CLINICAL TRIALS STUDY

Clinicopathologic factors influencing the accuracy of EUS for superficial esophageal carcinoma

Jung Im Jung, Gwang Ha Kim, Hoseok I, Do Youn Park, Tae Kyun Kim, Young Hwa Cho, Yong Wan Sung, Mun Ki Choi, Bong Eun Lee, Geun Am Song

Jung Im Jung, Gwang Ha Kim, Tae Kyun Kim, Young Hwa Cho, Yong Wan Sung, Mun Ki Choi, Bong Eun Lee, Geun Am Song, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan 602-739, South Korea
Hoseok I, Department of Chest Surgery, Pusan National University School of Medicine, Busan 602-739, South Korea
Do Youn Park, Department of Pathology, Pusan National University School of Medicine, Busan 602-739, South Korea

Correspondence to: Gwang Ha Kim, MD, PhD, Department of Internal Medicine, Pusan National University School of Medicine and Biomedical Research Institute, Pusan National University Hospital, 179, Gudeok-ro, Seo-Gu, Busan 602-739, South Korea. doc0224@pusan.ac.kr
Telephone: +82-51-2407869   Fax: +82-51-2448180

Abstract

AIM: To identify clinicopathologic factors influencing the accuracy of a high-frequency catheter probe endoscopic ultrasonography (EUS) for superficial esophageal carcinomas (SECs).

METHODS: A total of 126 patients with endoscopically suspected SEC, who underwent EUS and curative treatment at Pusan National University Hospital during 2005-2013, were enrolled. We reviewed the medical records of the 126 patients and compared EUS findings with histopathologic results according to clinicopathologic factors.

RESULTS: A total of 114 lesions in 113 patients were included in the final analysis. The EUS assessment of tumor invasion depth was accurate in 78.9% (90/114) patients. Accuracy did not differ according to histologic type, tumor differentiation, tumor location, or macroscopic shape. However, accuracy significantly decreased for tumors $\geq$ 3 cm in size (P = 0.002). Overestimation and underestimation of the invasion depth occurred for 11 (9.6%) and 13 lesions (11.4%), respectively. In multivariate analyses, tumor size $\geq$ 3 cm was the only factor significantly associated with EUS accuracy (P = 0.031), and was specifically associated with the underestimation of invasion depth.

CONCLUSION: EUS using a high-frequency catheter probe generally provides highly accurate assessments of SEC invasion depth, but its accuracy decreases for tumors $\geq$ 3 cm.

Key words: Esophageal cancer; Endoscopic ultrasonography; Accuracy

Core tip: Endoscopic ultrasonography (EUS) using a high-frequency catheter probe generally provides a highly accurate assessment of the invasion depth of superficial esophageal cancers (SECs). However, accuracy decreases for tumors $\geq$ 3 cm in size, with a tendency towards underestimation for these tumors. Therefore, caution is warranted when selecting the treatment modality for SECs $\geq$ 3 cm in size on the basis of pretreatment EUS staging.

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INTRODUCTION

The recent development of endoscopic diagnostic techniques using iodine staining and narrow band imaging has been accompanied by an increase in the incidence of superficial esophageal carcinoma (SEC). Traditionally, radical surgery has been the treatment of choice for most cases of esophageal cancer, even for patients with cancer that is limited to the mucosa[1]. However, surgery is generally associated with high rates of mortality and morbidity[2,3]. Furthermore, surgery cannot be performed in a considerable proportion of patients because of advanced age or the presence of comorbidities[4,5]. In these situations, endoscopic treatment (such as endoscopic mucosal resection) may represent an alternative to esophagectomy for early-stage esophageal cancer[6,7].

Because endoscopic treatment is primarily indicated for patients with a low risk of lymph node metastasis (LNM), identifying such patients is particularly important[2,8]. The presence of LNM is strictly related to the depth of tumor invasion in the esophageal wall. Indeed, the risk of LNM is 0%-3% among lesions confined to the mucosa, but reaches 15%-50% when the submucosa has been invaded[9,10]. Therefore, when selecting patients for local endoscopic resection, it is crucial to distinguish between mucosal cancers and more advanced cancers that have infiltrated the submucosa.

EUS provides a detailed image of the esophageal wall. To date, it is the most accurate method that is available for staging esophageal carcinoma in terms of both depth of invasion (T stage) and presence or absence of involved lymph nodes (N stage)[11]. Additionally, EUS using a high-frequency catheter probe provides a high level of diagnostic accuracy for distinguishing between mucosal and submucosal esophageal cancers[12,13]. There are a few reports on clinicopathologic factors that can influence the accuracy of EUS[9,14]. Therefore, the aims of this study were to assess the accuracy of EUS conducted with a high-frequency (20 MHz) catheter probe for determining the depth of endoscopically suspected SEC, and then to identify clinicopathologic factors influencing the accuracy of EUS in distinguishing between mucosal and submucosal lesions.

MATERIALS AND METHODS

We retrospectively analyzed a database of all patients who had esophageal cancer and had undergone EUS for pretreatment staging at Pusan National University Hospital (Busan, Korea) between December 2005 and June 2013. We identified a total of 127 lesions in 126 patients with endoscopically suspected SEC. None of the patients had previously received chemotherapy or chemoradiotherapy. This study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital.

Endoscopy

After conventional examination by a high-resolution endoscope (GIF-H260, Olympus, Tokyo, Japan), all patients underwent chromoendoscopy with 3% iodine solution. Following the Paris classification system, the macroscopic shapes of SECs were categorized as either protruding (Ⅰ), non-protruding and non-excavated (Ⅱ), or excavated (Ⅲ)[15]. Type Ⅱ lesions were subclassified as slightly elevated (Ⅱa), flat (Ⅱb), or slightly depressed (Ⅱc). Next, all lesions were broadly classified into 3 groups: elevated (Ⅰ, Ⅱa), flat (Ⅱb) and depressed (Ⅱc, Ⅲ) types. The tumor location was also divided into 3 groups: upper, mid and lower esophagus. The upper esophagus was defined as extending from the upper esophageal sphincter (UES) to 5 cm distal to the UES. The lower esophagus was defined as extending from the lower esophageal sphincter (LES) to 5 cm proximal to the LES. The mid-esophagus was defined as the remaining region between the upper and the lower esophagus.

EUS

EUS was performed using a radial scanning 20 MHz catheter probe (UM3D-DP20-25R, Olympus) following the jelly-filled method[16,17]. The probe was passed through one instrument channel of a 2-channel endoscope (GIF-2T240, Olympus) and 20-40 mL of echo jelly (Daejin Co., Ltd., Seoul, South Korea) was instilled using a 10 Fr disposable oxygen catheter (HS-OC, Hyup Sung Medical Co., Ltd., Seoul, South Korea) through the other instrument channel until the esophageal lumen was filled. All examinations were performed under intravenous conscious sedation (midazolam with or without meperidine). At least 15 still EUS images were recorded for each patient, and these images were stored on magneto-optical disks. A review of the EUS photos was performed by a single experienced endosonographer (Kim GH) who had previously performed more than 1000 examinations and was blinded to the final diagnosis.

The probe yielded high-quality cross-sectional images of the esophageal wall and was easily directed to the small cancer lesions under the direct vision of the endoscopists[13]. The SECs were classified into 3 groups: mucosal, submucosal, or advanced. Lymph nodes were evaluated by using a radial scanning 12 MHz catheter probe (UM3D-DP12-25R, Olympus). Lymph nodes were considered malignant, if at least one of the following criteria was met: lymph node larger than 10 mm, delineated borders, hypoechoic structure resembling the primary tumor, and round in shape. Endosonographic lymph node classification was performed according to the sixth TNM system[18].

Clinicopathologic review

Endoscopic resection or esophagectomy was performed within 2-4 wk following EUS. The resected specimens

Characteristics	No. of lesions
Location	
Upper esophagus	18 (15.8)
Mid-esophagus	72 (63.2)
Lower esophagus	24 (21.1)
Histologic type	
Squamous cell carcinoma	108 (94.7)
Adenocarcinoma	3 (2.6)
Neuroendocrine carcinoma	3 (2.6)
Differentiation degree	
Well differentiated	43 (37.7)
Moderately differentiated	61 (53.5)
Poorly differentiated	10 (8.8)
Macroscopic shape	
Elevated	62 (54.4)
Flat	38 (33.3)
Depressed	14 (12.3)
Circumferential spread	
< 1/4	44 (38.6)
1/4–2/4	35 (30.7)
2/4–3/4	16 (14.0)
≥ 3/4	19 (16.7)
Tumor size (cm)	
< 3	74 (64.9)
≥ 3	40 (35.1)

were fixed in 10% formaldehyde. Carcinomas with adjacent non-neoplastic mucosa were serially cut into 2 mm slices in parallel and embedded in paraffin, and then sectioned and stained with hematoxylin-eosin for histological examination. Tumor location, macroscopic shape, circumferential spread, tumor size, histologic type, tumor differentiation, the depth of invasion, LNM, and other clinicopathologic findings were reviewed according to the World Health Organization recommendations[19]. The depth of invasion was classified as mucosal, submucosal, or advanced (the tumor had invaded the muscularis propria or deeper) according to the Japanese criteria[14].

Statistical analysis
The accuracy of EUS in relation to the clinicopathologic features was assessed using the χ^2 test or Fisher's exact test. Subsequently, a multivariate logistic regression analysis was performed to identify variables considered to have significant influences on the accuracy of EUS. Statistical calculations were performed using SPSS version 21.0 software for Windows (SPSS, Chicago, United States). Results were considered statistically significant for all *P* values < 0.05.

RESULTS

Demographic, endoscopic, and histologic characteristics
Of the 126 patients, 13 patients were excluded from the analyses because final histologic results were not available: 2 patients did not receive treatment because of underlying comorbid disorders, and 11 patients were lost

to follow-up after EUS. A total of 114 lesions in 113 patients (105 men and 8 women; age range: 39-84 years; mean age: 64 years) were included in the study analyses. Ninety-three lesions were treated with surgery and 21 lesions were treated with endoscopic resection. The predominant tumor location was the mid-esophagus (72/114, 63.2%), and squamous cell carcinoma was the most common histologic type (108/114, 94.7%). The mean size of lesions was 2.4 cm (range, 0.3-5.8 cm). The characteristics of lesions are summarized in Table 1.

Accuracy of EUS in staging superficial esophageal cancer
The overall accuracy of EUS assessment of tumor invasion depth was 78.9% (90 of 144 lesions), as detailed in Table 2. The accuracy of EUS did not differ according to the histologic type, tumor differentiation, tumor location, or tumor macroscopic shape. The accuracy of EUS somewhat decreased for tumors that involved more than three-fourths of the esophageal circumference, although the difference was not statistically significant (*P* = 0.136). The accuracy of EUS significantly decreased for tumors ≥ 3 cm in size (*P* = 0.002; Table 3). Multivariate analysis indicated that large tumor size (≥ 3 cm) was the only factor that was both significantly and independently associated with the accuracy of tumor invasion depth assessed using EUS (*P* = 0.031). The overall accuracy for detecting LNM was 86.0% (80/93). No variables were significantly associated with the diagnostic accuracy for LNM (Table 4).

Factors affecting the overestimation or underestimation of invasion depth using EUS
Overestimation of the invasion depth was observed for 11 lesions (9.6%). Tumors located in the lower esophagus tended to have a higher risk of overestimation than other parts of the esophagus (*P* = 0.074; Table 5). However, tumor location was not associated with overestimation in a multivariate analysis (Table 6).

Underestimation of the invasion depth was observed in 13 lesions (11.4%). Increased circumferential spread and tumor size ≥ 3 cm were associated with underestimation in univariate analyses (*P* = 0.001 and *P* = 0.001, respectively; Table 7). The results of a multivariate analysis suggested that tumor size ≥ 3 cm was the only factor that was both significantly and independently associated with underestimation (*P* = 0.049; Table 6).

DISCUSSION
To date, EUS is considered the best available technique for defining locally advanced, potentially curable lesions in patients with carcinomas of the esophagus or esophagogastric junction. In the present study, EUS conducted with a high-frequency (20 MHz) catheter probe accurately identified SEC invasion depth in 78.9% of the cases. However, the results of our multivariate analysis indicated that accuracy significantly decreased for tumors ≥ 3 cm in size. Our data confirm the usefulness of EUS for dis-

Table 2 Endosonographic assessment of the depth of lesions with superficial esophageal carcinoma

EUS	No.	Histopathology			Accuracy of EUS	Overestimation of EUS	Underestimation of EUS
		Mucosal	Submucosal	Advanced			
Mucosal	55	45	10	0	81.8%	0%	18.2%
Submucosal	56	11	42	3	75.0%	19.6%	5.3%
Advanced	3	0	0	3	100%	0%	0%
Total	114	56	52	6	78.9%	9.6%	11.4%

EUS: Endoscopic ultrasonography.

Table 3 Accuracy of endosonographic assessment of invasion depth in superficial esophageal carcinoma, according to clinicopathologic characteristics

Characteristics	No. of accurately assessed lesions	*P* value
Location		0.379
Upper esophagus	16/18	
Mid-esophagus	57/72	
Lower esophagus	17/24	
Histologic type		0.767
Squamous cell carcinoma	85/108	
Adenocarcinoma	2/3	
Neuroendocrine carcinoma	3/3	
Differentiation degree		0.617
Well differentiated	35/43	
Moderately differentiated	46/61	
Poorly differentiated	9/10	
Macroscopic shape		0.486
Elevated	46/62	
Flat	32/38	
Depressed	12/14	
Circumferential spread		0.136
< 1/4	37/44	
1/4–2/4	29/35	
2/4–3/4	13/16	
≥ 3/4	11/19	
Tumor size (cm)		0.002
< 3	65/74	
≥ 3	25/40	

Table 4 Accuracy of endosonographic assessment of lymph node metastasis in superficial esophageal carcinoma, according to clinicopathologic characteristics

Characteristics	No. of accurately assessed lesions	*P* value
Location		0.137
Upper esophagus	15/16	
Mid-esophagus	43/54	
Lower esophagus	22/23	
Histologic type		1.000
Squamous cell carcinoma	75/88	
Adenocarcinoma	2/2	
Neuroendocrine carcinoma	3/3	
Differentiation degree		0.182
Well differentiated	24/25	
Moderately differentiated	48/58	
Poorly differentiated	8/10	
Macroscopic shape		0.225
Elevated	47/58	
Flat	22/23	
Depressed	11/12	
Circumferential spread		0.356
< 1/4	25/28	
1/4–2/4	28/31	
2/4–3/4	14/16	
≥ 3/4	13/18	
Tumor size (cm)		0.769
< 3	47/54	
≥ 3	33/39	

tinguishing between tumors that have invaded the mucosa and those that have infiltrated the submucosa in agreement with the results of previous studies[9,12,13,18,20,21]. It is important to achieve such a distinction before choosing a nonsurgical therapeutic approach. Indeed, the risk of LNM is markedly increased among submucosal cancers, owing to the rich lymphatic network of the submucosa.

In the present study, EUS overestimated the invasion depth of 11 of the 114 lesions (9.4%). Five of these lesions (45.5%) were located in the lower esophagus (within 5 cm proximal to the lower esophageal sphincter). Overestimation can be attributed to the following factors[22,23]: (1) peritumoral inflammation, which leads to wall thickening that makes it difficult to distinguish the different layers; (2) inappropriate positioning of the ultrasound transducer due to anatomical locations (for example, in the lower esophagus near the esophagogastric junction) causing pseudo-thickening and a poor view of the layers; (3) massive invasion of the submucosa, which can reduce the thickness of the hyperechogenic medial layer such that it becomes unrecognizable; and (4) use of the water-

filled balloon method.

In previous reports, which mainly studied Barrett's adenocarcinoma, the overestimation rate was 20%[9,24]. Mucosal nodularity-like protruding shape was found to contribute to overestimation, probably because of the altered pattern of the sonographic layer due to inflammatory changes. However, in the present study, almost all SECs were squamous cell carcinomas, which were not usually accompanied by inflammatory changes. Therefore, macroscopic shape was not associated with the overestimation that was observed in the present study. Although tumor location was not significantly associated with overestimation in multivariate analysis, overestimation of invasion depth may be especially common in the lower esophagus. A true association could have been obscured by the limited sample size of the present study. When performing EUS with a catheter probe, it is not easy to dilate the lumen adequately in the lower esophagus because of external compression such as the diaphragm and the frequent passage of EUS medium into the stomach. Consequently, the tumor and esophageal wall become

Table 5 Clinicopathologic characteristics associated with overestimation of invasion depth by endoscopic ultrasonography in superficial esophageal carcinoma

Characteristics	No. of overestimated lesions	P value
Location		0.074
Upper esophagus	2/18	
Mid-esophagus	4/72	
Lower esophagus	5/24	
Histologic type		0.464
Squamous cell carcinoma	10/108	
Adenocarcinoma	1/3	
Neuroendocrine carcinoma	0/3	
Differentiation degree		0.805
Well differentiated	4/43	
Moderately differentiated	7/61	
Poorly differentiated	0/10	
Macroscopic shape		0.491
Elevated	7/62	
Flat	2/38	
Depressed	2/14	
Circumferential spread		0.266
< 1/4	7/44	
1/4-2/4	2/35	
2/4-3/4	0/16	
≥ 3/4	2/19	
Tumor size (cm)		0.513
< 3	6/74	
≥ 3	5/40	

Table 7 Clinicopathologic characteristics associated with underestimation of invasion depth by endoscopic ultrasonography in superficial esophageal carcinoma

Characteristics	No. of underestimated lesions	P value
Location		0.160
Upper esophagus	0/18	
Mid-esophagus	11/72	
Lower esophagus	2/24	
Histologic type		1.000
Squamous cell carcinoma	13/108	
Adenocarcinoma	0/3	
Neuroendocrine carcinoma	0/3	
Differentiation degree		0.903
Well differentiated	4/43	
Moderately differentiated	8/61	
Poorly differentiated	1/10	
Macroscopic shape		0.379
Elevated	9/62	
Flat	4/38	
Depressed	0/14	
Circumferential spread		0.001
< 1/4	0/44	
1/4–2/4	4/35	
2/4-3/4	3/16	
≥ 3/4	6/19	
Tumor size (cm)		0.001
< 3	3/74	
≥ 3	10/40	

Table 6 Multivariate analysis for endoscopic ultrasonography accuracy according to clinicopathologic factors

Variables[1]	Odds ratio (95%CI)	P value
Accuracy		
Tumor size ≥ 3 cm	0.229 (0.060-0.872)	0.031
Lower esophagus	0.433 (0.127-1.476)	0.181
Overestimation		
Lower esophagus	3.393 (0.785-14.664)	0.102
Underestimation		
Tumor size ≥ 3 cm	6.208 (1.005-38.338)	0.049
Circumferential spread ≥ 3/4	2.328 (0.542-9.995)	0.256

[1]All variables were included in the multivariate analysis, including those variables that were and were not significantly associated with accuracy, overestimation, and underestimation in univariate analyses.

somewhat thickened, making it difficult to maintain the proper distance between the probe and the lesion, which is necessary to acquire high-resolution images. As a result, the tumor invasion depth can appear exaggerated during EUS. Finally, the method of EUS examination could also influence the rate of overestimation. When using a water-filled balloon method, the balloon sheath can compress the lesion to the submucosa, until the mucosal cancer appears similar to a submucosal cancer. Thus, the overestimation rate would increase. This limitation could be overcome by relying on other methods such as the water-filled lumen method or the jelly-filled method. Indeed, in a study that included a water-filled balloon method, the overestimation rate was 18.6%[23], which is somewhat higher than the 9.4% overestimation rate in our study.

Although EUS overestimated the invasion depth in some cases, underestimation was observed in other cases. Particularly, EUS underestimated the invasion depth in 13 of 114 lesions (11.4%). In 10 of these cases (76.9%), the tumor was ≥ 3 cm in size. It was additionally observed that, as the circumferential spread of the tumor increased, the rate of underestimation also increased. Circumferential spread is ultimately similar to tumor size-both reflect large tumors. Consequently, only 1 of these findings (tumor size ≥ 3 cm) was significantly associated with underestimation in our multivariate analysis. Underestimation can be attributed to the following factors[19]: (1) tumor location near the esophagogastric junction; and (2) minute submucosal invasion, which is also known as sm1 cancer. If the tumor is located near the esophagogastric junction, there is a risk of underestimation because of the technical difficulty of EUS at this location (as discussed in the paragraph above). Because EUS resolution is around 200 µm on a 20 MHz probe[25], minute submucosal invasive cancer is difficult to diagnose. Indeed, of the 11 sm1 cancers in the present study, 6 were underestimated (data not shown). Compared with a conventional EUS transducer, the catheter probe used in this study is more capable of investigating small lesions and of examining suspicious foci that could invade most deeply[26]. Despite these advantages, SECs ≥ 3 cm in size tended to be underestimated by EUS, mainly because of a failure to detect focal areas with submucosal invasion. Therefore, endosonographers should always keep in mind the possibility of underestimation during EUS of large sized SECs. Additionally, this tendency

towards underestimation should be considered when selecting a treatment modality for SEC (*e.g.*, endoscopic resection *vs* surgery).

It remains difficult to depict the esophageal wall using an EUS probe because it is not easy to retain water within the esophageal lumen. To resolve this issue, methods have been developed to conduct the EUS probe with a water-filled balloon[27,28] or a device for continuous instillation of water[29]. However, the interposition of the balloon and the compression by the balloon may interfere with EUS images[21]. Further, attempts to inflate the esophagus by a continuous instillation of water may increase the risk of aspiration[30]. To avoid these obstacles, a jelly-filled method is applied for the evaluation of esophageal lesions[13,31]. This procedure is characterized by filling the esophageal lumen with jelly, which enables convenient observation without the use of a balloon[13]. In a comparison study of a jelly-filled method and a water-filled balloon method, the jelly-filled method provided superior assessments of invasion depth for SEC[7]. Therefore, we used the jelly-filled method in the present study.

In addition to the assessment of invasion depth, EUS plays an important role in the evaluation of potential LNM[11,32]. In the present study, we assessed LNM using only a 12 MHz probe, instead of the conventional EUS scope. Although spectrum bias is present because our study only included patients with SEC, the accuracy of LNM assessed with a 12 MHz probe was acceptable (86.0%). This result is similar to that in the previous reports[11,32,33]. In addition, we observed no clinicopathologic factors that were significantly associated with diagnostic accuracy for LNM. Therefore, combined assessment with low (12 MHz) and high (20 MHz) frequency probes would be adequate for selecting the treatment modality for patients with SEC.

This study had several limitations. First, this was a retrospective study that evaluated the accuracy of the EUS approach for determining the invasion depth of SEC. Additionally it is possible that some bias was introduced when retrospectively reviewing the EUS images. During the EUS examination, we took at least 15-30 endosonographic images. To some degree, this comprehensive collection of images could compensate for the retrospective nature of this study. Second, almost all SECs in the present study were squamous cell carcinoma, because Barrett's cancer is quite rare in Korea. Third, the EUS images were interpreted by a single experienced endosonographer, and interobserver variation was not evaluated. Although EUS is observer-dependent and the expertise improves with exposure to additional cases, interobserver agreement in EUS using a jelly-filled method is reported to be 82.3%[13]. Therefore, the use of the jelly method in our study could lessen this limitation.

In conclusion, EUS using a high-frequency catheter probe generally provides a highly accurate assessment of the SEC invasion depth. However, accuracy decreases for tumors $\geq$ 3 cm in size, with a tendency towards underestimation for these tumors, suggesting that caution is warranted when selecting a treatment for such tumors according to pretreatment EUS staging, particularly because the lesion might be underestimated. Therefore, caution is warranted when selecting the treatment modality for SECs $\geq$ 3 cm in size on the basis of pretreatment EUS staging.

COMMENTS

Background
Endoscopic ultrasonography (EUS) the most accurate method that is available for staging esophageal carcinoma in terms of both depth of invasion and presence or absence of involved lymph nodes. Additionally, EUS using a high-frequency catheter probe provides a high level of diagnostic accuracy for distinguishing between mucosal and submucosal esophageal cancers. However, there are a few reports on clinicopathologic factors that can influence the accuracy of EUS.

Research frontiers
In this study, the authors assessed the accuracy of EUS conducted with a high-frequency (20 MHz) catheter probe for determining the depth of endoscopically suspected superficial esophageal carcinomas (SECs). Additionally, they tried to identify clinicopathologic factors influencing the accuracy of EUS in distinguishing between mucosal and submucosal lesions.

Innovations and breakthroughs
The accuracy of EUS assessment for tumor invasion depth was 78.9%. Accuracy did not differ according to histologic type, tumor differentiation, tumor location, or macroscopic shape. However, accuracy significantly decreased for tumors $\geq$ 3 cm in size. In multivariate analyses, tumor size $\geq$ 3 cm was the only factor significantly associated with EUS accuracy, and was specifically associated with the underestimation of invasion depth.

Applications
EUS using a high-frequency catheter probe generally provides a highly accurate assessment of the SEC invasion depth. However, accuracy decreases for tumors $\geq$ 3 cm in size, with a tendency towards underestimation for these tumors, suggesting that caution is warranted when selecting a treatment for such tumors according to pretreatment EUS staging, particularly because the lesion might be underestimated.

Terminology
Superficial esophageal carcinoma is defined as mucosal or submucosal carcinoma with or without lymph node metastasis.

Peer review
This is a good study in which authors analyze the clinicopathologic factors influencing the accuracy of EUS in SECs. The results suggest caution when selecting the treatment modality for SECs $\geq$ 3 cm in size on the basis of pretreatment EUS staging.

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