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Novel Endoscopic Criteria for Predicting Tumor Invasion Depth in Superficial Esophageal Squamous Carcinoma

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ABSTRACT

Background: Accurate prediction of tumor invasion depth in superficial esophageal squamous carcinoma (SESC) is essential for deciding the appropriate treatment strategy. We proposed novel endoscopic criteria to differentiate between mucosal and submucosal esophageal cancers and to evaluate the diagnostic accuracy and usefulness of the criteria.

Methods: A total of 352 patients who underwent endoscopic or surgical resection for SESC between 1991 and 2010 were included. First, the novel endoscopic criteria were created based on the endoscopic features of 60 randomly selected patients as follows: for T1m cancers, I. flat or slightly elevated or depressed lesion with smooth/even surface of any size, II. slightly elevated lesion of ≤ 1 cm with granular or uneven surface, III. hyperemic flat lesion of ≤ 3 cm with granular or uneven surface, IV. slightly depressed lesion of ≤ 2 cm with uneven surface and for T1sm cancers, I. irregularly (unevenly) nodular or protruded lesion of any size, II. slightly elevated lesion of > 1 cm with granular or uneven surface, III. hyperemic flat lesion of > 3 cm with granular or uneven surface, IV. irregularly (unevenly) depressed lesion of > 2 cm, and V. ulcerative lesion of any size. Next, the endoscopic findings of the remaining 292 patients were reviewed according to the criteria.

Results: The accuracy of novel endoscopic criteria was 79.5% (232/292). The sensitivity and specificity of mucosal cancers were 78.4% and 81.0%, respectively, whereas those for submucosal cancers were 81.0% and 78.4%, respectively. The accuracy for mucosal cancers was high (97.3%, 72/74) when the lesions were flat or slightly elevated/depressed with smooth/even surface regardless of size, whereas that for submucosal cancers was high (85.7%, 18/21) when the lesions were irregular/nodular protrusions regardless of size. In multivariate analysis, macroscopic type IIb lesion was identified as an independent factor affecting accuracy ($P < 0.05$). The difference in recurrence-free survival rates between endoscopically mucosal and submucosal cancers was significant ($P = 0.026$).

Conclusion: The novel endoscopic criteria appear to be accurate and useful in predicting invasion depth in SESC. Our criteria might help not only to decide the treatment strategy between surgery and endoscopic resection but also to predict the outcomes of SESC.

Keywords: Esophageal Neoplasms; Endoscopy; Neoplasm Staging; Prognosis

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Disclosures

The authors have no potential conflicts of interest to disclose.

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INTRODUCTION

Endoscopic resection has been increasingly used for the treatment of superficial esophageal squamous carcinoma (SESC).^{1,2} To overcome the challenges of the inevitable morbidity and mortality associated with radical esophageal resection, endoscopists have been successfully using endoscopic resection as a minimally invasive treatment in recent years.¹⁻⁴ However, endoscopic resection with curative intent is indicated only for mucosal invasive tumors because these tumors rarely metastasize to the lymph nodes.⁵ Therefore, accurate prediction of invasion depth in SESC is crucial for making a proper decision on the treatment strategy.

Endoscopic ultrasonography (EUS) has become the investigation of choice for staging esophageal cancer in terms of both invasion depth and presence or absence of involved lymph nodes.⁶⁻⁸ Recent reports have suggested that magnifying endoscopic classification based on microvascular morphology can provide a more accurate prediction of tumor invasion depth.⁹ However, magnifying endoscopes are not available at all institutions and the procedure involves additional costs and time. There are concerns that multiplicity of classifications involving complicated criteria might confuse general endoscopists.⁹ Moreover, some authors have reported that EUS showed an accuracy of no greater than 70% in the T staging of superficial esophageal cancer.^{7,10,11} In addition, other authors have reported that there were no statistically significant differences among magnifying endoscopy (ME) with narrow-band imaging (NBI), high-frequency EUS, and high-resolution endoscopy in predicting invasion depth in SESC.^{12,13} The macroscopic classification of superficial neoplasia in the Paris classification may help predict the extent of invasion into the submucosa and thus the choice between endoscopic or surgical treatment, but it is not accurate in predicting submucosal invasion because it reflects only the height, but not the other characteristics, of the lesion.¹⁴ To the best of our knowledge, no standard endoscopic criteria for diagnosing SESC have been established to date.

Therefore, we proposed novel endoscopic criteria for predicting invasion depth in SESC and evaluated the diagnostic accuracy and usefulness of the criteria.

METHODS

Patients

We retrospectively analyzed the data of 939 patients with esophageal cancer who had undergone endoscopic or surgical resection between January 1991 and December 2010 at Asan Medical Center, Seoul, Korea. Of the 939 patients, 396 underwent surgical or endoscopic resection for SESC without preoperative therapy, such as radiotherapy and chemotherapy. Among them, we excluded 44 patients with ambiguous pathologic results or endoscopic images that were inadequate for the prediction of tumor invasion depth. In the absence of standard endoscopic criteria for differentiating between mucosal (T1m) and submucosal (T1sm) cancers, we randomly selected 60 of the 352 patients to identify characteristic endoscopic features of T1m and T1sm cancers and to create the novel endoscopic criteria. The details of 60 randomly selected tumors are shown in **Supplementary Table 1**. Finally, we analyzed the remaining 292 patients based on the novel criteria (**Fig. 1**).

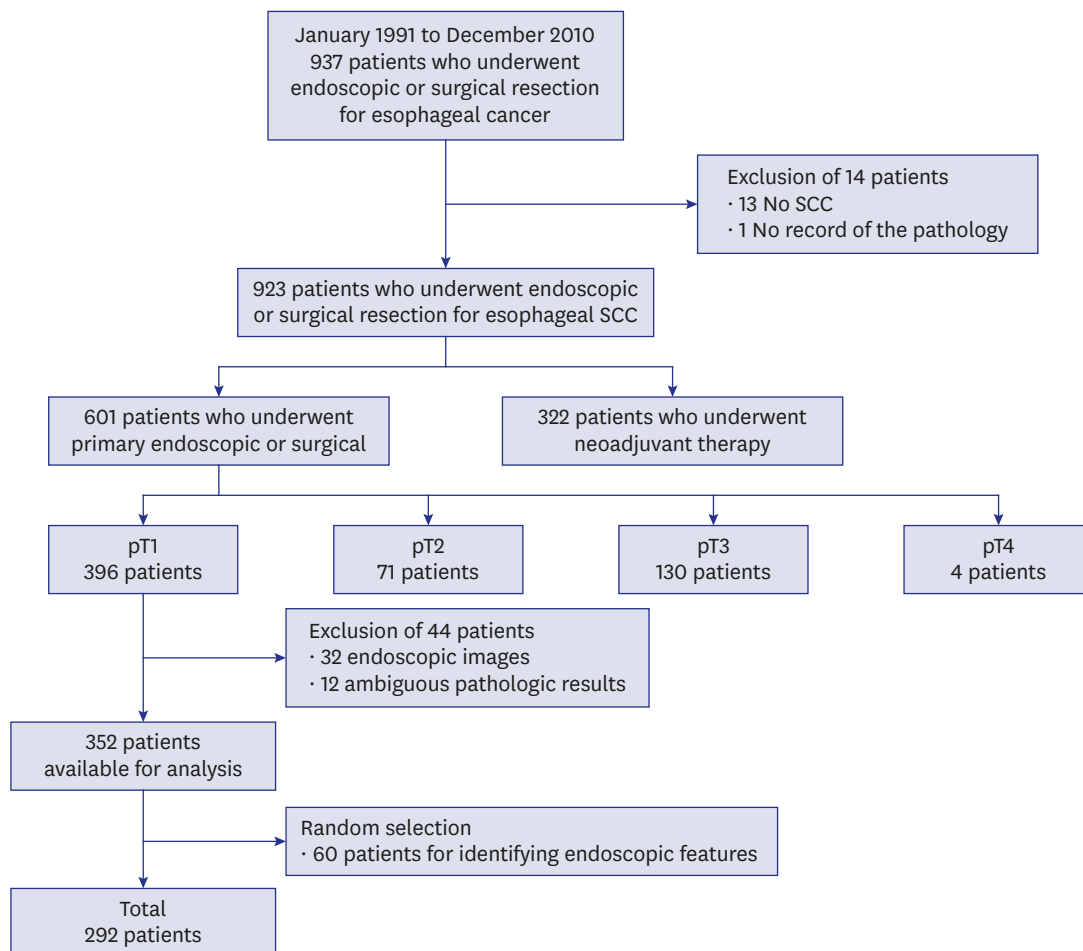


Fig. 1. Patient selection criteria.
SCC = squamous cell carcinoma.

Staging workup, treatment, and follow-up

Staging workup included endoscopy with biopsy, EUS, esophagography, and chest computed tomography (CT). In addition, patients with lower esophageal cancer underwent abdominal CT scans. After March 2001, positron emission tomography was routinely included in the staging workup. The endoscopes used in the staging workup were mainly GIF-H260 (Olympus Optical Co, Tokyo, Japan). Endoscopic resection was performed with endoscopic submucosal dissection and surgical resection was performed with a transhiatal, abdominal–right thoracic (Ivor–Lewis) or right thoracic–abdominal–cervical (McKeown) approach. After discharge, all patients entered a follow-up program according to a standard protocol. The endpoint of the oncological outcome was tumor recurrence. For the assessment of recurrence-free survival, recurrence was defined as the development of locoregional recurrence, distant metastasis, or de novo esophageal cancer (metachronous esophageal cancer) after endoscopic or surgical resection. All cases of recurrence were documented pathologically and/or by radiological imaging.

Endoscopic staging

We evaluated macroscopic morphology in accordance with the Japanese criteria¹⁵ after reviewing all endoscopic findings. The morphologic classification was published as follows:

Type 0 is divided into three categories corresponding to protruding (0–I), nonprotruding and nonexcavated (0–II), and excavated lesions (0–III). Type 0–I is subdivided into pedunculated (0–Ip) and sessile lesions (0–Is). Type 0–II is divided into three subtypes, a, b, and c, corresponding to slightly elevated, flat, and depressed lesions. Type 0–III is an ulcer.

In the absence of standard endoscopic criteria, we identified characteristic endoscopic features such as mucosal elevation/flatness/depression, tumor size, surface regularity and granularity of tumor base, nodularity and protrusion of tumor, and ulceration by reviewing and analyzing the recorded still images in 60 cases of pathologically proven SESC. Then we matched tumor depth by pathologic staging. When the surface was smooth and even, we found that it was more likely to be mucosal cancer than submucosal cancer, regardless of the size. Cases with endoscopic features such as a nodular/protruded or ulcerative lesion seemed like a submucosal cancer regardless of size. By contrast, when the surface was granular or irregular, the tumor depth varied depending on the tumor size and mucosal elevation/flatness/depression. In detail, flat lesions with a granular or uneven surface tended not to invade the submucosal layer even though they are large, whereas elevated or depressed lesions with a granular or uneven surface tended to invade the submucosal layer even though they are small. Therefore, the size of the submucosal invasion was set differently according to elevated, flat, and depressed lesions, and for simplification of clinical application, to 1, 3, and 2 cm, respectively, in these criteria for tumors with a granular or uneven surface. In other words, if the tumor with a granular or uneven surface was more than 1 cm in size for an elevated lesion, 3 cm for a flat lesion, and 2 cm for a depressed lesion, we classified it as a submucosal cancer. Finally, we developed novel endoscopic criteria on the basis of these results (Supplementary Fig. 1).

The novel endoscopic criteria for T staging in SESC were as follows: I. flat or slightly elevated or depressed lesion with smooth/even surface of any size, II. slightly elevated lesion of ≤ 1 cm with granular or uneven surface, III. hyperemic flat lesion of ≤ 3 cm with granular or uneven surface, IV. slightly depressed lesion of ≤ 2 cm with uneven surface for T1m cancer (Fig. 2) and I. irregularly (unevenly) nodular or protruded lesion of any size, II. slightly elevated lesion of > 1 cm with granular or uneven surface, III. hyperemic flat lesion of > 3 cm with granular or uneven surface, IV. irregularly (unevenly) depressed lesion of > 2 cm, V. ulcerative lesion of any size for T1sm cancers (Fig. 3). Using the novel endoscopic criteria, the endoscopic stage was determined based on the consensus of two experienced endoscopists blinded to histologic information. In detail, two endoscopists evaluated the lesions separately on the basis of the novel criteria and discussed the results if these did not match. If the lesions corresponding to different categories co-existed, we classified the lesions into the category that represented deeper invasion depth. Then, we evaluated the diagnostic usefulness of the endoscopic criteria for predicting invasion depth by comparing the endoscopic stages with the histology from the resected specimens.

Histopathology

Histologic examination of the endoscopically or surgically resected tumors was used as a standard to establish the accuracy of the novel endoscopic criteria. The specimens were analyzed using a standard method. All specimens were fixed in 10% formaldehyde, and the tumor and surrounding normal tissues were embedded in paraffin. The endoscopic and surgical specimens were serially sectioned perpendicularly at 2-mm and 5-mm intervals, respectively. Two pathologists with expertise in gastrointestinal cancer and blinded to the endoscopic findings examined the sections. Further, the size of the resected specimens and

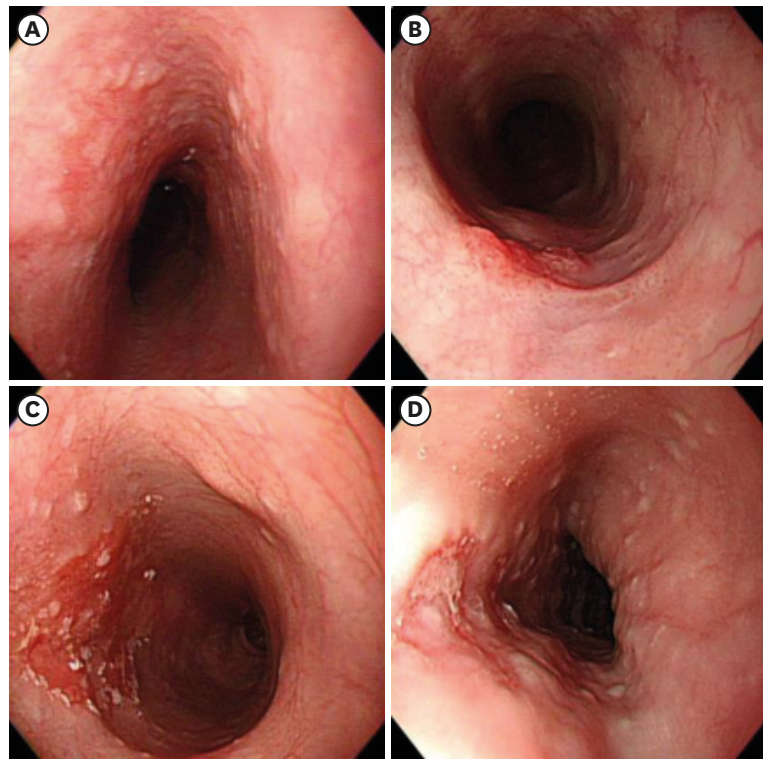


Fig. 2. Endoscopic criteria proposed for mucosal cancer. (A) flat or slightly elevated or depressed lesion with smooth/even surface of any size, (B) slightly elevated lesion of ≤ 1 cm with granular or uneven surface, (C) hyperemic flat lesion of ≤ 3 cm with granular or uneven surface, (D) slightly depressed lesion of ≤ 2 cm with uneven surface.

tumors, invasion depth, and histologic differentiation were evaluated. T1 cancer was further classified as T1m or T1sm, as described previously.¹⁶ The degree of differentiation was as recommended by the World Health Organization.¹⁷

Statistical analysis

To establish the criteria, some cases were randomly selected using simple random sampling with SPSS. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using standard definitions. The χ^2 test or Fisher's exact test was used to compare categorical variables, and the Mann–Whitney test was used to compare continuous variables. Univariate and multivariate logistic regression analyses were used to identify factors independently associated with the accuracy of endoscopic prediction. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the effect of variables influencing the accuracy. Oncologic outcomes were calculated using the Kaplan–Meier method and were compared using the log-rank test. A *P* value of < 0.05 was considered significant. All statistical tests were performed using SPSS versions 18.0 and 20.0 (IBM Corp., Armonk, NY, USA).

Ethics statement

This study was approved by the Institutional Review Board of Asan Medical Center, University of Ulsan College of Medicine (2011-0346). It was a retrospective study using medical records, and personal information protection measures were appropriately established so that the informed consent of the subject was exempted.

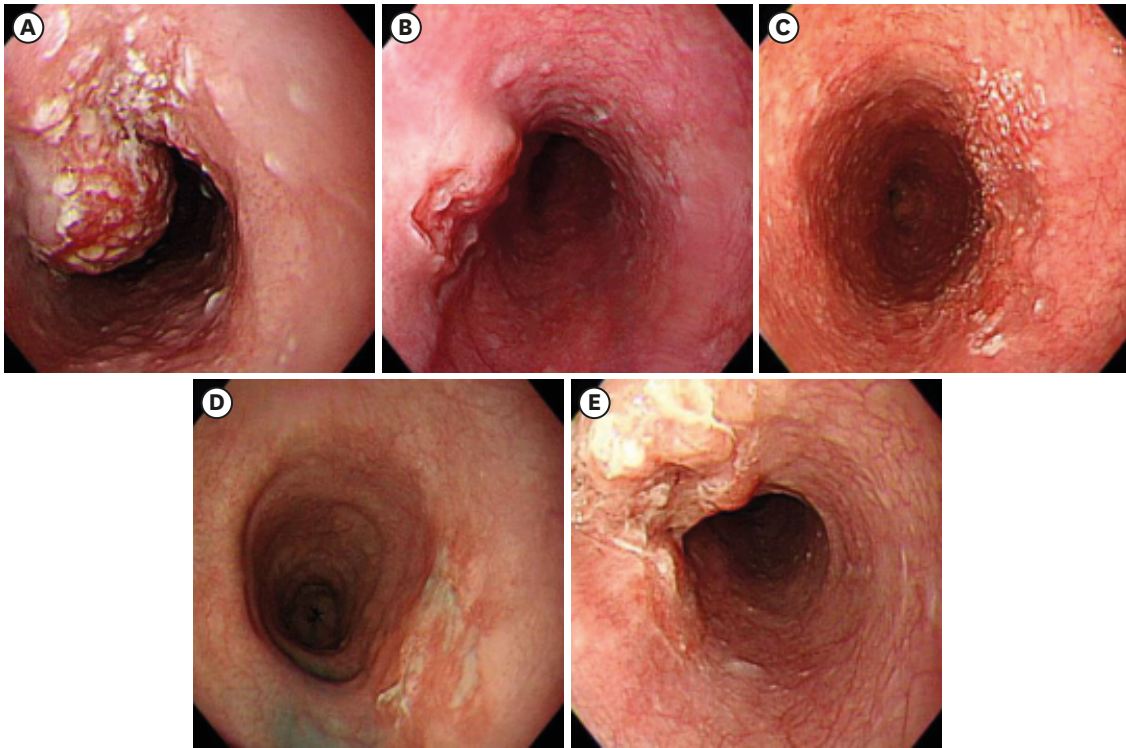


Fig. 3. Endoscopic criteria proposed for submucosal cancer. (A) irregularly (unevenly) nodular or protruded lesion of any size, (B) slightly elevated lesion of > 1 cm with granular or uneven surface, (C) hyperemic flat lesion of > 3 cm with granular or uneven surface, (D) irregularly (unevenly) depressed lesion of > 2 cm, (E) ulcerative lesion of any size.

RESULTS

Patient characteristics

A total of 292 patients (280 men, 12 women; median age 63 years, range 38–86 years) were enrolled in this study. Eighty-two (28.1%) and 210 (71.9%) patients underwent endoscopic resection and surgical resection, respectively. All lesions were squamous cell carcinomas and confirmed as T1 (171 lesions as T1m and 121 lesions as T1sm) on pathology. In detail, six (7.3%) of the 82 patients who underwent endoscopic resection were diagnosed pathologically with T1sm, three of whom had additional treatments (three radiotherapy and one chemoradiotherapy). The median tumor size was 2.1 cm (range, 0.2–11.8 cm), and other clinicopathological characteristics of patients are shown in **Table 1**.

Accuracy of endoscopic staging

The overall accuracy of T staging based on the novel endoscopic criteria was 79.5% (232/292; 95% CI, 74.3%–83.8%). The relationships between endoscopic staging and pathologic staging of the tumor invasion depth are detailed in **Table 2**. The sensitivity, specificity, PPV, and NPV for T1m cancers were 78.4%, 81.0%, 85.4%, and 72.6%, respectively, whereas those for T1sm cancers were 81.0%, 78.4%, 72.6%, and 85.4%, respectively. Among these 292 cases, the endoscopic staging of 60 (20.5%) were incorrect: 37 cases (12.7%) were overestimated (staged as T1sm for pathologic T1m cancer) and 23 cases (7.9%) were underestimated (staged as T1m for pathologic T1sm cancer). The relationship between accuracy and the novel endoscopic criteria was as follows (**Table 3**): for T1m cancer, a high diagnostic accuracy was observed for lesions of any size that were flat or slightly elevated or depressed

Table 1. Clinicopathological characteristics of 292 patients with superficial esophageal squamous cell carcinoma

Characteristics	Values
Sex	
Male	280 (95.9)
Female	12 (4.1)
Age, yr	63 (38–86)
Location	
Upper	22 (7.5)
Mid	125 (42.8)
Lower	145 (49.7)
Endoscopic macroscopic type (according to the Japanese criteria)	
I	21 (7.2)
IIa	71 (24.3)
IIb	169 (57.9)
IIc	18 (6.2)
III	13 (4.5)
Endoscopic ulcer	
Absent	270 (92.5)
Present	21 (7.2)
Scar	1 (0.3)
Treatment	
Endoscopic resection	82 (28.1)
Surgical resection	210 (71.9)
Ivor-Lewis operation	139 (47.6)
Mckeown operation	47 (16.1)
Transhiatal operation	2 (0.7)
Colon interposition	22 (7.5)
Tumor size, cm	2.1 (0.2–11.8)
Differentiation degree	
Well-differentiated	82 (28.1)
Moderately differentiated	194 (66.4)
Poorly differentiated	14 (4.8)
Unknown differentiated	2 (0.7)
Depth of invasion	
Mucosa	171 (58.6)
Submucosa	121 (41.4)
Total	292 (100.0)

Data are presented as number (%) or median (range).

Table 2. Accuracy rate of the novel endoscopic criteria for T staging

Stage	Pathologic stage			Accuracy, %
	Mucosa	Submucosa	Total	
Endoscopic stage				
Mucosa	134	23	157	85.4
Submucosa	37	98	135	72.6
Total	171	121	292	79.5

(97.3%, 72/74), whereas a low diagnostic accuracy was observed for slightly elevated lesions of < 1 cm in size with granular or uneven surface (53.3%, 8/15). For T1sm cancer, a high diagnostic accuracy was observed for lesions of any size with irregular/nodular protrusions (85.7%, 18/21), whereas a low diagnostic accuracy was observed for hyperemic flat lesions of >3 cm with granular or uneven surface (55.0%, 22/40). All the details of accuracy rates with regard to the novel endoscopic criteria are shown in **Table 3**.

Clinicopathological parameters related to the accuracy of the novel endoscopic criteria

The accuracy of endoscopic staging tended to be higher for lesions located in the mid or lower-third esophagus, macroscopic type IIb lesions, and those with a tumor size between 2 and 3 cm.

Table 3. Accuracy rates according to each item of the novel endoscopic criteria for mucosal and submucosal cancers

Variables	No.	Pathologic T staging		Endoscopic assessment		
		T1m	T1sm	Proportion of accurately assessed lesions	95% CI	P value
Criteria for mucosal cancer				% (T1m/No.)		
I. Any size of flat or slight elevation or slight depression with smooth/even surface	74	72	2	97.3 (72/74)	89.7–99.5	$< 0.001^a$
II. Slightly elevated lesion of ≤ 1 cm with granular or uneven surface	15	8	7	53.3 (8/15)	27.4–77.7	
III. Hyperemic flat lesion of ≤ 3 cm with granular or uneven surface	57	47	10	82.5 (47/57)	69.7–90.8	
IV. Slightly depressed lesion of ≤ 2 cm with uneven surface	11	7	4	63.6 (7/11)	31.6–87.6	
Overall	157	134	23	85.4 (134/157)	78.6–90.3	
Criteria for submucosal cancer				% (T1sm/No.)		
I. Irregularly (unevenly) nodular or protruded lesion of any size	21	3	18	85.7 (18/21)	62.6–96.2	0.036^a
II. Slightly elevated lesion of > 1 cm with granular or uneven surface	54	10	44	81.5 (44/54)	68.1–90.3	
III. Hyperemic flat lesion of > 3 cm with granular or uneven surface	40	18	22	55.0 (22/40)	38.7–70.4	
IV. Irregularly (unevenly) depressed lesion of > 2 cm	7	2	5	71.4 (5/7)	30.3–94.9	
V. Ulcerative lesion of any size	13	4	9	69.2 (9/13)	38.9–89.6	
Overall	135	37	98	72.6 (98/135)	64.1–79.4	0.007^b

CI = confidence interval, T1m = mucosal cancer, T1sm = submucosal cancer.

^aIntragroup comparison using χ^2 test; ^bIntergroup comparison using χ^2 test.

Table 4. Univariate and multivariate analyses of variables affecting the endoscopic prediction accuracy

Variables	No.	Univariate analysis			Multivariate analysis	
		Correct No. (%)	OR (95% CI)	P value	OR (95% CI)	P value
Location						
Upper	22	15 (68.2)	1.000		1.000	
Mid	125	100 (80.0)	2.405 (0.906–6.382)	0.078	2.431 (0.879–6.722)	0.087
Lower	145	117 (80.7)	2.388 (0.913–6.246)	0.076	2.566 (0.936–7.036)	0.067
Macroscopic type						
I, IIa	92	72 (78.3)	1.383 (0.554–3.456)	0.488	1.920 (0.733–5.032)	0.184
IIb	169	139 (82.2)	1.895 (0.794–4.525)	0.150	2.722 (1.069–6.934)	0.036
IIc, III	31	21 (67.7)	1.000		1.000	
Endoscopic ulcer						
Absent	270	216 (80.0)	1.000			
Present	21	15 (71.4)	0.625 (0.232–1.686)	0.353		
Scar	1	1 (100)	-	-		
Histology						
W/D, M/D	276	221 (80.1)	1.000			
P/D, U/D	16	11 (68.8)	0.548 (0.183–1.641)	0.282		
Tumor size, cm						
≤ 1	53	40 (75.5)	1.000		1.000	
1 < tumor ≤ 2	89	73 (82.0)	1.483 (0.648–3.391)	0.351	1.555 (0.667–3.626)	0.306
2 < tumor ≤ 3	59	52 (88.1)	2.414 (0.882–6.609)	0.086	2.360 (0.841–6.618)	0.103
> 3	91	67 (73.6)	0.907 (0.416–1.980)	0.807	0.723 (0.320–1.636)	0.437
Depth of invasion						
Mucosa	171	134 (78.4)	1.000			
Submucosa	121	98 (81.0)	1.177 (0.657–2.105)	0.584		

OR = odds ratio, CI = confidence interval, W/D = well differentiated, M/D = moderately differentiated, P/D = poorly differentiated, U/D = unknown differentiated.

Multivariate analysis revealed that the variable that affected the accuracy of endoscopic prediction was macroscopic type IIb lesion (OR, 2.722; 95% CI, 1.069–6.934; $P = 0.036$) (Table 4).

Clinicopathological parameters affecting the accuracy in subgroups diagnosed with mucosal and submucosal cancers on endoscopy

On univariate analysis of 157 patients with endoscopically diagnosed mucosal cancer (M), location of the lesion in the mid or lower-third esophagus and macroscopic type IIb significantly affected the accuracy of endoscopic prediction. Multivariate analysis revealed that macroscopic type IIb lesion (OR, 6.152; 95% CI, 1.525–24.807; $P = 0.011$) was an independent factor that affected the accuracy of the endoscopic prediction in the M group

Table 5. Univariate and multivariate analyses of variables affecting the endoscopic prediction accuracy in 157 patients with endoscopically diagnosed mucosal cancer

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Location				
Upper	1.000		1.000	
Mid	5.926 (1.496–23.478)	0.011	4.490 (0.985–20.471)	0.052
Lower	5.926 (1.496–23.478)	0.011	3.900 (0.875–17.377)	0.074
Macroscopic type				
I, IIa	1.000		1.000	
IIb	8.667 (2.821–26.628)	< 0.001	6.152 (1.525–24.807)	0.011
IIc, III	2.370 (0.463–12.138)	0.300	2.090 (0.361–12.113)	0.110
Endoscopic ulcer				
Absent	1.000			
Present	0.508 (0.051–5.104)	0.508		
Scar	-	-		
Histology				
W/D, M/D	1.000		1.000	
P/D, U/D	0.159 (0.021–1.191)	0.074	0.080 (0.005–1.230)	0.070
Tumor size, cm				
≤ 1	1.000			
1 < tumor ≤ 2	1.992 (0.711–5.584)	0.190	0.862 (0.245–3.036)	0.817
2 < tumor ≤ 3	3.135 (0.808–12.158)	0.098	1.397 (0.276–7.060)	0.686
> 3 cm	8.108 (0.991–66.355)	0.051	6.500 (0.379–111.603)	0.197

OR = odds ratio, CI = confidence interval, W/D = well differentiated, M/D = moderately differentiated, P/D = poorly differentiated, U/D = unknown differentiated.

(Table 5). Univariate analysis for 135 patients with endoscopically diagnosed submucosal cancer (SM) revealed that macroscopic type IIb lesion significantly affected the accuracy of the endoscopic prediction. Multivariate analysis revealed that macroscopic type IIb lesion (OR, 0.278; 95% CI, 0.086–0.903; $P = 0.033$) had an independent effect on the prediction accuracy in the SM group (Table 6).

Table 6. Univariate and multivariate analyses of variables affecting the endoscopic prediction accuracy in 135 patients with endoscopically diagnosed submucosal cancer

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Location				
Upper	1.000			
Mid	0.925 (0.216–3.968)	0.916		
Lower	1.046 (0.251–4.357)	0.951		
Macroscopic type				
I, IIa	1.000		1.000	
IIb	0.256 (0.108–0.608)	0.002	0.278 (0.086–0.903)	0.033
IIc, III	0.489 (0.158–1.511)	0.214	0.395 (0.117–1.335)	0.135
Endoscopic ulcer				
Absent	1.000			
Present	0.893 (0.292–2.735)	0.843		
Scar	-	-		
Histology				
W/D, M/D	1.000			
P/D, U/D	1.146 (0.293–4.488)	0.845		
Tumor size, cm				
≤ 1	1.000		1.000	
1 < tumor ≤ 2	1.111 (0.103–12.037)	0.931	1.394 (0.125–15.530)	0.787
2 < tumor ≤ 3	1.917 (0.157–23.347)	0.610	2.906 (0.219–38.624)	0.419
> 3	0.609 (0.060–6.191)	0.675	1.463 (0.123–17.353)	0.763

OR = odds ratio, CI = confidence interval, W/D = well differentiated, M/D = moderately differentiated, P/D = poorly differentiated, U/D = unknown differentiated.

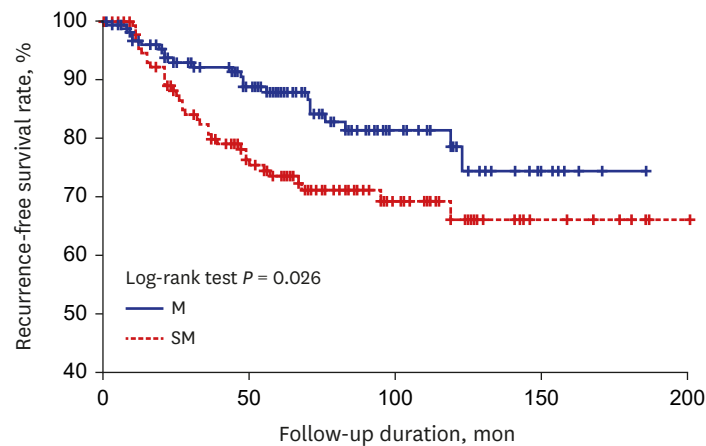


Fig. 4. Kaplan-Meier curve for recurrence-free survival in patients with endoscopically diagnosed M or SM. The difference between the M and SM groups was statistically significant (log-rank test, $P = 0.026$). M = mucosal cancer, SM = submucosal cancer.

Oncological outcomes according to the novel endoscopic criteria

The median follow-up duration for 292 patients with SESC was 69 months (interquartile range [IQR], 42–106 months). During the follow-up, recurrence was observed in 59 patients (20.2%), 23 (14.6%) of which were in the M group and 36 (26.7%) in the SM group. The risk of recurrence was significantly different between the M and SM groups (hazard ratio [HR] for the SM group was 2.12; 95% CI, 1.18–3.80; $P = 0.011$). The 5- and 10-year recurrence-free survival rates were 87.8% and 81.3%, respectively, for the M group and 73.7% and 66.4%, respectively, for the SM group; the differences between the two groups were statistically significant ($P = 0.026$) (Fig. 4).

DISCUSSION

This relatively large-scale study showed that the novel endoscopic criteria using conventional endoscopy alone are useful for predicting invasion depth in SESC. The overall accuracy rate of this criteria was approximately 80%, which is sufficiently accurate for clinical use. In addition, we found that the novel criteria can not only help determine how to treat but also predict clinical outcomes before endoscopic or surgical resection. The Kaplan–Meier curve for recurrence-free survival showed significant differences between the M and SM groups.

Since endoscopic resection has become an established therapeutic option for mucosal cancer, differential diagnosis between mucosal and submucosal cancers in the gastrointestinal tract, especially in the esophagus, has become critical.¹⁸ Although EUS has been considered to be the method that most accurately predicts invasion depth in SESC,¹⁹ it is associated with several limitations. Conventional EUS systems are not ideal for assessing early neoplastic changes, particularly mucosal and submucosal cancers.¹³ Recently, EUS using high-frequency catheter probe has played a central role in endoscopic work-up for esophageal cancer staging.^{12,19} However, it is more difficult in the esophagus than in the other portions of the gastrointestinal tract because filling the esophageal lumen with water is often inhibited by esophageal peristalsis, or cardiac/aortic motion prevents taking a fine EUS image.^{12,19} Several recent studies have demonstrated that ME with or without NBI is useful for estimating superficial tumor depth.^{7,12,18} However, the ME classification of SESC

invasion depth, which is based on intrapapillary capillary loop morphological alteration, has never been validated by an independent observer agreement study. Moreover, more advanced equipment such as EUS or ME-NBI are not available at all institutions and operating them requires skill and experience as they are often based on complicated and difficult standards.^{9,19} Therefore, they could not be a useful standard for non-experts.

Our study proposed novel endoscopic criteria using conventional endoscopy alone for predicting invasion depth in SESC, and we tried to prove this with many patients. With approximately 300 patients, the present study is currently the largest investigation assessing the value of conventional endoscopy in SESC. Moreover, our criteria are based on relatively simple and objective standards, which can be highly practical and reproducible. We sought to improve the prediction accuracy by reflecting not only on the macroscopic type but also on surface regularity, granularity of the tumor base, and tumor size, although most studies on endoscopic staging of esophageal cancer were conducted using the macroscopic type according to the Paris endoscopic classification or Japanese classification.^{13,15,20-22} Thus, the novel criteria would help us visually differentiate between mucosal and submucosal invasions of SESC under endoscopy, particularly in medical institutions that do not possess experienced endoscopists or other modalities such as EUS or ME.

Our novel criteria showed sensitivities of 78.4% and 81.0% and specificities of 81.0% and 78.4% for T1m and T1sm, respectively, and an accuracy rate of 79.5% (232/292). The accuracy was also comparable to or higher than previously reported accuracy of other techniques such as EUS, ME, and NBI.^{8,10,19} In particular, the accuracy of lesions corresponding to the criteria I for T1m cancer (flat or slightly elevated or depressed lesion with smooth/even surface of any size) was very high (72/74, 97.3%). Only two were incorrect. This result suggested that the flat lesions with smooth/even surface were potential candidates for curative treatment by endoscopic resection. Furthermore, the overestimation and underestimation rates were 12.7% (37/292) and 7.9% (23/292), respectively, which were acceptably low. This could be partly explained by the fact that our study included a similar proportion of mucosal (58.6%, 171/292) and submucosal cancers (41.4%, 121/292). The difference in the proportions of mucosal and non-mucosal cancers may account for the higher rate of overestimation and underestimation rates.¹⁹

In our criteria for T1sm cancer, hyperemic flat lesion of > 3 cm with granular or uneven surface (criteria III) did not sufficiently predict submucosal invasion. In addition, although not statistically significant, we found that tumors larger than 3 cm tended to be less accurate than smaller lesions in the analysis of the variables that affected the prediction accuracy. Overall, these findings indicate that our endoscopic criteria should be interpreted with caution in relation to tumor size of > 3 cm, and further research is needed to improve the accuracy. On the other hand, macroscopic type IIB lesions were significantly predictive of tumor invasion depth ($P = 0.036$). In our criteria for T1m cancer, most of the flat or slightly elevated or depressed tumors with smooth/even surface of any size (criteria I) were diagnosed with mucosal cancer and showed high accuracy (97.3%). Therefore, flat lesions can be diagnosed with more confidence using our criteria. However, further studies with more detailed endoscopic findings suggesting submucosal invasion in the flat lesions are required to identify lesions that require curative surgical esophagectomy.

Our study has some limitations. First, in this study, endoscopic staging was determined based on the consensus between two experienced endoscopists. Therefore, if an endoscopist with less experience determines the invasion depth alone, the accuracy rate may be reduced. Second,

endoscopic staging was retrospectively performed using still images, whereas in clinical practice, this is likely to be performed by viewing moving images in dynamic situations. These limitations indicated that additional studies involving non-experts are required to determine the true diagnostic accuracy of endoscopic staging. Third, this endoscopic staging was not developed strictly according to the statistical data due to small sample size. Therefore, another validation cohort will be required. Fourth, because we have not obtained information about LN metastasis based on surgical cases, whether ESD can be indicated with these criteria alone is difficult to clearly determine. Therefore, a further validation study based on data containing information about LN metastasis is needed. Finally, because the data of recurrence-free survival involved many selection biases such as treatment modality, a decision on additional treatment, and lymphovascular invasion, care should be taken when predicting the clinical outcomes.

In conclusion, conventional endoscopy provides reliable accuracy for predicting tumor invasion depth in SESC. Careful endoscopic examination with the novel endoscopic criteria for SESC can help decide the best treatment strategy between endoscopic and surgical resection. Furthermore, it might also help provide useful information about oncologic outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The details of 60 randomly selected tumors for identifying endoscopic features and creating the novel endoscopic criteria

[Click here to view](#)

Supplementary Fig. 1

The diagnostic algorithm for predicting invasion depth using our novel endoscopic criteria and Paris classification in SESC.

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