89.5	88.5	93.9	88.5	79.3	78.0	81.0	83.9
T_2	46.5	55.9	31.0	75.9	50.0	60.4	37.9	75.9
T_3	54.5	35.3	90.9	37.7	54.5	36.4	90.9	37.7
T_4	0	0	33.3	33.3	0	0	33.3	33.3
Overall accuracy (%)	74.7		76.9		61.7		63.8	
Determining serosal invasion (%)	89.9		88.1		80.9		76.6	

†Cases that were not detected upon multidetector row computed tomography (MDCT) (T_0) were incorporated into T_1. EUS, endoscopic ultrasonography; PPV, positive predictive value.

Table 4 Comparison of N-staging accuracy between EUS and MDCT

Pathological stage	*n*	%	EUS			MDCT			
			N_0	N_1	N_2	N_0	N_1	N_2	N_3
N_0	164	66	158	6		140	20	2	2
N_1	33	13	29	4		24	7	2	
N_2	42	17	34	7	1†	21	13	8	
N_3	8	3	4	4		1	4	3	
Total	247	100	225	21	1	186	44	15	2
Overall accuracy (%)				66.0			62.8		
Presence of lymph node metastasis (%)				70.4			71.7		

†Endoscopic ultrasonography (EUS) N_2 corresponds to pathological $N_{2/3}$ because EUS N_2 was defined as lymph node metastasis >3 cm from the primary lesion. MDCT, multidetector row computed tomography.

Table 5 Accuracy of EUS and MDCT for T staging and clinicopathological features

	Total (*n*)	EUS		MDCT	
		Accuracy (*n*)	%	Accuracy (*n*)	%
Location					
Cardia	15	8	53.3	5	33.3***
Body	48	29	60.4	34	70.8
Angle	24	10	41.7*	14	58.3
Antrum	46	33	71.7	31	67.4
Prepyloric	8	7	87.5	6	75.0
Histology					
Differentiated	70	46	65.7	43	61.4
Undifferentiated	71	41	57.7	47	66.2
Gross (EGC)					
0-I	3	1	33.3	1	33.3
0-IIa	7	6	85.7	7	100.0
0-IIb	5	4	80.0	3	60.0
0-IIc	43	35	81.4	36	83.7
Ulcerative change (EGC)					
Yes	13	4	30.8**	8	61.5
No	45	42	93.3	39	86.7
Gross (AGC)					
1	3	2	66.7	3	100.0
2	10	5	50.0	2	20.0***
3	59	31	52.5	30	50.8
4	10	3	30.0	8	80.0
Size†					
≤20 mm	27	22	81.5*	22	81.5***
20–40 mm	45	27	60.0	27	60.0
≥40 mm	67	36	53.7	39	58.2

*$P < 0.05$, compared with other endoscopic ultrasonography (EUS) groups; **$P < 0.01$, compared with other EUS groups; ***$P < 0.05$, compared with other multidetector row computed tomography (MDCT) groups. †Two patients with residual disease at the resection margin after endoscopic submucosal dissection were excluded because the size could not be accurately assessed. AGC, advanced gastric cancer; EGC, early gastric cancer.

Accuracy in relation to clinicopathological features

Among the 141 patients with visualized primary lesions on MDCT, T-staging accuracy in relation to the clinicopathological features was analyzed (Table 5; Figs 1,2). The lesions at the angle revealed the lowest accuracy by EUS (41.7%), followed by lesions at the cardia (53.3%). When compared to other groups, the lesions at the angle showed a statistically significant difference ($P = 0.037$). For MDCT, the accuracy of the lesions at the cardia was the lowest (33.3%, $P = 0.012$), followed by lesions at the angle (58.3%). The performance of EUS and MDCT for the combination group of lesions at the cardia and angle had also significantly lower accuracy than the other groups ($P = 0.019$ and $P = 0.031$, respectively). With regard to size, the accuracy of both modalities tended to decline as the tumor increased. The difference

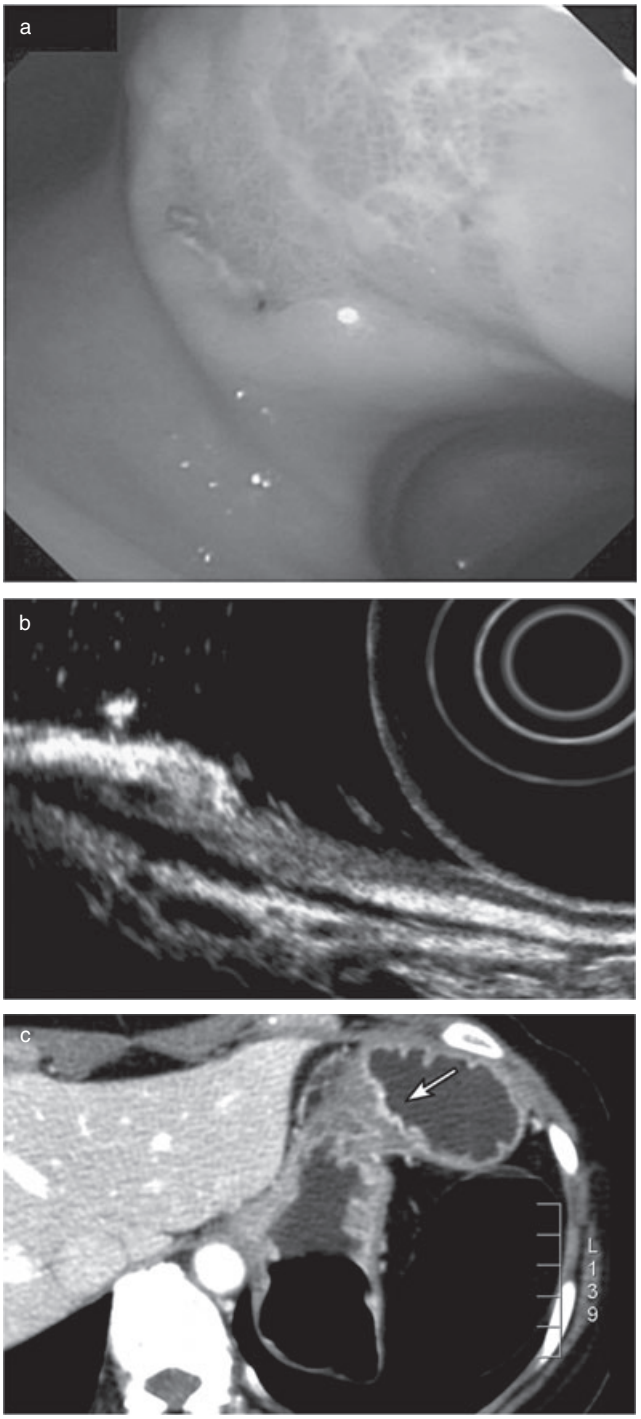

Figure 1 Early gastric cancer in a 47-year-old woman. (a) Endoscopic view of a superficial flat and depressed lesion (type IIb + IIc) on the lesser curvature of the lower body. (b) Endoscopic ultrasonography of a hypoechoic lesion confined to sonographic layer 3. (c) Contrast-enhanced multidetector-row computed tomography shows the focal wall thickening with enhancement (arrow). Low-attenuation outer layer of the gastric wall is preserved. This finding suggests a T_1 lesion. After surgery, the lesion was confirmed to be a submucosal cancer.

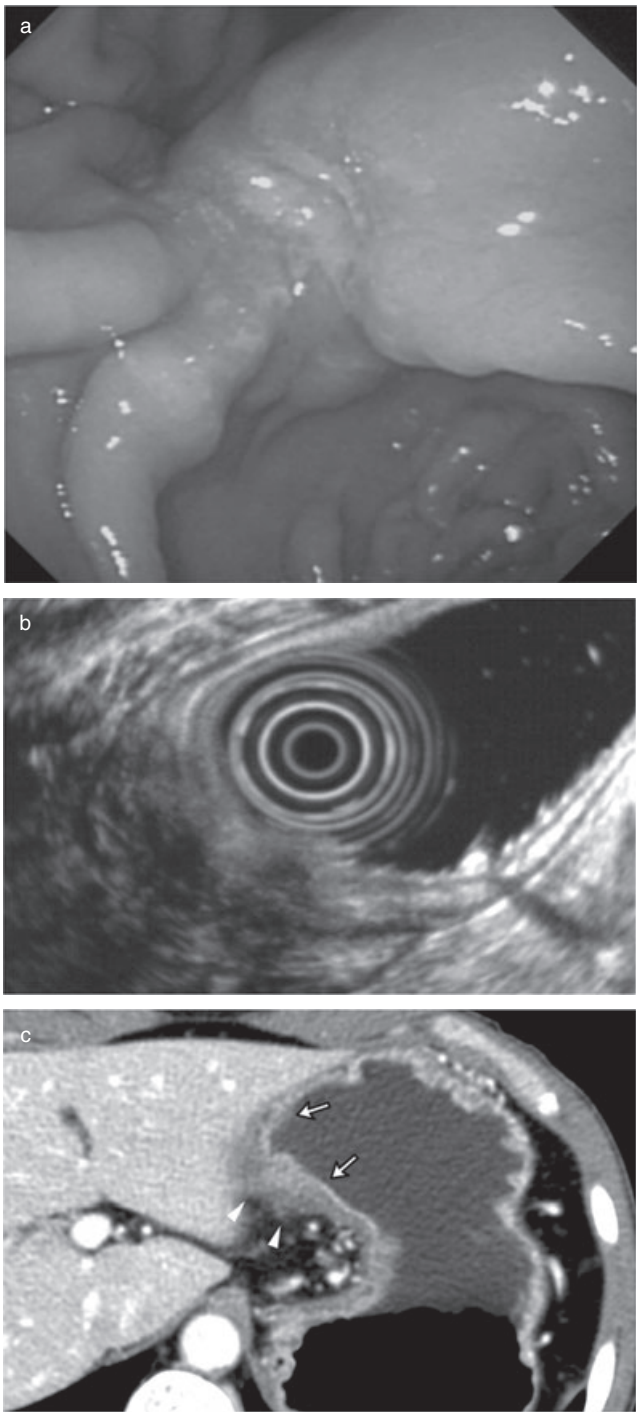

Figure 2 Early gastric cancer in a 45-year-old man. (a) Endoscopic view of an ulcerative lesion on the lesser curvature of the angle. (b) Infiltration into subserosal layer was observed by endoscopic ultrasonography. Examination was difficult due to the angulation and folding of the gastric wall. (c) Contrast-enhanced multidetector-row computed tomography shows the irregular wall thickening with destruction of the mucosal lining (arrows). Perigastric infiltration is suspected (arrowheads), and this finding suggests a T_3 lesion. After surgery, the lesion was confirmed to be a submucosal cancer.

in accuracy between the ≤20-mm group and other groups was statistically significant for both EUS and MDCT ($P = 0.026$ and $P = 0.044$, respectively).

For EGC lesions with ulcerative changes, EUS demonstrated a significantly lower accuracy rate when compared to lesions without ulcerative changes ($P = 0.00001$). In contrast, the accuracy of MDCT for lesions with and without ulcerative changes was not significantly different. For the analysis of gross morphology, MDCT showed a significantly lower accuracy for Bormann type 2 lesions when compared to the other groups ($P = 0.042$). EUS showed a low accuracy for the Bormann type 4 lesions (30%), while MDCT correctly diagnosed eight of 10 lesions. The gross type of EGC and histology showed no statistically significant differences.

Discussion

During the 1990s, EUS was reported to have very high T-staging accuracy ranging from 75% to 92%, and since then, has been accepted as the most reliable imaging method for T staging.[8,9] Although there have been few studies directly comparing the accuracy of EUS and conventional CT, EUS has been considered more accurate than CT.[10,19,20] Two prior reports comparing single-/two-detector helical CT and EUS demonstrated the increased accuracy of CT, but the accuracy of EUS was still higher than CT.[12,14] Recently, studies using MDCT for T staging of gastric cancer have shown improved accuracy, approaching that of EUS. In the studies performed with the 16 or 64 MDCT alone, the T-staging accuracy has been reported to be up to 89%.[13,15,21,22] In addition, Bhandari *et al*. reported that EUS and the 4 MDCT had comparable accuracy with regard to T staging (87.5% in EUS; 83.3% in the 4 MDCT).[11] Some authors have suggested that the accuracy of MDCT for T staging had almost caught up with that of EUS, and that MDCT might replace EUS for preoperative staging.[12] However, there have been no prior studies directly comparing the accuracy of EUS with 16 or 64 MDCT for individual T staging.

In this study, there were 181 EGC patients (65%) from the 277 patients. The biased case selection was mainly due to two factors: the general population screening programs in Korea and the exclusion of advanced cases in which gastrectomy was not performed. The high proportion and low-detection rate of EGC could have underestimated the performance of MDCT; only 37% of EGC cases were visualized on MDCT, and when T_0 lesions were considered a different stage from T_1, the overall accuracy of T staging by MDCT was 32.5%. Considering prior studies using MDCT, the result was not acceptable.[13,15,21,22] In addition, it was suggested in a previous report that the presence of non-visualized primary lesions on MDCT might reflect the presence of EGC without regional lymph node metastasis,[23] of which the results are consistent with the present study. Therefore, to correct the underestimation for the appropriate comparison of EUS with MDCT, we analyzed the performance for T staging in two steps: all patients with the incorporation of T_0 into T_1, and 136 patients with visualized primary lesions on MDCT. The results from these two steps are consistent with recent studies on the accuracy of MDCT, which show it to be very close to that of EUS.[11,13,15] The rate of EGC (41%) in the visualized lesion group was also adequate when compared to those reported in previous studies, from 46% to 53%.[24,25]

The EUS criteria used for lymph node metastasis are controversial. In several reports, simple criteria based on size alone have been shown not to be inferior to other criteria,[8,10,14] and were used in the present study. At the time of the procedures, the criterion of 5 mm was chosen to obtain high sensitivity. For the analysis of N staging, the criterion of 8 mm, used in previous studies,[12,14] was chosen for both EUS and MDCT. Accordingly, the involvement of lymph nodes was reevaluated from the medical records. The performance found in the present study (Table 4) was similar to that of prior studies, in which the results ranged from 67% to 90% for EUS and from 70% to 77% for MDCT.[12,14] As expected from previous studies,[14,26] EUS showed very low sensitivity for N staging, especially for the detection of $pN_{2/3}$, which is technically difficult to observe. MDCT revealed better results in the detection of N_1 and N_2, but no pN_3 lesions were correctly diagnosed.

The accuracy of EUS and MDCT in this study was inferior to previous studies. The performance can be influenced by several factors, such as the interpreter's experience, study group, and different methodology. Moreover, the recently-published reports suggested the possibility of a lower accuracy of EUS in the clinical setting than previously reported.[27] Several recent reports, in which the T- and N-staging accuracy of EUS was from 50% to 67%, support this possibility.[14,26] Similarly, prior reports of MDCT with very high detection rates and diagnostic accuracy usually included virtual gastroscopy, various sets of multiplanar reconstructions, and repetitive interpretation of the images by multiple radiologists.[13,15,28]

For evaluating the depth of EGC invasion, the presence of ulcerative change, size, location, and histology have been established as important factors that influence the staging accuracy of EUS.[29–31] However, until now, the influences from the clinicopathological factors have not been defined for MDCT. In the present study, the performance of both modalities was analyzed for both EGC and AGC in relation to the clinicopathological factors (Table 5). With regard to location and size, both scanning modalities showed a similar tendency. A pilot study with EUS showed similar findings to those of the present study,[32] which could be due to inadequate filling of water at the cardia and gastric wall folding at the angle.[30] For EGC lesions with ulcerative changes, the accuracy of EUS was significantly low; this finding is consistent with previous studies.[30,31] In cases with a diffuse infiltrative morphology (Bormann type 4), the performance of EUS was also low, although the result was not statistically significant. Seven of 10 diffused infiltrative lesions were very large, over 100 mm, and the low accuracy can be explained by the difficulty of a thorough examination of very large lesions with EUS. When a lesion with ulceration or a large, diffused infiltrative lesion is suspected upon preoperative evaluation, MDCT might be more accurate than EUS. However, this requires further study in a larger sample for confirmation. Among the 10 lesions classified as Bormann type 2, only two lesions were correctly staged by MDCT. However, all 10 lesions were pT_2; the sensitivity of MDCT was much lower than for pT_1 and pT_3, and the result can be considered incidental.

The present study demonstrated that the performance of the 64 MDCT was better than that of the 16 MDCT. However, the EUS accuracy of the 64 MDCT group was also better than that of the 16 MDCT group. The small and different study population might have influenced our accuracy results between the 16 and 64

MDCT. Previously, the performance of the 64 MDCT has been reported to be similar to that of the 16 MDCT.[13,15]

For differentiating mucosal lesions from submucosal lesions, EUS is the first-line imaging modality; this is because it shows more detail of the five-layer structure of the gastric wall than CT. However, in determining the individual T and N stage, the present study showed that the accuracy of MDCT was very close to that of EUS. When a large lesion or a lesion at the angle or cardia is examined by both modalities, cautious interpretation is necessary for T staging. EGC lesions with ulceration should be also meticulously interpreted by EUS. In conclusion, both EUS and MDCT are useful, complementary modalities for the preoperative evaluation of gastric cancer.

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