Original Article

Preoperative accuracy of gastric cancer staging in patient selection for preoperative therapy: race may affect accuracy of endoscopic ultrasonography

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Background: Over the last 15 years, large randomized controlled studies have validated the benefit of preoperative therapy for patients with resectable gastric cancer. Computed tomography (CT) and endoscopic ultrasonography (EUS) are commonly used to select patients for preoperative treatment, but studies of preoperative staging accuracy that focus on patient selection for preoperative therapy are rare; therefore, whether CT or EUS can reliably identify patients eligible for preoperative therapy is still unclear. Our purpose was to determine the accuracy of EUS and CT for preoperative staging of gastric cancer and to identify factors that may affect their usefulness in selecting patients for preoperative therapy.

Methods: We reviewed the medical records of 8,260 patients with gastric or gastroesophageal adenocarcinoma treated at our institution from 1995 to 2013, identifying those who underwent gastrectomy without preoperative treatment. We compared T stage and N status from preoperative EUS and CT reports with those drawn from surgical pathology reports. Clinicopathologic and demographic variables associated with incorrect preoperative staging were investigated using univariate and multivariate analyses.

Results: We identified 187 patients who underwent preoperative staging by EUS (n=145) and/or CT (n=134) before gastrectomy. The accuracy, sensitivity, and specificity of EUS in distinguishing stage T1 from more advanced tumors were 82%, 78%, and 85%, respectively. Variables associated with underestimation of EUS T stage were lymphovascular invasion [odds ratio (OR), 7.51; 95% confidence interval (CI), 1.91–29.50; P<0.01] and white race (OR, 3.75; 95% CI, 1.31–10.75; P=0.01). The accuracies, sensitivities, and specificities for determining N status were, respectively, 65%, 49%, and 79% with CT and 66%, 29%, and 95% with EUS. Lymphovascular invasion was associated with a false negative result (OR, 3.79; 95% CI, 1.34–10.70; P=0.01), and well- or moderately differentiated histology was associated with a false positive result for CT N status (OR, 7.14; 95% CI, 2.00–25.44; P<0.01).

Conclusions: EUS is accurate in distinguishing T1 from T2–T4 lesions; both CT and EUS have low sensitivities and high specificities in determining N status. These accuracies and variables associated with inaccurate staging, including race, should be considered when selecting gastric cancer patients for preoperative therapy.

Keywords: Gastric cancer; endoscopic ultrasonography (EUS); computed tomography scan (CT scan)

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Introduction

Over the last 15 years, large randomized controlled studies have validated the benefit of preoperative therapy for patients with resectable gastric cancer (1-4). Preoperative staging using computed tomography (CT) and endoscopic ultrasonography (EUS) is used to select patients for preoperative treatment (5,6). Patients are generally considered good candidates for preoperative therapy if they have clinical stage T2 or higher tumors or positive lymph nodes. If preoperative staging is inaccurate, patients with early-stage gastric cancer may receive inappropriate preoperative treatment that delays surgical intervention. Conversely, patients with advanced gastric cancer may miss out on beneficial preoperative treatment if their disease is understaged. Several reports and meta-analyses regarding the accuracy of preoperative EUS T staging have been published (7-10), but the reported accuracies differed substantially (8). Furthermore, studies of preoperative staging accuracy that focus on patient selection for preoperative therapy are rare; therefore, whether EUS can reliably identify patients eligible for preoperative therapy (i.e., those with stage T2 or higher lesions) is still unclear. In addition, a recent meta-analysis demonstrated significant differences in the accuracy of EUS T staging between Western and Eastern reports. Sensitivities to distinguish T1 from T2 tumors were 71% in Western reports and 92% in Eastern reports (P<0.01), indicating that race or ethnicity may affect EUS accuracy (11). However, no prior studies have examined the role of race and ethnicity in particular in staging accuracy.

The main purpose of this retrospective study was to determine whether EUS accurately identifies patients with stage T2 or higher or node-positive disease who should be considered for preoperative therapy. We also sought to determine what variables, including race or ethnicity, are associated with the staging accuracy of EUS. Finally, we examined the accuracy of CT imaging for detecting lymph node metastasis and identified factors associated with it.

Methods

Patient selection

Having received Institutional Review Board approval, we conducted a retrospective review of a prospectively maintained database of the medical records of 8,260 patients with gastric or gastroesophageal adenocarcinoma treated at The University of Texas MD Anderson Cancer Center from 1995 to 2013. We identified patients who underwent gastrectomy after preoperative staging with EUS or CT. Patients with pathologic stage T0 tumors (no persistent cancer in the surgical specimen) were excluded from this study because the accuracy of pathologic staging after extensive biopsies or endoscopic mucosal resection is unknown. Because preoperative therapy affects both T and N staging (1,4), we excluded patients who had undergone such therapy. Patients' demographic and clinicopathologic characteristics were collected. These characteristics included age, sex, race/ethnicity, smoking history, date of staging procedure (CT or EUS), date of surgery, tumor location, tumor size, presence of ulceration, presence of lymphovascular invasion, number of lymph nodes examined, histological grade (well/moderately or poorly differentiated adenocarcinoma), and presence of signet ring cell morphology.

Assessment of EUS T and N staging accuracy

T stage and N status as determined by preoperative EUS were compared with postoperative pathologic T and N staging to determine accuracy. T stage was defined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual, and N status was defined as positive or negative. Before 2003, our institution's EUS system used linear-probe endoscopes from Pentax Medical Co. (Tokyo, Japan). In 2003, we switched to linear-probe endoscopes from Olympus Optical Co. (Tokyo, Japan). Nodal status was determined by the endoscopists at the time of the EUS procedure based on the shape and size of the visualized lymph nodes. Fine-needle aspiration of the lymph nodes was not required to confirm the staging.

Assessment of CT N staging accuracy

To assess the accuracy of CT in detecting lymph node metastasis, we reviewed the included patients' preoperative CT images. The images had to have been taken at MD Anderson Cancer Center, used intravenous contrast, and be of adequate quality. The original images were reviewed by a physician (N Ikoma) who was blinded to the EUS and surgical pathology results, tumor location, and other clinical information. Lymph nodes were considered positive when the short axis diameter was ≥6 mm on CT images. N status was defined as positive or negative.

Definition of staging accuracy

In general, patients with stage T2 or higher and/or node-positive tumors have significantly diminished survival rates (12,13). Based on the National Comprehensive Cancer Network (NCCN) guidelines and results from two large randomized trials (1,4) that have shown a survival benefit from adjunctive chemotherapy for such patients, our institution considers patients with clinical stage T2 or higher and/or node-positive tumors to be candidates for preoperative therapy (14). Therefore, for the purposes of this study, we defined the T-staging accuracy of EUS as its ability to distinguish early gastric cancer (stage T1a or T1b) from more advanced tumors (stage T2 or higher). Accuracy, sensitivity, and specificity were calculated based on this definition. For the purpose of comparing our results with previous reports, we also calculated the accuracy, sensitivity, and specificity of EUS for identifying summary T stage (T1–T4) and detailed T stage (T1a, T1b, T2–T4). Within the category of early T-stage tumors (T1 or T2), we also evaluated the ability of EUS to distinguish T1a tumors from T1b–T2 tumors by calculating accuracy, sensitivity, and specificity.

To examine factors associated with inaccurate EUS T staging, we defined overstaging as an EUS T stage that was higher than that indicated in the pathology report and understaging as an EUS T stage lower than that found in the pathology report, based on the 7th edition of the AJCC staging manual.

N status as determined by CT and EUS was compared to that indicated in the pathology report. Accuracy, sensitivity, and specificity for determining N status were calculated for both imaging modalities. EUS N status showed lower sensitivity than CT N status in this study, so we did not perform further analysis on EUS N status.

Statistical analysis

Univariate and multivariate analyses were performed to evaluate the association between clinicopathologic variables and inaccurate staging (overstaging or understaging of EUS T stage, false positive/false negative of EUS/CT N stage). The univariate analyses used the chi-square or Fisher exact tests as appropriate. The multivariate analyses used logistic regression models. Factors with a P value ≤0.25 in the univariate analysis were included in the logistic regression model, and the final models were determined using a stepwise method. Statistical analyses were performed using SAS software version 9.3 for Windows (SAS Institute, Cary, NC). All reported P values are 2-sided and were considered significant at the P<0.05 level.

Results

Patient characteristics

We identified 225 patients who had undergone gastrectomy without receiving preoperative treatment during the study period. We excluded patients who had no residual disease in the gastrectomy specimen (n=22), patients who had had a previous gastrectomy (n=8), and patients who did not undergo either CT or EUS at our institution within 3 months before surgery (n=10). We identified 187 patients who had undergone preoperative staging using EUS (n=145, 1995–2013) and/or CT (n=134, 2000–2013) prior to gastrectomy and whose images were adequate and available for review. Patient characteristics are detailed in *Table 1*. The patients were approximately 53% White, 19% Asian, 19% Hispanic, and 9% Black. Tumor location was most commonly in the antrum (approximately 47%). Approximately 47% of patients had early-stage (T1a/b) cancer, 44% had positive lymph nodes, 75% had tumors with poorly differentiated histology, and more than 50% had lymphovascular invasion.

Accuracy of EUS T stage

Detailed results of EUS T staging for each pathological T stage are shown in *Table 2*. The accuracy of EUS in identifying summary T stage (T1–T4) was 66% (96/145), and the accuracy of EUS in identifying detailed T stage (T1a, T1b, and T2–T4) was 52% (75/145). The accuracy, sensitivity, and specificity of EUS in distinguishing T1 from more advanced (T2–T4) tumors were 82%, 78%, and 85%, respectively. The accuracy, sensitivity, and specificity of EUS in distinguishing T1a from T1b–T2 tumors were 74%, 55%, and 86%, respectively.

Variables associated with inaccurate diagnosis were investigated for 38 patients with EUS T-stage overstaging and 32 patients with understaging by comparing them to 75 patients with accurate EUS T staging. In the univariate analysis, tumor location (P=0.02) and lymphovascular invasion (P<0.01) were significantly associated with overstaging or understaging. Race/ethnicity approached a significant association with EUS accuracy (P=0.10). Histological grade (P=0.90), presence of signet ring cell

Table 1 Demographic and clinicopathologic characteristics of 187 patients with gastric cancer

Characteristic	No. of patients [%]
Age (years)	
<65	86 [46]
≥65	101 [54]
Sex	
Female	81 [43]
Male	106 [57]
Race/ethnicity[a]	
Asian	35 [19]
Black	16 [9]
Hispanic	36 [19]
White	100 [53]
Smoking history (yes)	83 [44]
Location of tumor	
Body	60 [32]
Antrum	88 [47]
GEJ	23 [12]
Cardia	16 [9]
Preoperative symptoms	
None	166 [89]
Yes	21 [11]
Bleeding	12 [6]
Obstruction	11 [6]
Pathologic T stage	
T0 (surgical specimen)	14 [7]
T1a	45 [24]
T1b	43 [23]
T2	21 [11]
T3	34 [18]
T4	30 [16]
Pathologic N status	
Negative	105 [56]
Positive	82 [44]
Metastasis	
No	177 [95]
Yes	10 [5]
Histological grade	
Well differentiated	4 [2]
Moderately differentiated	24 [13]
Poorly differentiated	141 [75]
Unknown	18 [10]
Signet-ring-cell features	
No	94 [50]
Yes	93 [50]
Tumor size (mm)	
<20	43 [23]
20–50	75 [40]
>50	34 [18]
Unknown	35 [19]
Lymphovascular invasion	
No	67 [36]
Yes	102 [55]
Unknown	18 [10]
Ulceration	
No	112 [60]
Yes	62 [33]
Unknown	13 [7]
Number of LN examined	
<15	59 [32]
≥15	128 [68]

[a], patient-reported. GEJ, gastroesophageal junction; LN, lymph nodes.

Table 2 Accuracy of endoscopic ultrasonography (EUS) for T staging

Pathological T stage	EUS T stage					Total
	T1		T2	T3	T4	
	T1a	T1b				
T1a	21	15	1	1	0	38
T1b	6	20	9	3	2	40
T2	2	5	8	2	1	18
T3	0	3	5	16	4	28
T4	0	0	4	7	10	21
Total	29	43	27	29	17	145

Note: data are number of patients.

Table 3 Multivariate analysis of factors predicting T-staging accuracy of endoscopic ultrasonography

Variable	Overstaged (n=38)			Understaged (n=32)		
	OR	95% CI	P value	OR	95% CI	P value
Race/ethnicity (ref. Others)			0.85			0.01
White	1.08	0.46–2.54		3.75	1.31–10.75	
LV invasion (ref. No)			0.23			<0.01
Yes	0.60	0.26–1.39		7.51	1.91–29.50	
Tumor location (ref. Others)			0.42			0.61
GEJ	0.50	0.09–2.71		1.39	0.38–5.03	
Differentiation (ref. Poor)			0.86			0.25
Well/moderately differentiated	1.10	0.39–3.11		2.04	0.61–6.80	

OR, odds ratio; CI, confidence interval; LV, lymphovascular; GEJ, gastroesophageal junction.

histology (P=0.58), presence of ulceration (P=0.80), and the interval between EUS and surgery (<1, 1–2, or >2 months; P=0.74) were not associated with inaccurate staging. In the multivariate analysis, lymphovascular invasion [odds ratio (OR), 7.51; 95% confidence interval (CI), 1.91–29.50; P<0.01] and white race (OR, 3.75; 95% CI, 1.31–10.75; P=0.01) significantly predicted EUS T-stage understaging (*Table 3*).

Accuracy of EUS/CT N status

The accuracy, sensitivity, and specificity of N status were 65%, 49%, and 79% with CT and 66%, 29%, and 95% with EUS, respectively. Sensitivities and specificities of EUS and CT in determining N status for each T stage are shown in *Table 4*. In the univariate analysis, histological grade (P=0.01) and lymphovascular invasion (P=0.09) were associated with incorrect determination of N status on CT. Tumor size (P=0.21), location (P=0.33), patient race/ethnicity (P=0.62), presence of signet ring cell morphology (P=0.16), presence of ulceration (P=0.20), and interval between CT and surgery (P=0.21) were not significantly associated with inaccurate determination of N status on CT. In the multivariate analysis, lymphovascular invasion was associated with false-negative N status on CT (OR, 3.79; 95% CI, 1.34–10.73; P=0.01), and well- or moderately differentiated histology was associated with false-positive N status on CT (OR, 7.14; 95% CI, 2.00–25.44; P<0.01) (*Table 5*).

Discussion

In this study, we found that EUS T staging is reasonably

Table 4 Rate of positive lymph nodes and EUS and CT accuracy

T stage	N-positive rate		EUS		CT	
	%	No. patients	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
T1	23	20/88	0	98	47	85
T2	43	9/21	14	100	50	78
T3	71	24/34	44	70	53	44
T4	97	29/30	45	100	48	100
Overall	47	82/173	29	95	49	79

EUS, endoscopic ultrasonography; CT, computed tomography.

Table 5 Multivariate analysis of factors predicting N-staging accuracy of computed tomography

Variable	False negative (n=32)			False positive (n=15)		
	OR	95% CI	P value	OR	95% CI	P value
Race (ref. Others)			0.16			0.25
White	0.52	0.21–1.30		0.47	0.13–1.69	
LV invasion (ref. No)			0.01			0.76
Yes	3.79	1.34–10.73		1.21	0.34–4.30	
Tumor location (ref. Others)			0.42			0.74
GEJ	1.73	0.45–6.58		0.67	0.06–7.14	
Differentiation (ref. Poor)			0.32			<0.01
Well/moderately differentiated	1.76	0.57–5.38		7.14	2.00–25.44	

OR, odds ratio; CI, confidence interval; LV, lymphovascular; GEJ, gastroesophageal junction.

accurate (82%) for distinguishing early-stage (T1) from more advanced (≥T2) gastric cancer. EUS and CT had unexpectedly low sensitivities (29% and 49%) and high specificities (95% and 79%) for determining N status. We also found that race can affect EUS T-staging accuracy. As expected, the presence of lymphovascular invasion was a risk factor for understaging T stage on EUS and for false-negative CT N-status findings. Our results indicate that EUS T stage can identify candidates for preoperative therapy (patients with stage T2 or higher tumors) with high accuracy.

Accurate preoperative staging is imperative for patient selection for preoperative therapy. The main difference of this study from previous ones is its focus on EUS's ability to distinguish T1 from T2–T4 lesions. The vast majority of previous reports and review articles about EUS accuracy have evaluated its ability to distinguish T1–T2 from T3–T4 tumors (7,10,11,15), although no previous high-powered randomized studies of preoperative treatment for gastric cancer applied such criteria for patient selection (1,4). Previously published data showed that gastric cancer patients with stage T2 or higher tumors and/or node-positive disease benefit from perioperative chemotherapy (1,4). In the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, which showed the benefit of perioperative chemotherapy in patients with gastric cancer, 32% of the study cohort had stage T2 tumors; patients with T2 lesions are likely to benefit from preoperative treatment (1). Reports showing lower survival rates in patients with T2 lesions than in those with T1 lesions, independent of lymph node status, further support the idea of providing pre- or post-operative treatment for patients with T2 lesions (12,16). Because we consider, in accordance with NCCN guidelines, that patients with stage T2 and higher tumors are likely to benefit from preoperative treatment, we aimed to assess the ability of

EUS to distinguish T1 *vs.* T2–T4 lesions.

Reports of EUS T-staging accuracy have shown significant heterogeneity (7,8,10,11); therefore, special caution must be taken when using EUS to select patients for preoperative therapy. A recent Cochrane review reported that EUS had 85% sensitivity and 90% specificity in differentiating T1 from T2 tumors (11) and that better sensitivity was found in Eastern reports than Western reports (92% *vs.* 71%; P<0.01). We found three other studies reporting the accuracy of EUS from the United States after 2000 (17-19), and they uniformly reported that EUS T staging had low accuracy (41–57%). The results of our study show relatively higher accuracy than those studies did (accuracy for summary T stage of EUS was 66%), but not as high as that reported in studies from Asia. This prompted us to evaluate whether the racial or ethnic component of the patient cohorts could account for these discrepancies; we found that white race was associated with understaging of EUS on multivariate analysis. In addition, lymphovascular invasion, which is found in the majority of gastric cancer cases in the United States, was associated with understaging. More racially diverse patient populations and the higher frequency of lymphovascular invasion, reflecting the more aggressive morphology of gastric cancer in the West, may explain the discrepancies between the accuracies reported in Western and Asian studies.

Preoperative diagnosis of lymph node involvement in gastric cancer patients is challenging. Even intraoperative tactile assessment of nodes has low accuracy. Sano *et al.* (20) studied 522 patients with early-stage gastric cancer and reported 32% sensitivity and a false-positive rate of 69% for intraoperative assessment of lymph node involvement. Seto *et al.* (21) reported that intraoperative lymph node evaluation had lower sensitivity for determining N status in patients with undifferentiated tumors. These reports indicate that the size of the lymph nodes is not a reliable marker of lymph node involvement, especially in patients whose tumors have poorly differentiated histology. In a review article, Kwee *et al.* (22) reported a wide range of reported sensitivities (16.7–96.8%) and specificities (48.4–100%) for EUS and sensitivities (62.5–91.9%) and specificities (50.0–87.9%) for CT in evaluating lymph node status. The authors concluded that no imaging modality consistently detects lymph node involvement in gastric cancer, even in this era of advanced technology. The results of our study support these previous reports and confirm that neither EUS nor CT imaging N status can reliably be used for patient selection for preoperative therapy.

It remains unknown whether T1N1 tumors benefit from pre- or postoperative therapy. The current NCCN guidelines (version 3, 2016), based on the Adjuvant Capecitabine and Oxaliplatin for Gastric Cancer After D2 Gastrectomy (CLASSIC) trial (23), recommend adjuvant chemotherapy for all patients with node-positive tumors; however, only 1% of patients in the CLASSIC trial cohort had T1N1 disease. The Japan Clinical Oncology Group (JCOG) 8801 trial failed to demonstrate a benefit for adjuvant chemotherapy in serosa-negative gastric cancer patients (T1–T3); approximately one third of the patients in that cohort had T1 lesions (24). Considering the results of the JCOG 8801 trial, a subsequent trial in Japan, The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer trial (3), excluded T1N+ patients and showed a benefit for adjuvant chemotherapy in patients with stages II/III gastric cancer. Future studies are warranted to determine the benefit of including N status in assessing eligibility for preoperative therapy, and such studies should include a multicenter trial in the West. In the meantime, the low accuracies of preoperative lymph node evaluation reported in this study and in previous Western studies, along with the questionable benefit of perioperative therapy in patients with T1N1 lesions, should be taken into account when considering patients for perioperative treatment.

The major limitation of this study is its retrospective nature, which carries an unavoidable risk of selection bias. Since the vast majority of patients with advanced gastric cancer at MD Anderson receive preoperative therapy, our sample of patients who did not receive such therapy was limited. The relatively long study period (18 years) is another limitation. To improve the validity of the study, only patients for whom high-quality CT images were available were included. As a result, the study population was smaller for CT imaging than for EUS. Differences in technical skills and the experience of the endoscopist may have affected the accuracy of EUS, but this is a limitation of all EUS studies, and the gastroenterologists who participated in this study all have had subspecialty training and experience in a high-volume practice focusing on gastric and gastroesophageal cancer.

In conclusion, EUS was highly accurate for differentiating stage T1 from stages T2–T4 gastric cancer, but both CT and EUS had low sensitivities and high specificities for determining N status. These accuracies and associated variables should be considered when selecting patients for preoperative therapy in gastric cancer. EUS T stage may better guide indications for preoperative therapy than

clinical N stage on EUS or CT imaging. White race and presence of lymphovascular invasion were associated with T-stage understaging on EUS.

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Footnote

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Ethical Statement: The study was approved by Institutional Review Board, with protocol number of PA13-0168.

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