DISEASES OF THE ESOPHAGUS

Original article

Staging accuracy of endoscopic ultrasound performed by nonexpert endosonographers in patients with resectable esophageal squamous cell carcinoma: is it possible?

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SUMMARY. The accuracy of endoscopic ultrasound (EUS) is operator-dependent. According to learning curve study, the accuracy of EUS T-staging for esophageal cancer has been reported to be greater in an investigator who had performed at least 100 EUS examinations. We determined comparative study regarding T-staging accuracy of EUS for esophageal squamous cell carcinoma between expert and nonexpert endoscopic ultrasonographers. We retrospectively identified 73 consecutive patients with esophageal squamous cell carcinoma who underwent EUS and endoscopic mucosal resection, endoscopic submucosal dissection, or surgery. EUS was performed by expert (Group 1) and nonexpert (Group 2) endoscopic ultrasonographers in multitertiary hospitals. Groups 1 and 2 were 37 and 36 patients during 2005–2011, respectively. Forty-two patients (57.5%) of the overall patients underwent surgical exploration. Correct endoscopic ultrasonographic T-staging of Group 1 was observed in 34 (91.9%) patients, while that of Group 2 was observed in 26 (72.2%) patients. And there was significant difference in correct endoscopic ultrasonographic T-staging between Group 1 and Group 2 (*P* = 0.035). The incorrect endoscopic ultrasonographic T-staging of Group 1 were three cases that were overstaging (8.1%), but in Group 2 there were seven overstaging (19.4%) and three understaging (8.3%). There was no significant difference in overstaging or understaging of incorrect endoscopic ultrasonographic T-staging between Group 1 and Group 2 (*P* = 0.528). This study first provides evidence that endoscopic ultrasonographic T-staging of nonexpert endoscopic ultrasonographers was inferior to be correct, compared with that of expert endoscopic ultrasonographers. EUS staging for esophageal cancer should be performed by expert endoscopic ultrasonographers to provide appropriate management strategy.

KEY WORDS: endoscopic ultrasound, esophageal squamous carcinoma, staging accuracy.

INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide and the third most frequent cancer affecting the digestive tract.[1] Endoscopic ultrasound (EUS) has played an important role in the diagnostics and staging of esophageal cancer. EUS is superior to other imaging modalities, such as computed tomography (CT) and magnetic resonance imaging, for locoregional staging.[2,3] With the advent of endoscopic treatment modalities for early esophageal cancers, accurate staging of these cancers has had an important impact.[4,5] Furthermore, EUS can help triage patients with advanced esophageal cancers to surgery alone, neoadjuvant therapy followed by surgery, chemoradiation therapy, or palliative treatment only.[6,7]

However, EUS is an operator-dependent technique, despite its advantages for esophageal cancer staging. Acceptable accuracy of EUS T-staging for esophageal cancer is achieved after 100 examinations.[8–10] EUS

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training improves the accuracy of EUS T-staging for esophageal cancer from 64% to 90%, but not N-staging.[11] Practicing in low-volume centers (50 EUS/endoscopist/year) decreases T1- and T2-stage accuracy but not N-stage or T3-stage sensitivity.[9] Therefore, many endoscopists believe that EUS performed by nonexperts could lead to both clinical and reimbursement problems. Specialized EUS centers perform simple and completely normal EUS studies daily. The volume of demand in these centers creates long patient wait times and consequent delays in reports by expert endosonographers. No comparative study of EUS staging accuracy for esophageal squamous cell carcinoma according to the level of expertise has been conducted.

Therefore, this retrospective study compared EUS staging accuracy for esophageal squamous cell carcinoma between expert and nonexpert EUS sonographers.

PATIENTS AND METHODS

Patient population

This multicenter retrospective study consisted of a retrospective EUS database review of 281 patients with esophageal squamous cell carcinoma from December 2005 to May 2011 at two tertiary referral hospitals in the Republic of Korea: Soonchunhyang Seoul University Hospital and Kyunghee University Hospital.

Study design and data collection

The EUS database was queried for the following items: endosonographer, age, gender, pathology, location, ulceration, dysphagia, endosonographic T- and N-stages, treatment type, and pathological T- and N-stages. A total of 208 (74.0%) of all patients with esophageal squamous cell carcinoma were excluded due to neoadjuvant/palliative chemoradiation therapy ($n = 110$) and lack of EUS performance ($n = 98$). We identified 73 consecutive patients with esophageal squamous cell carcinoma that was resected by endoscopic mucosal resection, endoscopic submucosal dissection, or surgery.

The level of expertise was classified by the number of EUS examinations and EUS comprehensive competence recommended by the American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology;[10] expert endosonographers were characterized by both performance of >500 EUS examinations of the hollow viscus and achievement of EUS comprehensive competency recommended by the ASGE and AGC before our study period (December 2005). Nonexpert endosonographers comprised endoscopic fellow or junior staff

with limited EUS experience or without achievement of EUS comprehensive competency.

All patients were given conscious sedation with midazolam for the EUS examinations and were examined in the left lateral position. The procedures were carried out using a radial echoendoscope (GF-UM2000; Olympus Co., Tokyo, Japan) or ultrasonic miniprobe (UM-2R, UM-3R; Olympus Co.). All EUS procedures were performed with knowledge of the patient's medical history and prior imaging studies.

The institutional review boards of the two centers gave their authorization to conduct the present study and to share information between the two participating centers.

Statistical analysis

Data were analyzed using the SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Sensitivity, specificity, and accuracy of the experts and nonexperts were calculated. The EUS-determined cancer stage was compared with the post-treatment pathological stage for each patient. Data were analyzed using Student's t, Fisher's exact, and chi-squared tests. Factors affecting the accuracy of EUS T- and N-staging were subjected to logistic analysis. Diagnostic accuracy was compared by means of kappa values, which were analyzed using a test for equal kappa coefficients. Incorrect findings were distinguished by over- and underdiagnosis. Exact 95% confidence intervals (CIs) were calculated for each measure of diagnostic efficacy. We performed univariate and multivariate analyses to identify factors affecting the accuracy of EUS T- and N-staging.

RESULTS

Of the 73 patients (66 males; mean age, 61.62 years; range, 41–77 years) with esophageal squamous cancer identified by our database, an esophagectomy was performed in 42 patients (57.5%). Thirty-one patients underwent endoscopic submucosal dissection (ESD) or endoscopic mucosal recection (EMR). Twenty-eight of the 31 patients were treated with ESD and the other three patients received EMR. Their pathological differentiation varied; one patient in the ESD group showed poor differentiation, 15 showed moderate differentiation, and 12 were well differentiated. One patient in the EMR group was well differentiated; the other two were moderately differentiated. The resection margins of all of these patients were negative. Only one patient who underwent EMR had a positive deep margin; that patient underwent an esophagectomy and was included in the surgery group. EUS was performed by three expert endosonographers in 37 patients with esophageal squamous cell carcinoma (Group 1) and in 36 patients by nine nonexpert

Table 1   Demographics and clinical features

Characteristics	Group 1 (n = 37)	Group 2 (n = 36)	P-value
Age (mean ± SD)	59.97 ± 9.69	63.31 ± 7.51	0.106*
Gender			0.711**
Female	3 (8.11)	4 (11.11)	
Male	34 (91.89)	32 (88.89)	
Differentiation			0.001**
Well	23 (62.16)	9 (25.00)	
Moderate	11 (29.73)	25 (69.44)	
Poor	3 (8.11)	2 (5.56)	
Location			0.939***
Middle (15~28 cm)	11 (29.73)	11 (30.56)	
Lower (>28 cm)	26 (70.27)	25 (69.44)	
Ulceration			0.665***
Present	12 (32.43)	10 (27.78)	
Not present	25 (67.57)	26 (72.22)	
Dysphagia			0.844***
Present	10 (27.03)	9 (25.00)	
Not present	27 (72.97)	27 (75.00)	
Treatment method			0.199***
EMR or ESD	13 (35.14)	18 (50.00)	
Surgery	24 (64.86)	18 (50.00)	
Pathological T-staging			0.300***
pT1a	22 (59.46)	21 (58.33)	
pT1b	3 (8.11)	7 (19.44)	
pT2	12 (32.43)	8 (22.22)	
Pathological N-staging†			0.307***
pN0	17 (70.83)	10 (55.56)	
pN1	7 (29.17)	8 (44.44)	

*P-value by Student's t-test; **P-value by Fisher's exact test; ***P-value by Pearson's chi-squared test. †Only operation case. Values are mean ± SD or number of patients (%) unless otherwise indicated. EMR, endoscopic mucosal recection; ESD, endoscopic submucosal dissection; SD, standard deviation.

endosonographers (Group 2). We compared the EUS nodal staging with the pathological nodal staging obtained by esophagectomy. Therefore, 24 patients in Group 1 and 18 in Group 2 were subjected to analysis of EUS nodal staging. No significant differences in age, gender, location, ulcer, dysphagia, treatment type, or pathological T- and N-staging were observed between the two groups (Table 1).

EUS T- and N-staging, and pathological T- and N-staging

The accuracy of EUS T-staging versus the pathological assessment of the resected tumor is summarized in Table 2. The kappa value (95% CI) of EUS T-staging

Table 2   Endosonographic T-staging versus pathological staging

	Group 1 (n = 37)	Group 2 (n = 36)	P-value
Accurate	34 (91.9%)	26 (72.2%)	0.028*
Kappa (95% CI)	0.86 (0.70–1.00)	0.56 (0.33–0.79)	0.035**
			0.041***
Corrected	34 (91.9%)	26 (72.2%)	—
Overstaged	3 (8.1%)	7 (19.4%)	—
Understaged	0 (0.0%)	3 (8.3%)	—

*P-value by Pearson's chi-squared test; **P-value by test for equal kappa coefficients; ***P-value by Fisher's exact test. CI, confidence interval.

Table 3   Endosonographic N-staging versus pathological staging

	Group 1 (n = 24)†	Group 2 (n = 18)†	P-value
Accuracy	18 (75.0%)	8 (44.4%)	0.044*
Kappa (95% CI)	0.33 (–0.08–0.76)	–0.21 (–0.48–0.05)	0.028**
			0.063***
Corrected	18 (75.0%)	8 (44.4%)	—
Overstaged	2 (8.3%)	2 (11.2%)	—
Understaged	4 (16.7%)	8 (44.4%)	—

*P-value by Pearson's chi-squared test; **P-value by test for equal kappa coefficients; ***P-value by Fisher's exact test. †Only operation case. CI, confidence interval.

in Group 1 was significantly higher than that in Group 2 (0.86 [0.70–1.00] vs. 0.56 [0.33–0.79], P = 0.035) (Table 2).

The experts identified cancer that had invaded the mucosal layer or muscular mucosa (T1a) with a 100% positive predictive value (PPV), whereas the PPV of the submucosal layer (T1b) was 75%. However, the nonexperts showed a lower PPV (88%) than that of the experts for both T1a (88%) and T1b (42%).

Node status of the full length of the esophagus and also in the proximal and celiac gastric regions was assessed by conventional EUS. We compared the EUS N-staging with pathological nodal staging. Group 1 included 24 patients who underwent esophagectomy, and Group 2 included 18 patients. Correct endosonographic N-staging in Group 1 was found in 18/24 (75%) patients, whereas that in Group 2 it was found in 8/18 (44.4%) patients.

The EUS N-staging kappa value (95% CI) for Group 1 was significantly higher than that of Group 2 (0.33 [–0.08–0.76] vs. –0.21 [–0.48–0.05], P = 0.028), although the kappa value indicated significantly lower accuracy (Table 3).

DISCUSSION

This is the first study to compare the EUS staging accuracy of resectable esophageal squamous cell carcinoma between expert and nonexpert endosonographers.

Endoscopy is widely used to screen for gastric cancer in the Republic of Korea, even in individuals without symptoms.[12] Endoscopic resection is also increasingly used to treat early esophageal and gastric cancer in Korea. Therefore, the increased workload for endosonographers has grown not only in endoscopy volume but also in EUS demand. Western EUS surveys have reported that a lack of experienced endosonographers is the most common barrier to widespread use of EUS.[13] This training issue is not only the case for Western countries but also for Korea. EUS staging of resectable esophageal squamous cell carcinoma could be assessed by

nonexpert endosonographers in the real clinical field, despite the potential problems (clinical or reimbursement).

Our results show that EUS had a kappa value (95%) for T-staging of 0.86 for expert and 0.56 for nonexpert endosonographers. As expected, significantly higher correct T-staging was conducted by the expert endosonographers. The important point is that a poorly acceptable diagnostic accuracy of T1b cancer was achieved by nonexpert endosonographers. The nonexperts understaged and overstaged far more often than the experts. Understaged patients can be identified by the T-stage of an endoscopically resected specimen; additional treatment – such as esophagectomy – can then be performed. However, an esophagectomy performed in overstaged patients cannot be reversed. Overstaging a misdiagnosis is more critical. These results suggest that correct preoperative T-staging is very important. If T1a cancer is misdiagnosed by EUS as T1b or T2, then patients who can be effectively treated by an endoscopic technique would undergo an unnecessary esophagectomy. This is due to the strong relationship between the depth of tumor invasion and lymph node metastasis.[14] A recent meta-analysis reported that EUS has a pooled sensitivity of 85% for T1a staging and 86% for T1b-staging. Similarly, EUS has a specificity of 86–87% for both stages.[15]

Incorrect T-staging by both expert and nonexpert endosonographers tends toward overestimation. According to some studies, overstaging can be attributed to several factors,[16] including (i) peritumoral inflammation, which leads to wall thickening, making the different layers less easily distinguishable; and (ii) inappropriate positioning of the ultrasound transducer, causing a pseudo-thickening and a poor view of the layers (a problem overcome by the use of a mini probe).

In this respect, EUS performed by nonexpert endosonographers is believed to provide inappropriate information, particularly which of staging accuracy for mucosal carcinoma, in which endoscopic resection is highly feasible, leading to clinical problems with the therapeutic decision. Endosonographic criteria suggestive of malignant involvement of visible lymph nodes include a width >10 mm, round shape, smooth border, and hypoechoic pattern.[17] A meta-analysis reported that EUS has high sensitivity and specificity for diagnosis of N-stage esophageal cancer.[18] The addition of fine-needle aspiration improves sensitivity (85–97%) and specificity (85–96%) of EUS for assessment of the N-stage.

In a meta-analysis by Kelly et al., the accuracy of N-staging by conventional EUS was 79%.[19] Correct EUS N-staging accuracy by nonexpert endosonographers (44.4%) was notably lower than those in the meta-analysis. Lower N-staging accuracy might have been a result of the lack of fine-needle aspiration.

However, this suggests that accurate EUS N-staging is more difficult, particularly for nonexpert endosonographers, because of the subjective nature of EUS criteria.

There are some limitations to the present study. First, the EUS examinations were performed without blinding of other imaging modalities, such as CT. However, CT is unable to accurately distinguish T-stages, particularly T1 and T2.[20] Furthermore, the assessment of staging for esophageal squamous cell carcinoma is not performed by EUS alone in actual clinical practice. Second, the small sample size was also a limitation. A total of 208 (74.0%) of all patients with esophageal squamous cell carcinoma were excluded due to neoadjuvant/palliative chemoradiation therapy ($n = 110$) and lack of EUS performance ($n = 98$). Interestingly, EUS was not performed in 34.9% of esophageal squamous cell carcinoma cases at the two centers during the study period. This suggests that some physicians have questions regarding the application of EUS to staging of esophageal cancer, i.e. who should perform the EUS (expert vs. nonexpert endosonographer).

Finally, we did not provide information regarding the inter-observer variations in EUS staging between expert and nonexpert endosonographers. This main limitation is a direct result of the retrospective study design. Further prospective large studies of EUS staging accuracy of expert and nonexpert endosonographers should be conducted to confirm these results.

In conclusion, EUS performed by nonexpert endosonographers is likely to lead to unnecessary surgery for endoscopically resectable esophageal squamous cell carcinoma. Therefore, before credentialing, at least the number of cases recommended by ASGE and AGC should be performed.

Acknowledgment

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