—Original Article—

Value of EUS in determining infiltration depth of early carcinoma and associated precancerous lesions in the upper gastrointestinal tract

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ABSTRACT

Objective: The objective is to evaluate the value of EUS in the determination of infiltration depth of early carcinoma and precancerous lesions in the upper gastrointestinal tract and to analyze the various factors affecting the accuracy of EUS. **Methods:** One hundred and sixty-three patients diagnosed with early gastric cancer or early esophageal cancer, and associated precancerous lesions, who were seen in our hospital in the recent 10 years were selected. These patients received EUS before endoscopic submucosal dissection or surgery. With a pathological diagnosis as the gold standard, the accuracy, sensitivity, specificity, and misjudgment rate of EUS in determining the invasion depth were evaluated using the pathological stratification (mucosa, M1/2; muscularis mucosa, M3; submucosa, [SM]; and muscularis propria) or TN stratification (mucosa, T1a; SM, T1b), and the possible causes of miscalculation were analyzed. **Results:** Based on the pathological stratification, the overall accuracy of EUS was 78.5%, and the overestimation and underestimation rates were 17.8% and 3.7%, respectively. Based on the TN stratification, the overall accuracy of EUS was 81%, and the overestimation and underestimation rates were 16.6% and 2.5%, respectively. There was a significant difference between the groups in terms of overestimation and underestimation rates ($P < 0.05$), indicating that EUS was more likely to overestimate the depth. Univariate analysis showed that the factors affecting accuracy included lesion size, macroscopic features, sunken mucosa, mucosa with granular and nodular changes, and ulceration. Multivariate logistic regression analysis revealed that larger lesions, mucosa with granular and nodular changes, and ulceration were independent risk factors for the overestimation of infiltration depth by EUS. **Conclusion:** EUS is highly accurate in determining the infiltration depth of early cancer and precancerous lesions in the upper gastrointestinal tract. It also has a good reference value for treatment selection and prognostication. However, attention should be paid to its overestimation, especially accompanied by the aforementioned factors.

Key words: early esophageal cancer, early gastric cancer, early upper gastrointestinal cancer, EUS, infiltration depth, precancerous

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INTRODUCTION

With the recent improvement of material living standards and changes in dietary habits, the incidence of gastrointestinal tumors is also increasing yearly, it is now as high as 40%.[1-3] Early detection, diagnosis, and treatment of carcinoma have a great impact on the prognosis and long-term survival of these patients. For early tumors, the main treatments include endoscopic mucosal resection, endoscopic submucosal dissection (ESD), and surgery.[4-6] Compared with surgery, endoscopy has the advantages of less trauma, a higher cure rate, and faster recovery.[7,8] However, the selection of treatment is based on the invasion depth and lymph node and distant metastases. Conventional endoscopy (CE) only can be limited to superficial mucosal lesions, and its accuracy for deeper lesions is distinctly low.[9,10] EUS combines endoscopy and an ultrasonic mini-probe to directly detect mucosal surface lesions under endoscopy. At the same time, ultrasonic real-time scanning can be employed to determine the lesions infiltrating each layer of the tube wall and their relationship with the surrounding tissues. It can also be used to evaluate the size, shape, histological type, origin layer, and invasion depth of the lesions, thereby improving the detection rate of early cancer. The purpose of our study was to assess the value of EUS in determining the invasion depth of early carcinoma and precancerous lesions.

MATERIALS AND RESEARCH METHODS

EUS

A total of 163 patients who were admitted to our hospital between January 2009 and December 2020 were selected. They were instructed to take dyclonine glue for anesthesia and defoaming before examination for 6 h to relieve the symptoms of nausea and to reduce gastrointestinal motility. First, the suspicious lesions were detected using CE or staining endoscopy + magnifying endoscopy, the air in the stomach was sucked out, and an optimal amount of degassed water was injected into the esophagus or gastric cavity to completely cover the lesions. Subsequently, a high-frequency ultrasound mini-probe (model UM-DP20-25R, mainframe MAJ-935, frequency 20 MHz) was utilized to scan and obtain images. The size, morphological characteristics, level of origin, infiltration depth, internal echo, and boundary of the lesions were used to initially assess the nature of the tumor. Then, ESD or surgical operation was selected to completely remove the lesions, and all these postoperative pathological specimens were sent for examination and were pathologically confirmed as early gastric or early esophageal cancer, and its precancerous lesions.

Early gastric cancer (EGC) involves the mucosa or submucosa (SM), regardless of lymph node metastasis. Superficial esophageal cancer (formerly known as early esophageal cancer) is limited to the mucosa and SM without lymph node metastasis. Precancerous lesions are pathological changes that have been proven to be closely related to the occurrence of cancer, which can be divided into low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN).[11,12]

The exclusion criteria were as follows: such as patients who could not be accessed by ultrasound endoscopic probe due to GI narrowing, patients who had adjacent organs or distant metastases, and patients for whom ESD was not necessary because LGIN could be followed up. Those who met the following conditions were included: The pathological specimens following by ESD or surgical excision were all confirmed to be the above lesions, and have complete case data. The final cases actually included in our study were EGC, superficial esophageal cancer, and associated HGIN. All patients signed informed consent before enrollment in the study. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (Approval No. KJ2020-129-01).

When tumor cells infiltrate, EUS shows the destruction of normal five-layer structure and a thickened hypoechoic mass. The EUS diagnostic criteria based on pathological stratification were as follows: Mucosal layer (M): The first layer was thickened or irregular, and the second was intact; muscularis mucosa (MM): Layers 1 and 2 were destroyed and had disappeared, but they did not break through layer 3; submucosal layer (SM): Layers 1, 2, and 3 were blurred and had an uneven echo, and layer 3 was uninterrupted; muscularis propria (MP): Layer 3 was broken off, and a punctate high echo could be observed in layer 4. The criteria based on TN stratification were as follows: T1a: Invasion of the mucosal layer and MM and T1b: Invasion of the SM.

Under CE and EUS, the image of EGC scanned using a 20MHZ mini-probe is shown in Figure 1a and b.

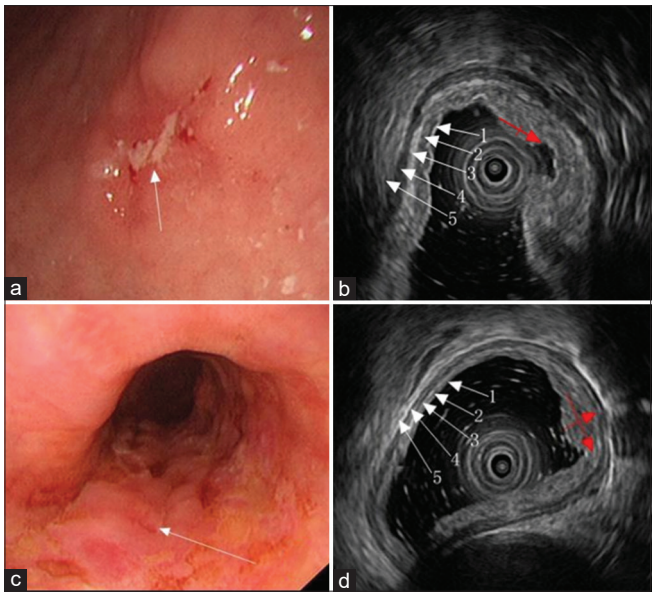

Figure 1. (a) White light endoscopic image of early gastric cancer with uneven mucosal surface and superficial ulcer formation. (b) The stomach wall has five layers: the hyperechoic layer, mucosa (M); hypoechoic layer, MM; hyperechoic, SM; hypoechoic, MP; and hyperechoic, serosal layer (SS). As shown by the red arrow, the lesion infiltrated the M, showing a thickened and slightly hypoechoic structure, and the SM is intact, consistent with the pathological diagnosis. Pathologically, it is an intramucosal carcinoma of the gastric antrum and HGIN in some areas are moderately differentiated. (C) White light endoscopic image of early esophageal cancer. (d) As shown by the red arrow, the M of the middle and lower esophagus is damaged and hypoechoic, and the hypoechoic lesions have infiltrated the MM. The pathological findings are squamous cell carcinoma, moderately differentiated, with cancer tissue infiltrating the MM (type M3) MM: Muscularis mucosa, SM: Submucosa, MP: Muscularis propria, SS: Serous layer, HGIN: High-grade intraepithelial neoplasia

The image of early esophageal cancer is shown in Figure 1c and d.

Pathological examination

Complete pathological specimens were obtained through ESD or surgical resection, and they were fixed with neutral formaldehyde solution for 24 h. After routinely implementing paraffin embedding and slicing, eosin and hematoxylin staining was conducted, and two experienced pathologists analyzed the slices and made a pathological diagnosis.

Investigated variables

To compare EUS and pathological studies in judging the depth of tumor microinvasion, the patients were divided into two groups according to the consistency of the diagnosis: inconsistent and consistent diagnosis groups. Various factors affecting the accuracy of the results were analyzed. The upper one-third of the stomach was considered to include the fundus and cardia; the middle one-third includes the body of the stomach, and the lower one-third includes the angle, antrum, and pylorus. The upper segment of the esophagus is <24 cm, the middle segment is 24–32 cm, and the lower segment is 33–40 cm from the incisor. The macroscopic types based on endoscopy are as follows: 0–I (elevated type), 0–II (flat type), and 0–III (depression type), of which the 0–II type can be further separated into the superficial elevated type (0–II a), superficial flat type (0–II b), and the superficial depression type (0–II c). A sunken mucosa is characterized as superficial erosion or ulcer-like changes in the mucosa, which is classified as II c + III of the macroscopic type. The irregular mucosal surface is defined as rough and uneven, accompanied by granular and nodular changes or abnormal edges. Mucosal erythema or paleness is defined as changes in hyperemia or decreased color. Ulceration is characterized as active ulcers or ulcers with fibrotic scars.[13,14]

Statistical methods

All the data were analyzed using SPSS 26.0. (IBM SPSS, Chicago, IL, US). Continuous data are expressed as mean ± standard deviation (X ± S) or quartiles and were compared using *t*-test or nonparametric test. Categorical data are presented as rates and percentages. Chi-square test (χ^2) or continuity correction or Fisher's exact test was used for univariate comparison, and binary logistic regression analysis was used for the multivariate comparison of the intergroup. $P < 0.05$ were considered statistically significant.

RESULTS

General clinical, EUS, and pathological data of the patients

The data of 163 patients, comprising 117 males and 46 females, were retrospectively analyzed. The average age of the patients was 68.44 ± 10.84 years; the average tumor size was 1.8 cm, with a range of 1.2–2.5 cm; 53 cases involved the esophagus, with the middle third being the most; 110 cases involved the stomach, with the lower third being the most. In total, 93 lesions (57.1%) were of the flat macroscopic type. ESD was performed for 144 cases (88.3%) and surgery was performed for 19 cases. Based on the pathological diagnosis, there were 56 cases of HGIN, 75 cases of intramucosal carcinoma, and 32 cases of submucosal carcinoma; and 20 lesions (12.3%) were of the undifferentiated type. The details are shown in Table 1.

Table 1. Clinical, EUS, and pathological features of the 163 patients and their lesions

Variable types	Grouping	*n* (%)
Sex	Male	117 (71.8)
	Female	46 (28.2)
Age, years	≤60	45 (27.6)
	>60	118 (72.4)
Tumor size (cm)	≤2	113 (69.3)
	>2	50 (30.7)
Location	Upper	6 (3.7)
Esophagus	Middle	36 (22.1)
	Lower	11 (6.7)
	Upper	20 (12.3)
Gastric	Middle	36 (22.1)
	Lower	54 (33.1)
Macroscopic type	0-I (elevated)	37 (22.7)
	0-II (flat)	93 (57.1)
	0-III (depressed)	33 (20.2)
Sunken mucosa	No	87 (53.4)
	Yes	76 (46.6)
Irregular mucosal surface	No	53 (32.5)
	Yes	110 (67.5)
Mucosa erythema or paleness	No	6 (3.7)
	Yes	157 (96.3)
Ulcer	No	116 (71.2)
	Yes	47 (28.8)
Resection method of specimen	ESD	144 (88.3)
	Surgery	19 (11.7)
Invasion depth of EUS	M1/2	87 (53.4)
	M3	24 (14.7)
	SM	45 (27.6)
	MP	7 (4.3)
Invasion depth of pathology	M1/2	101 (62.0)
	M3	30 (18.4)
	SM	32 (19.6)
Pathological type	HGIN	56 (34.4)
	Intramucosal cancer	75 (27.6)
	Submucosal cancer	32 (19.6)
Histological type	Differentiated	143 (87.7)
	Undifferentiated	20 (12.3)

HGIN: High-grade intraepithelial neoplasia; SM: Submucosa; MP: Muscularis propria

Accuracy of EUS in determining the invasion depth according to pathological stratification

Based on the pathological stratification, the sensitivities of EUS for the determination of the infiltration depth of the mucosa, MM, and SM were 81.2%, 70.0%, and 78.1%; the specificities were 91.9%, 97.7%, and 84.7%; the accuracies were 85.3%, 92.6%, and 83.4% (overall accuracy was 78.5%); and the positive predictive values were 94.3%, 87.5%, and 55.6%, respectively. The Jordan indices were 0.73, 0.68, and 0.63, and the Kappa values were 0.701, 0.734, and 0.545, respectively. There were 35 cases of misjudgment, 29 cases of overestimation, and 6 cases of underestimation. The overall misjudgment rate was 21.5%: The overestimation and underestimation rates were 17.8% and 3.7%, respectively, with a significant difference between the two values ($P < 0.01$), indicating that EUS was more likely to overestimate the infiltration depth according to the pathological stratification, as shown in Tables 2 and 3.

Accuracy of EUS for determination of invasion depth based on TN stratification

Based on the TN stratification, the sensitivities of EUS for M and SM were 81.7% and 78.1%; the specificities were 87.5% and 84.7%; the accuracies were 82.8% and 83.4% (overall accuracy: 81%); and the positive predictive values were 96.4% and 55.6%, respectively. The Jordan indices were 0.69 and 0.63, and the Kappa values were 0.560 and 0.545, respectively. There were 31 cases of misjudgment: 27 cases of overestimation and 4 cases of underestimation. The overall misjudgment rate was 19.0%: The overestimation and underestimation rates were 16.6% and 2.5%, respectively, with a significant difference between the two values ($P < 0.01$). This indicated that EUS was more likely to overestimate the infiltration depth according to TN stratification, as shown in Tables 4 and 5.

Considering that EUS could yield inconsistent results on the infiltration depth results based on the pathological and TN stratifications, we compared both stratifications in the overestimation and underestimation groups, and found that the difference was not statistically significant ($P > 0.05$), indicating that both stratifications could be introduced to determine the infiltration depth. The results are shown in Table 6.

Analysis of various factors affecting the inconsistencies in eus and pathological examination results

results of univariate analysis

The effects of various factors on the accuracy of the diagnosis based on EUS were analyzed using a nonparametric test or Chi-squared test. We found that there were no significant differences in age, sex, location, mucosal erythema or paleness, specimen resection method, pathological stratification, and histopathological type ($P > 0.05$). The proportion of large diameters, the 0–III macroscopic type (depression type), sunken mucosa, mucosa with granular and nodular changes, and cases of ulceration were greater in the inconsistent diagnosis group, and the difference was statistically significant ($P < 0.05$). These factors contributed to the

Table 2. Comparison of EUS and pathological investigations for determination of infiltration depth according to histopathological stratification

EUS diagnosis	Total	Pathological diagnosis		
		M1/2	M3	SM
M1/2	87	82	2	3
M3	24	2	21	1
SM	45	15	5	25
MP	7	2	2	3
Total	163	101	30	32

SM: Submucosa; MP: Muscularis propria

Table 3. Inconsistent results of EUS compared with those of pathological examinations

Lamination	Misjudgment	
	Overestimation	Underestimation
M1/2	19	0
M3	7	2
SM	3	4
Total	29	6

SM: Submucosa

Table 4. Comparison of EUS and pathological investigations based on the TN stratification

EUS diagnosis	Total	Pathological diagnosis	
		T1a	T1b
T1a	111	107	4
T1b	45	20	25
MP	7	4	3
Total	163	131	32

MP: Muscularis propria

Table 5. Inconsistent results of EUS compared with those of pathological examinations

Lamination	Misjudgment	
	Overestimation	Underestimation
M	24	0
SM	3	4
Total	27	4

SM: Submucosa

Table 6. Differences between the misjudgment rates for the pathological and TN stratifications

	Pathological	TN	*P*
Over	29	27	-
Under	6	4	-
Total	35	31	0.892

inconsistency between EUS and pathological diagnosis. The results are shown in Table 7. In addition, the EUS stratification covers the MP, and all cases involving this layer belonged to the inconsistent diagnosis group, the statistical difference of this layer was not clinically significant, so it was not included.

Results of multivariate logistic regression analysis

The single factor with statistical significance [Table 7] was included in the multivariate analysis and used to establish a binary logistic regression model. Comprehensive analysis based on the research purpose of this study showed that lesion diameters of >2 cm, irregular mucosa associated with granular and nodular changes, and ulceration are independent risk factors affecting the accuracy of EUS on the infiltration depth ($P < 0.05$). With more risk factors, the accuracy of EUS will gradually decrease. The results are shown in Table 8.

DISCUSSION

The incidence of early upper gastrointestinal cancer is increasing each year, and it is critical to accurately appraise the infiltration depth of lesions before operation. EUS can be combined with endoscopy and an ultrasound probe to discover deep-penetrating lesions, which can make up for the shortcomings of CE.[15,16] Several previous studies have found differences in the accuracy of EUS in determining the infiltration depth of early upper gastrointestinal cancer, which roughly ranges from 75% to 92%.[10,17,18] Our study found that the overall accuracies for the pathological and TN stratifications were 78.5% and 81%, respectively, which were consistent with the previous. Regarding the misjudged cases, there was no significant difference between the two methods, and both of them can be adopted, but the overestimation of the infiltration depth was more frequent than the underestimation ($P > 0.05$), indicating that EUS is more likely to overestimate the infiltration depth of early upper gastrointestinal cancer. Furthermore, the EUS stratification includes the MP, and the pathological stratification only includes the M, MM, and SM, hence, the overall consistency of EUS and pathological outcomes cannot be calculated by the Kappa value, and only reckoned the consistency of each layer. If the cases of infiltration into the MP detected by EUS and pathologically diagnosed with early cancer are excluded, the misdiagnosis rate of EUS will decrease, especially with respect to overestimation. This is also not in line with actual clinical practice. In summary, our study covered the MP and used the Kappa value to calculate the consistency of each layer.

With pathological stratification, the sensitivities of EUS for M1/2, M3, and SM were 81.2%, 70%, and 78.1%, respectively. With TN stratification, the sensitivities

Table 7. Univariate analysis of risk factors affecting the accuracy of EUS

Factors	Total number	Consistent group, *n* (%)	Inconsistent group, *n* (%)	χ^2	*P*
Sex, male	117	91 (77.8)	26 (22.2)	0.138	0.71
Age (years)	163	66 (59-72)	67 (53-74)	-	1
Tumor size (cm)					
≤2	113	95 (84.1)	18 (15.9)	6.71	0.01
>2	50	33 (66.0)	17 (34.0)		
Location					
Esophagus upper	6	6 (100.0)	0 (0)	-	0.61
Middle	36	30 (83.3)	6 (16.7)		
Lower	11	8 (72.7)	3 (27.2)		
Gastric upper	20	17 (85.0)	3 (15.0)		
Middle	36	28 (77.8)	8 (22.2)		
Lower	54	39 (72.2)	15 (27.8)		
Macroscopic type					
0-I (elevated)	37	33 (89.2)	4 (10.8)	22.43	0
0-II (flat)	93	79 (84.9)	14 (15.1)		
0-III (depressed)	33	16 (48.5)	17 (51.5)		
Sunken mucosa	76	53 (69.7)	23 (30.3)	6.53	0.011
Irregular mucosal surface	110	79 (71.8)	31 (28.2)	9.03	0.003
Mucosal erythema or paleness	157	123 (78.3)	34 (21.7)	-	1
Ulcer	47	25 (53.2)	22 (46.8)	25.14	0
Resection method of specimen					
ESD	144	116 (80.6)	28 (19.4)	2.07	0.15
Surgery	19	12 (63.2)	7 (36.8)		
Pathological type					
HGIN	55	50 (90.9)	5 (9.1)	5.31	0.07
Intramucosal cancer	75	57 (76.0)	18 (24.0)		
Submucosal cancer	33	25 (75.8)	8 (24.2)		
Histopathological type, undifferentiated	20	15 (75.0)	5 (25.0)	0.014	0.905

ESD: Endoscopic submucosal dissection; HGIN: High-grade intraepithelial neoplasia

Table 8. Multivariate analysis of risk factors affecting the accuracy of EUS

Factors	Regression coefficient β	*P*	OR	95% CI
Tumor size (cm)	0.945	0.039	2.573	1.051-6.299
Macroscopic type	-	0.359	-	-
0-II (flat)	0.604	0.380	1.830	0.475-7.052
0-III (depressed)	1.409	0.155	4.093	0.588-28.507
Sunken mucosa	−1.228	0.144	0.293	0.056-1.523
Irregular mucosal surface	1.784	0.004	5.954	1.784-19.870
Ulcer	2.124	0.026	8.369	1.287-54.414

OR: Odds ratio; CI: Confidence interval

of EUS for T1a and T1b were 81.7% and 78.1%, respectively. This demonstrated that EUS is the most likely to find out lesions in the mucosa among all the layers, but the accuracy of pathological stratification is slightly lower than that of TN stratification. This may be attributed to the subdivision of the mucosa into M1/2 and M3. Like the tumor, the MM is also a narrow hypoechoic segment on ultrasound images, and the original hypoechoic band thickens or changes with tumor invasion, therefore, the resolution effect of the image is poor. The M and SM are hyperechoic areas. When the lesion invades, the original hyperechoic cord is destroyed or thickened, which is more obvious on the image and easier to distinguish; this is why the accuracy of MM is the lowest. In view of this, the ultrasonic probe with a higher frequency can be applied to obtain a clearer image.

Previous studies have reported that the accuracy of EUS for upper gastric lesions is the lowest,[10,19] which may be attributed to the lesion located above the reflex being out of reach of the ultrasonic probe, and the SM layer of the gastric fundus being thin, with more blood vessels and fibrous tissue. This study discovered that the misjudgment rates for the lower esophagus and lower gastric regions were the highest, which were not in accord with the previous studies. Thirteen of the 54 cases were located within the gastric angle, which is a concave mark near the small curvature of the stomach and is located at the anatomical reflection. However, because the ultrasound mini-probe is a hard pipe without bending, which is not easily accessible

to it and is difficult to scan at the standard position. On the other hand, the lower esophagus is adjacent to the cardia, where the squamous epithelium merges with the columnar epithelium, which may also lead to misjudgment. In short, when scanning the lower esophagus, gastric antrum, and gastric angle, we should attach great importance to the direction and position of the ultrasonic probe to reduce misjudgment.

This study discovered that tumor size, irregular mucosal surfaces with granular and nodular changes, and ulcers were essential relevant to misjudgment, especially in the overestimation group, and the difference was statistically significant ($P < 0.05$). The reasons may be as follows. For lesion size, several previous studies have reported that the accuracy for large lesions is likely to decrease,[20-22] which is in keeping with the results of our study. The diameters of lesions in the inconsistent diagnosis group were larger than those of lesions in the consistent group ($P < 0.05$). A possible reason is that the penetration of ultrasound is reduced when the tumor is larger, and small surrounding or deeply infiltrating foci may be easily missed, one of the solutions to this is to use a probe with a lower frequency for observation. For lesions with ulcers or scar formation after ulceration,[13,23] the surrounding tissues are often affected by inflammatory processes, which are prone to hyperemia or edema. With the development of fibrous hyperplasia, surrounding tissues will gather, converge, or adhere to each other. This often occurs in the SM so that the accuracy for SM is reduced. Therefore, we should take a biopsy at fixed points with the help of staining and ME. Finally, some previous studies have indicated that irregular mucosa and tumor-like marginal elevation can affect accuracy,[9] which are consistent with the findings of our research. The mucosa with granular or nodular changes and uneven surfaces makes it difficult for ultrasound mini-probe to align properly, and some heterogeneous structures appear as mixed echoes on the ultrasound image, which also influences the accuracy of EUS.

Furthermore, lesions that are difficult to accurately judge using EUS can be assessed with a combination of computed tomography, magnetic resonance imaging, and other imaging examinations to detect lymph node metastasis and adjacent organ invasion,[24,25] as well as a comprehensive assessment of the clinical symptoms of the patient. The number of cases in our study was limited, and the number of cases in each layer was unbalanced; therefore, large-sample and multi-center research should be carried out to reduce the difference. Furthermore, our study was retrospective, and the postoperative prognostic assessment and 3-year, 5-year, and 10-year survival rates of the patients were not evaluated. Therefore, these should be explored in further research to determine the accuracy of EUS in early carcinoma.

In summary, EUS has good accuracy for evaluating the infiltration depth of early carcinoma and precancerous lesions in the upper gastrointestinal tract, and it has clinical value for the selection of treatment and prognostication. However, it may overestimate the infiltration depths of tumors, especially in large lesions, mucosa with granular and nodular changes, and ulceration, which may reduce its accuracy.

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Conflicts of interest

There are no conflicts of interest.

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