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Impact of endoscopic ultrasonography on the accuracy of T staging in esophageal cancer and factors associated with its accuracy

A retrospective study

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Abstract

The sensitivity and specificity of endoscopic ultrasound (EUS) for esophageal cancer are variable. The aim of the present study was to determine the accuracy of EUS for the T staging of esophageal cancer and to explore the factors that affect the accuracy.

This was a retrospective study of patients with esophageal cancer who underwent EUS between January 2018 and September 2019 at the author's hospital. All patients underwent EUS, surgery, and pathological examination. The diagnostic value of ultrasound-based T (uT) staging was evaluated using the pathological T (pT) staging as the gold standard.

Finally, 169 patients were included. Among the 169 patients, 37 were overstaged by EUS, 33 were understaged, and 99 were correctly staged. The overall accuracy of EUS was 58.6%. Sensitivity was low, at 0% to 70.8% depending upon the pT stage, but specificity was higher, at 71.0% to 100.0%, also depending upon the pT stage. The multivariable analysis revealed that highly differentiated tumors (odds ratio = 9.167, $P = .041$) and pT stage ≥T2 (odds ratio = 2.932, $P = .004$) were independent factors of accurate uT stage.

The staging of esophageal cancer using EUS has low sensitivity but high specificity. Highly differentiated tumors and pT stage ≥2 tumors were associated with the accuracy of uT staging.

Abbreviations: CI = confidence interval, EUS = endoscopic ultrasound, pT = pathological T, uT = ultrasound-based T.

Keywords: accuracy, endoscopy, esophageal neoplasms, neoplasm staging, ultrasound

1. Introduction

There were an estimated 572,034 cases of esophageal cancer in 2018.[1] The most common histological subtypes of esophageal cancer are squamous cell carcinoma and adenocarcinoma.[2–4] The most likely risk factors for esophageal cancer include tobacco use and excessive alcohol use, obesity, and a history of gastroesophageal reflux disease and/or Barrett esophagus.[3,4] The treatment of esophageal cancer is a comprehensive approach that includes surgery, chemotherapy, targeted therapy, and radiation therapy.[4] Most tumors are found with regional or distant metastasis, which decreases the overall 5-year survival from 39% in cases of a localized disease to 4% in cases of distant metastases.[3] Tumor size and T stage are associated with the prognosis of esophageal cancer.[4,5]

Endoscopy is used to determine the presence and location of esophageal cancer to determine the distance of the cancer to the teeth, the length of the tumor, the extent of circumferential involvement, the degree of obstruction, and the presence of mucosal nodules.[2,4] Nevertheless, those signs are not always easy to visualize. The clinical staging of esophageal cancer mainly depends on computed tomography and endoscopic ultrasound (EUS).[4] For T staging, EUS performs better than computed tomography.[7–9] EUS can be considered as the most accurate imaging modality for the staging of esophageal cancer,[10] and it is recommended by the NCCN guidelines.[4] A more accurate staging using EUS can improve the survival of patients with M0 esophageal cancer.[11] Nevertheless, EUS might be less accurate if the disease is limited to the mucosal layer,[2–4,6] can be limited by esophageal stricture, and carries a risk of perforation.[2,4]

The clinical staging of esophageal cancer is critical in determining perioperative management and treatment options, especially the T staging. However, it takes a few days to obtain

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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pathological staging results after surgery, so accurate pre-operative clinical staging is particularly important. Although previous studies have analyzed T staging of esophageal carcinoma by EUS, accurately determine pre-operative T staging remains difficult.[12] Studies reported variable diagnostic value for EUS in patients with esophageal cancer. Specifically, EUS may have moderate-to-high specificity for tumor staging.[9] EUS may have poor sensitivity but high specificity for advanced esophageal cancer in patients with Barrett's esophagus and high-grade dysplasia or with esophageal adenocarcinoma.[13] The factors affecting the accuracy of EUS are still poorly known.

Therefore, the aim of the present study was to determine the accuracy of EUS for the T staging of esophageal cancer and to explore the factors that affect the accuracy. The results could help determine the categories of patients in whom the EUS might be more accurate.

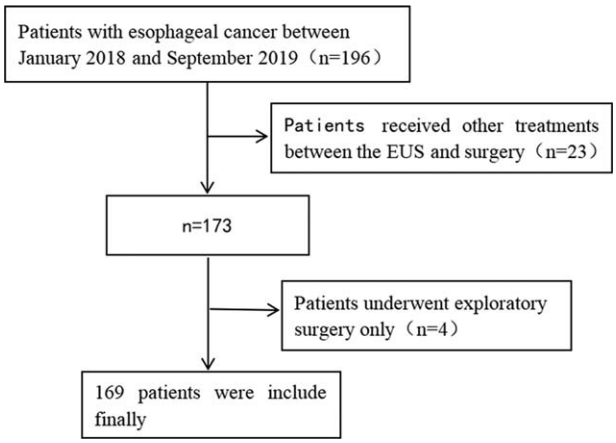

Figure 1. The flow diagram.

2. Methods

2.1. Ethics

This was a retrospective study of patients who underwent EUS between January 2018 and September 2019 at the Department of Thoracic Surgery of the author's hospital. This study was approved by the ethics committee of the hospital, and was in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent for this study was waived due to the retrospective nature of this study. All the patients signed examination informed consent for the EUS before the examination.

2.2. Study design

2.2.1. Selection and description of participants. The inclusion criteria were: >18 years of age; diagnosis of esophageal cancer (both squamous cell carcinoma and adenocarcinoma) before surgery, any stage but eligible for surgery; no history of malignant tumors other than the esophageal cancer being investigated; and with complete clinical data. The exclusion criteria were: EUS was not performed due to the large tumors with an obstruction or the patient did not cooperate; the patient underwent exploratory surgery only; or the patient received neoadjuvant therapy before the surgery. It is routine practice at the authors' institution to carry out EUS before esophageal cancer surgery. See the flow diagram for details (Fig. 1).

2.2.2. T staging by EUS. EUS was performed by 5 doctors with over 10 years' experience in EUS. A gastroscope (GIFH260, Olympus, Tokyo, Japan), a EUS system (EUM2000, Olympus), and an ultrasound microprobe (UM-2R/3R, Olympus) were used for the EUS examinations. The patients fasted for 8 hours before the examination. The patient was lying on the left side for gastroscopy. After the lesion was located, an appropriate amount of degassed water was filled in, and the air inside the lumen was aspired to allow the lesion and the microprobe to be fully immersed. The microprobe was used to scan along with the lesion, from the proximal end to the distal end.

The gastrointestinal tract wall can be classified into 5 layers by EUS: the hyperechoic band that represents the surface and the superficial layer of mucosa; the hypoechoic layer that represents the mucosa and muscularis mucosa; the hyperechoic band that represents the submucosa; the hypoechoic band that represents the mucosa propria; and the hyperechoic band that represents the adventitia of the esophagus wall.[9] The pre-operative T staging was made according to the eighth edition of the UICC/AJCC TNM staging system for esophageal cancer[14]: Tx, tumor cannot be assessed; T0, no evidence of primary tumor; Tis, high-grade dysplasia, defined as malignant cells confined by the basement membrane; T1, tumor invades the lamina propria, muscularis mucosae, or submucosa; T2, tumor invades the muscularis propria; T3, tumor invades the adventitia; T4, tumor invades adjacent structures.

2.2.3. Surgery and pT staging. The surgery was performed 1 to 2 weeks after the EUS examination by the same team of surgeons led by an experienced thoracic surgeon with 30 years of professional experience. Patients underwent standardized invasive esophagectomy, open operation, or thoracoscopy combined with laparotomy based on their own preference and the surgeons' experience. The postoperative pathological staging was confirmed by the same group of pathologists according to the 8th edition of the UICC/AJCC TNM staging system for esophageal cancer.[14]

2.2.4. Outcomes. Patient characteristics and clinical data were extracted from the charts into a secured database, including age, sex, body mass index, smoking, drinking, hypertension, diabetes and other complications, nutritional risk screening score (NRS 2002),[15] and tumor marker levels (carcinoembryonic antigen, cancer antigen 199, squamous cell cancer antigen, and cytokeratin fragment).

The EUS examination provided the ultrasound-based T staging (uT stage). The pathological examination provided the maximal diameter of the tumor, pathological type, degree of differentiation, incision margins (R0: complete resection under the microscope; R1: residuals left under the microscope; and R2: residuals left by bare eyes), and pathological T staging (pT stage).

2.2.5. Statistics. All analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY). As none of the continuous variables followed the normal distribution, they were presented as medians (interquartile ranges) and analyzed using the Mann-Whitney *U* test. The categorical variables were presented as frequencies and percentages and analyzed using the chi-square test or Fisher exact test. Using the pT staging as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value,

accuracy, and 95% confidence interval (CI) of the EUS-based T staging was calculated. The univariable and multivariable logistic regression analyses (enter method) were performed to explore the factors independently associated with the accuracy of the uT stage. The characteristics with $P < .10$ in the univariable analyses were entered into the multivariable analysis. P values $< .05$ were considered statistically significant.

3. Results

3.1. Characteristics of the patients

Table 1 shows the characteristics of the patients. A total of 196 patients were eligible, but 4 were excluded because they underwent exploratory surgery only and 23 because they received other treatments between the EUS and surgery. Finally, 169 patients were included. The median age was 65 (59–69) years, 67.5% of the patients were male, and 94.1% had esophageal squamous cell carcinoma. There were no differences between the patients accurately or inaccurately staged by EUS, except regarding squamous cell cancer antigen levels, tumor differentiation, and pT stage (Table 1).

3.2. EUS and pT stagings

Table 2 presents the uT and pT stages. Among the 169 patients, 37 (21.9%) were overstaged by EUS, and 33 (19.5%) were understaged, with 99 (58.6%) being correctly staged by EUS. The highest rate of concordance was for uT1 tumors (94.1%), followed by uT3 (77.8%), uT2 (28.8%), uT4a (27.3%), and uT4b (0%).

3.3. Accuracy of EUS staging

Table 3 presents the diagnostic accuracy parameters of EUS staging. The overall accuracy of EUS was 58.6% (51.2%–

Table 1

Baseline information of the patients.

Characteristics	All patients (n = 169)	Inaccurately staged by EUS (n = 70)	Accurately staged by EUS (n = 99)	P
Demographic features				
Age (yrs), median (IQR)	65 (59–69)	65 (57–70)	65 (60–69)	.801
Male, n (%)	114 (67.5)	49 (70.0)	65 (65.7)	.553
Body mass index, kg/m^2, median (IQR)	23.05 (21.2–25.6)	22.4 (21.0–25.2)	23.4 (21.2–25.9)	.299
Smoking index, n (%)				.961
0	75 (44.4)	31 (44.3)	44 (44.4)	
0–399	45 (26.6)	18 (25.7)	27 (27.3)	
≥400	49 (29.0)	21 (30.0)	28 (28.3)	
Alcohol, n (%)				.365
Never	93 (55.0)	34 (48.6)	59 (59.6)	
Often	42 (24.9)	20 (28.6)	22 (22.2)	
Every day	34 (20.1)	16 (22.9)	18 (18.2)	
Hypertention, n (%)	56 (33.1)	26 (37.1)	30 (30.3)	.352
Diabetes, n (%)	5 (3.0)	1 (1.4)	4 (4.0)	.405
Cirrhosis, n (%)	1 (0.6)			.414
Chronic heart disease, n (%)	9 (5.3)	3 (4.3)	6 (6.1)	.737
Nutrition risk screening score, median (IQR)	1 (1–1)	1 (1,2)	1 (1,1)	.096
Tumor maker, median (IQR)				
CEA (ng/mL)	2.37 (1.59–3.64)	2.49 (1.76–3.64)	2.22 (1.44–3.68)	.367
CA199 (U/mL)	9.67 (6.24–14.42)	10.51 (5.43–18)	9.62 (6.37–13.22)	.438
SCC (ng/mL)	1.0 (0.7–1.6)	1.1 (0.8–2.1)	0.9 (0.63–1.4)	.044
CYFRA (ng/mL)	2.205 (1.71,3.075)	2.05 (1.7–2.83)	2.30 (1.74–3.28)	.467
Pathological features				
Tumor diameter (cm), median (IQR)	5 (3–6)	5 (3–6)	5 (4–6)	.307
Tumor type, n (%)				.354
Squamous cell carcinoma	159 (94.1)	1 (1.4)	4 (4.0)	
Adenocarcinoma	5 (3.0)	68 (97.1)	91 (91.9)	
Others	5 (3.0)	1 (1.4)	4 (4.0)	
Tumor differentiation, n (%)				.034
None	90 (53.3)	37 (52.9)	53 (53.5)	
Low	21 (12.4)	6 (8.6)	15 (15.2)	
Mediate	48 (28.4)	26 (37.1)	22 (22.2)	
High	10 (5.9)	1 (1.4)	9 (9.1)	
pT stage, n (%)				<.001
pTis	1 (0.6)	1 (1.4)	0 (0)	
pT1	37 (21.9)	21 (30.0)	16 (16.2)	
pT2	24 (14.2)	7 (10.0)	17 (17.2)	
pT3	92 (54.4)	29 (41.4)	63 (63.6)	
pT4a	13 (7.7)	10 (14.3)	3 (3.0)	
pT4b	2 (1.2)	2 (2.9)	0 (0)	

CA = cancer antigen, CEA = carcinoembryonic antigen, CYFRA = cytokeratin fragment, EUS = endoscopic ultrasound, IQR = interquartile range, pT = pathological T, SCC = squamous cell cancer antigen, SD = standard deviation.

Table 2

EUS-based and pathological T staging.

Number	pTis	pT1	pT2	pT3	pT4a	pT4b	Total	Correct, n (%)
uT1	1	16	0	0	0	0	17	16 (94.1)
uT2	0	17	17	22	3	0	59	17 (28.8)
uT3	0	4	7	63	6	1	81	63 (77.8)
uT4a	0	0	0	7	3	1	11	3 (27.3)
uT4b	0	0	0	0	1	0	1	0
Total	1	37	24	92	13	2	169	99 (58.6)
Over-staged	1	21	7	7	1	/	37	/
Under-staged	/	/	0	22	9	2	33	/

EUS = endoscopic ultrasound, pT = pathological T, uT = ultrasound-based T.

66.0%). Sensitivity was low, at 0% to 70.8% depending upon the pT stage, but specificity was higher, at 71.0% to 100.0%, also depending upon the pT stage.

3.4. Factors associated with the accuracy of EUS staging

Only tumor differentiation and pT stage ≥T2 had *P* values of <.10 in the univariable analyses and were included in the multivariable analyses. Table 4 presents the multivariable analysis of the factors associated with the accuracy of EUS for the staging of esophageal cancer. The results revealed that highly differentiated tumors (odds ratio = 9.167, 95%CI: 1.096–76.651, *P* = .041) and pT stage ≥T2 (odds ratio = 2.932, 95% CI: 1.399–6.146, *P* = .004) were independent factors for accurate uT staging.

4. Discussion

The sensitivity and specificity of EUS for esophageal cancer are variable.[9,13,16] This study aimed to determine the accuracy of EUS for the T staging (uT stage) of esophageal cancer and to explore the factors that affect the accuracy. The results showed that the staging of esophageal cancer using EUS has low sensitivity but high specificity. Highly differentiated tumors and pT stage ≥2 tumors were associated with the accuracy of uT staging. These results might help determine the categories of patients in whom the EUS might be considered more reliable, in whom better treatment options could be made, therefore hinting toward some clinical doubts in patients who do not match those characteristics. Esophageal cancer is more common in Asia than in Western countries[4]; therefore, providing additional data about Chinese patients is important. Notably, since neoadjuvant therapy has a great effect on T staging, patients who received neoadjuvant therapy before the surgery were exclude.

Since there are important differences in management and treatment options among the different T stages of esophageal cancer, determining the T stage as precisely as possible is essential for the correct management of the patients,[4] and inaccurate pre-treatment staging may impact survival.[17,18] In the present study, 58.6% of the patients were correctly staged by EUS. This is lower than the 82% observed by Bartel et al[19] and 91.9% by Lee et al[20] but similar to Yang et al[21] (58.2%). The differences among studies might lie in the different populations of patients. Previous studies mainly included early stage patients. Indeed, in the study by Bartel et al,[19] 78% of the patients were pT0, compared with <1% in the present study. In the study by Lee et al,[20] all the patients were pT1 or pT2, compared with 36.7% in the present study, and the sample size was smaller (73 cases). The T distribution in the present study was more similar to that observed in the study by Yang et al.[21] A meta-analysis of 12 studies showed that the concordance rate was 65%,[22] while another meta-analysis of 19 studies showed sensitivity and specificity of 85% and 87%,[23] and a meta-analysis of 44 studies reported an accuracy of 79% for the T stage.[9] The discrepancies could also be due to differences in the training of the physicians. Indeed, the learning curve should not be dismissed,[24] and access to different training and ultrasound systems might influence the results. Importantly, DaVee et al[25] suggest that EUS should be part of the pre-operative examinations for esophageal cancer, but that it should not be the only examination guiding the treatments, as also supported by Bartel et al[19] and Krill et al.[26]

The present study showed that the sensitivity of EUS for the staging of esophageal cancer was low, even poor, but that the specificity was moderate to high. This is supported by previous studies that consistently showed low sensitivity by higher specificity for the extent of invasion of esophageal cancer.[9,13,27] Ishihara et al[16] and Bartel et al[19] reported a moderate sensitivity with high specificity. A large meta-analysis of over

Table 3

The accuracy of EUS-based T staging.

	pTis	pT1	pT2	pT3	pT4a	pT4b
Sensitivity, % (95%CI)	0.0 (0.0–97.5)	43.2 (27.1–60.5)	70.8 (48.9–87.4)	68.5 (58.0–77.8)	23.1 (5.0–53.8)	0.0 (0.0–84.2)
Specificity, % (95%CI)	100.0 (97.8–100.0)	99.2 (95.9–100.0)	71.0 (62.9–78.3)	76.6 (65.6–85.5)	94.9 (90.2–97.8)	99.4 (96.7–100.0)
PPV, % (95%CI)	NA	94.1 (68.7–99.2)	28.8 (22.0–36.8)	77.8 (69.5–84.3)	27.3 (10.2–55.5)	0.0
NPV, % (95%CI)	99.4 (99.4–99.4)	86.2 (82.5–89.2)	93.6 (88.7–96.5)	67.1 (59.5–73.8)	93.7 (91.6–95.2)	98.8 (98.8–98.8)
Overall accuracy, % (95%CI)	58.6 (51.2–66.0)					

CI = confidence interval, EUS = endoscopic ultrasound, NPV = negative predictive value, PPV = positive predictive value, pT = pathological T.

Table 4

The univariable and multivariable logistic regression analysis for independently associated factors of the accuracy of EUS-based T staging.

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95%CI	P	OR	95%CI	P
Tumor differentiation, n (%)						
None	Reference	/	/	Reference	/	/
Low	1.355	(0.532,3.45)	.524	1.207	(0.464,3.135)	.700
Mediate	0.568	(0.296,1.09)	.089	0.569	(0.29,1.115)	.101
High	7.451	(0.927,59.897)	.059	9.167	(1.096,76.651)	.041
pT stage ≥T2, n (%)	2.620	(1.302,5.272)	.007	2.932	(1.399,6.146)	.004

CI = confidence interval, EUS = endoscopic ultrasound, OR = odds ratio, pT = pathological T.

2500 patients reported high sensitivity and high specificity of EUS,[28] but the included patients covered the 1986 to 2006 period, which is not contemporary and could be influenced by the available imaging systems. Two other meta-analyses were finally confounded by the inclusion of a too wide variety of patients, resulting in high heterogeneity.[22,23] Young et al[22] concluded that EUS does not stage esophageal cancer adequately, while Thosani et al[23] concluded that EUS had good accuracy. Those 2 meta-analyses should be considered with caution.

In the present study, tumors ≥pT2 were independently associated with a higher likelihood of being correctly staged by EUS. This is supported by Luo et al[9] who showed that for T1 and T2 staging cancer, the sensitivity was 66% to 77%, compared with 84% to 87% for T3 and T4 staging cancer, despite of similar specificity. Nevertheless, Zuccaro et al[29] showed that the discrepancy rate was 45%, and most of their patients were stage ≥pT2. In addition, a highly differentiated tumor was also an independent factor associated with a correct staging, and tumor grade can be determined on the initial biopsy. Tumors with a high differentiation are considered to have a better prognosis than poorly differentiated ones as they are less aggressive and tend to be less invasive.[4] Therefore, the possibility of finding invasive foci that could lead to a larger tumor size is less likely, increasing the likelihood of correct EUS staging. Nevertheless, it should be stressed that a biopsy has a possibility of showing different results from that of endoscopic mucosal resection or esophagectomy.[30] Therefore, the results of the present study might help determine the categories of patients in whom the EUS might be considered more reliable, therefore hinting toward some clinical doubts in patients who do not match those characteristics. Of course, the physicians must remain cautious, especially since the pathological stage is determined after resection, but the tumor differentiation can be obtained on a biopsy.

This study has limitations. The sample size was small since the patients were from a single hospital. The patients were selected, which could limit the generalizability of the results. Because of the retrospective nature of the study, we were limited to the data available in the charts, but this could closer to the data obtained in routine clinical practice. Although the 5 endoscopists had extensive experience, the differences between them should be taken into account. Finally, all patients underwent esophagectomy, which does not represent the routine clinical practice since small lesions can be removed by endoscopic mucosal resection.[28] Multicenter studies are necessary to determine the diagnostic value of EUS for esophageal cancer.

In conclusion, this study suggests that the staging of esophageal cancer using EUS has low sensitivity but high specificity. Highly differentiated tumors and pT stage ≥2 tumors were associated with the accuracy of uT staging. These results might help determine the categories of patients in whom the EUS might be more accurate.

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