

Diagnostic Efficacy of Type B Vessels in the Japan Esophageal Society Classification for the Depth of Invasion of Superficial Esophageal Squamous Cell Carcinoma

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AIM: The preoperative diagnostic method for superficial esophageal squamous cell carcinoma (SESCC) invasion depth based on the Japan Esophageal Society (JES) classification has been promoted. However, there have been a few investigations into its diagnostic performance in clinical settings. Therefore, we aimed to elucidate the actual diagnostic performance of the JES classification using a single-center retrospective study design.

METHODS: We retrospectively analyzed the clinical data of 315 newly diagnosed SESC patients who underwent narrow-band imaging magnifying endoscopy (NBI-ME) examination and received endoscopic submucosal dissection (ESD) or esophagectomy in our center during the past 5 years. To evaluate the diagnostic performance of JES classification in assessing the depth of invasion of SESC, clinical data of these patients were collected, and the concordance between NBI-ME findings and postoperative pathology reports was analyzed. **RESULTS:** This study included a total of 338 lesions. The diagnostic accuracy of vascular morphology was 76.0%. The sensitivity (87.0%) and positive predictive value (PPV, 85.4%) of B1 vessels were high, but the specificity (42.0%) and negative predictive value (NPV, 45.3%) were low. The specificity (86.9% and 98.8%) and NPVs (87.5% and 96.8%) of B2 and B3 vessels were high, but the sensitivity (36.4% and 21.4%) and PPVs (35.1% and 42.9%) were low. Furthermore, only a few lesions (n = 57) described avascular area, but the overall diagnostic accuracy was not ideal (21.1%). However, if lesions invading the superficial submucosa or shallower were included in the category of “suitable for ESD”, the overall accuracy of the JES classification was found to be 95.6%.

CONCLUSIONS: In actual clinical settings, the overall accuracy of the JES classification system decreases, but the diagnostic performance of each subtype retains its original characteristics. Additionally, this classification is appropriate for determining whether type 0-II SESC lesions are suitable for ESD.

Keywords: intrapapillary capillary loop; superficial esophageal squamous cell carcinoma; narrow-band imaging magnifying endoscopy

Introduction

Esophageal cancer is currently the 11th most prevalent cancer and the 7th deadliest cancer globally, with the highest incidence rates reported in East Asia and East Africa [1]. In East Asia, particularly China, esophageal squamous cell carcinoma (SCC) is the predominant histological subtype [2]. Superficial esophageal squamous cell carcinoma (SESCC) without lymph node metastasis can be curatively resected using endoscopic submucosal dissection (ESD) [3]. The risk of lymph node metastasis in SESC is closely correlated with the depth of invasion into the mucosa or submucosa [4], highlighting the significance of early diagnosis and treatment in managing SESC.

The morphology of intrapapillary capillary loops (IPCL) in the esophageal squamous epithelium can be used to estimate the invasion depth of SESC [5]. Previous study has established classification systems based on the morphology of IPCL observed under narrow-band imaging magnifying endoscopy (NBI-ME) to evaluate the invasion depth of SESC preoperatively [5]. However, these two diagnostic systems are relatively complex and challenging to master, hindering their widespread adoption. In 2011, the Japan Esophageal Society (JES) proposed a simplified IPCL classification system and validated its effectiveness through a prospective study [6].

The JES classification is widely used, but the findings from previous studies may not accurately reflect its actual performance. Furthermore, retrospective reinterpretation of NBI-ME images might also overestimate its diagnostic capability. Considering the complexity of clinical settings, the diagnostic performance of the JES classification may decline in practical applications, although the level of this decline is yet to be determined. Elucidating its diagnostic performance is essential for improving management strategies for SESC patients. Therefore, we aim to investigate the diagnostic performance of this issue through a single-center retrospective study based on electronic medical records.

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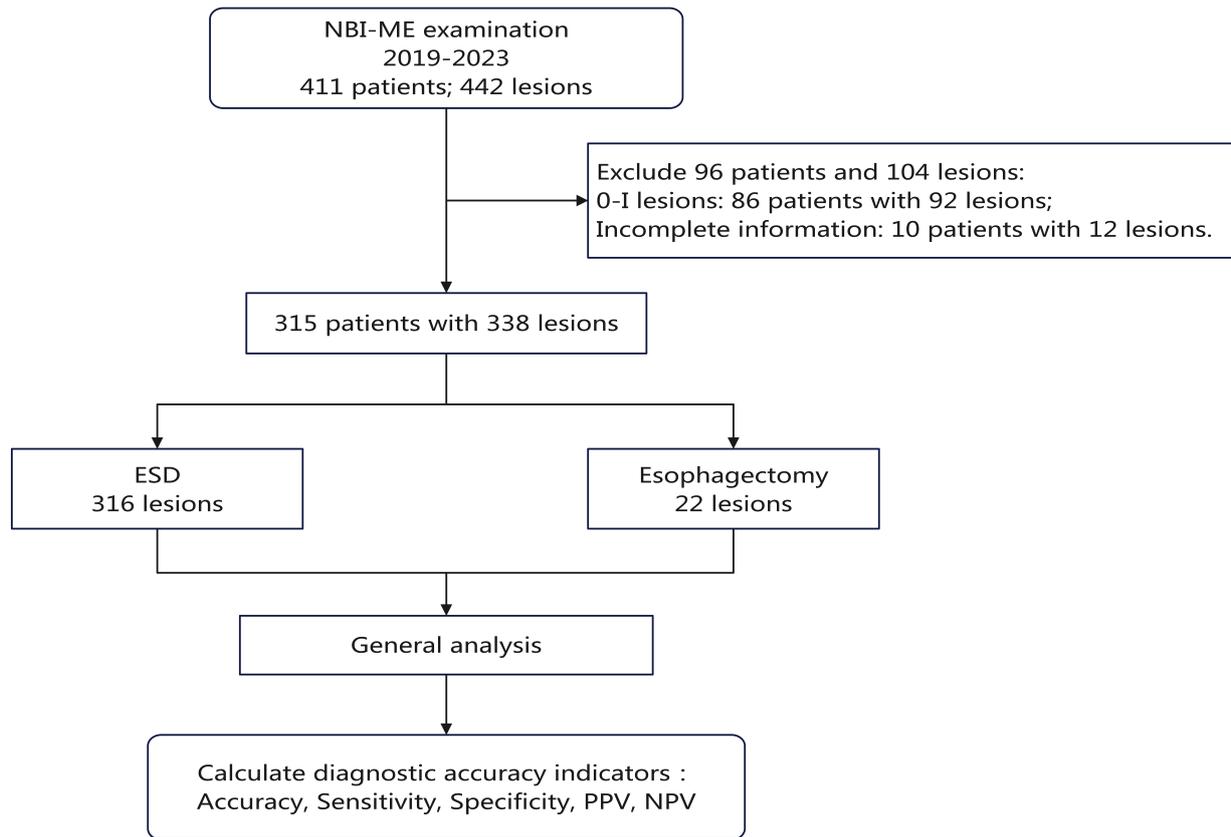


Fig. 1. The overall process of this experiment. NBI-ME, narrow-band imaging magnifying endoscopy; ESD, endoscopic submucosal dissection; PPV, positive predictive value; NPV, negative predictive value.

Materials and Methods

Research Participants

This study included newly diagnosed SESCC patients who underwent NBI-ME examination and received ESD or esophagectomy at the First Affiliated Hospital of Soochow University between January 1, 2019, and December 31, 2023. None of the patients received any therapeutic measures before undergoing the NBI-ME examination. The electronic medical records of these patients were retrieved, and information from the NBI-ME and histopathological reports was collected (Fig. 1).

All patients signed informed consent forms before undergoing the NBI-ME examination or subsequent treatment. The study design adhered to the Declaration of Helsinki, and all data were obtained from routine clinical procedures without involving patient privacy. The Ethics Committee of the First Affiliated Hospital of Soochow University approved this study (Approval No. 2024-362).

Endoscopic Examinations

Endoscopes, either GIF-H260Z (2734751, Olympus Corp., Tokyo, Japan) or GIF-H290Z (2934792, Olympus Corp., Tokyo, Japan) were used for magnifying endoscopy. According to our center's policy, all NBI-ME examinations were performed by physicians with over 10 years of experience in digestive endoscopy.

We performed the NBI-ME examination procedure as follows: During insertion, the esophagus is thoroughly observed with a white light mode, rinsed, and the mucus adhering to the mucosal surface is suctioned. During withdrawal, the gross morphology of the esophageal mucosa is observed at the lesion site using white light and NBI mode. After this, the endoscope lens is brought close to the lesion and adjusted for the NBI-ME examination. During this procedure, the morphology of the esophageal IPCL is carefully observed under 80 to 100 times magnification.

Related Definitions and Standards

The location of lesions can be classified into the upper esophagus (15–20 cm), the middle esophagus (20–30 cm), and the lower esophagus (30–40 cm) based on the distance from the incisors [7].

The invasion depth of SESCC, from superficial to deep, is categorized as within the epithelium (EP), lamina propria mucosae (LPM), muscularis mucosae (MM), and submucosa (SM) [8]. The SM category is further divided into two grades: invasion within 200 μ m or not exceeding the upper third of the submucosa (SM1) and invasion beyond 200 μ m or exceeding the upper third of the submucosa (SM2). SM1 is defined as 200 μ m or shallower in the tumor-invasion submucosa in ESD specimens or within the upper one-third of the invasion submucosa in esophagectomy specimens.

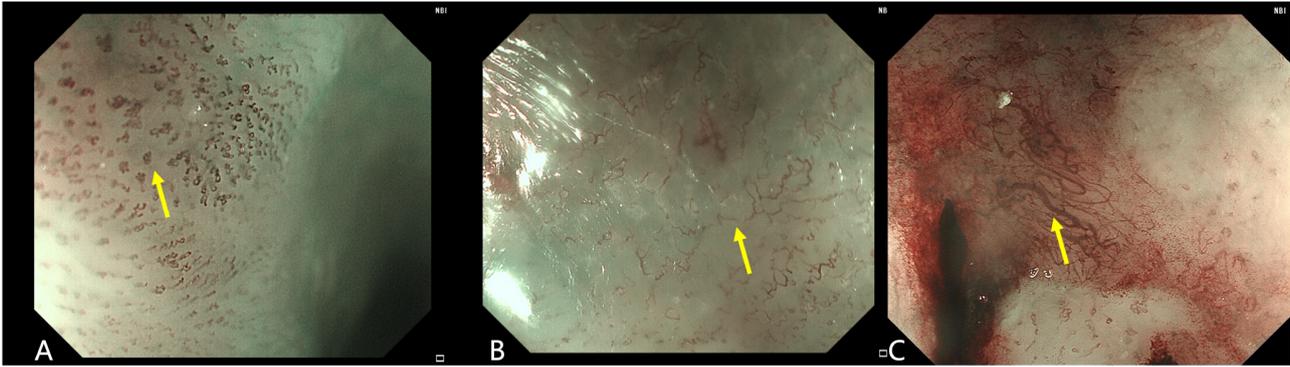


Fig. 2. The type B intrapapillary capillary loops. (A) Type B1 is dilated, tortuous, unevenly thick, and variably shaped loop capillaries, as indicated by the arrow. (B) Type B2 is atypical capillaries without loops as indicated by the arrow. (C) Type B3 is a highly dilated irregular vessel with diameter three times that of type B2 vessels as indicated by the arrow. These sample images were obtained from cases that underwent narrow-band imaging magnifying endoscopy examinations.

SM2 is defined as more than 200 μm in ESD specimens or more than the upper one-third in esophagectomy specimens.

The evolution of SCC proceeds sequentially, progressing from low-grade intraepithelial neoplasia (LGIN) to high-grade intraepithelial neoplasia (HGIN) and ultimately to SCC [9]. LGIN is defined as the involvement of solely the lower half of the epithelium and is associated with mild cytological atypia. HGIN is characterized by either the involvement of more than half of the epithelium or severe cytological atypia, irrespective of the extent of epithelial involvement [10]. SCC represents a definitive malignant transformation, including both *in situ* and invasive carcinoma.

According to the JES classification system [11], IPCL observed under ME-NBI can be categorized into types A and B. Type A consists of capillary loops with mild or no atypia, suggesting intraepithelial neoplasia. Type B comprises capillaries with a higher degree of atypia, suggesting SCC. Furthermore, type B can be divided into three subtypes: B1, B2, and B3. Type B1 is dilated, tortuous, unevenly thick, and variably shaped loop capillaries, suggesting an invasion depth of EP/LPM. Type B2 consists of atypical capillaries without loops, suggesting an invasion depth of MM/SM1. Type B3 is a highly dilated irregular vessel with diameter three times that of type B2 vessels, indicating an invasion depth of SM2 (Fig. 2).

An avascular area (AVA) is a region without or with poor vessels, surrounded by Type B vessels. Based on size, it can be further divided into AVA-small (≤ 0.5 mm), AVA-middle (0.5–3.0 mm), and AVA-large (≥ 3.0 mm), suggesting EP/LPM, MM/SM1, and SM2 invasion, respectively.

According to the Paris classification [12], SESCC is macroscopically classified as follows: Type 0-I represents protruding lesions, Type 0-II represents non-protruding and non-excavated lesions, and Type 0-III represents excavated

lesions. Type 0-II is further subdivided into Type 0-IIa (slightly elevated), Type 0-IIb (completely flat), and Type 0-IIc (slightly depressed).

The highest malignant degree reported in NBI-ME and histopathological examinations are considered definitive for composite lesions.

Statistical Analysis

After reviewing the data, individuals with incomplete data were excluded from the study. Normally distributed continuous data were presented as mean \pm standard deviation, while count data were expressed as frequencies. The gold standard for assessment includes postoperative pathological results following ESD and esophagectomy. Diagnostic accuracy was assessed using accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results

General Characteristics of the Study Participants and their Lesions

This study included 315 cases with complete information, which involved 338 lesions. Among them, 316 lesions underwent ESD, while 22 cases underwent esophagectomy. The average age of the patients was 66.3 ± 7.1 years. Type 0-II SECC was predominantly observed in the middle esophagus ($n = 179$), followed by the lower esophagus ($n = 152$), and was less commonly observed in the upper esophagus ($n = 7$). Lesions with less than 1/3 circumferential involvement were most frequent ($n = 201$), followed by those with 1/3 to 2/3 involvement ($n = 98$), and those exceeding 2/3 involvement were the least common ($n = 39$). Morphologically, Type 0-IIb was the most prevalent ($n = 281$), followed by Type 0-IIa ($n = 43$) and Type 0-IIc ($n = 14$). The distribution of type B IPCL included B1 in 274 lesions, B2 in 57, and B3 in 7. AVA status was not reported in 279 lesions. Among the remaining AVAs, 55 were iden-

Table 1. Baseline characteristics of patients and lesions.

Categories	Value
Number (patients/lesions)	315/338
Age (mean \pm standard deviation) (years)	66.3 \pm 7.1
Tumor location (upper/middle/lower)	7/179/152
Tumor circumference ($\leq 1/3$, $>1/3$ to $\leq 2/3$, $>2/3$)	201/98/39
Paris classification (0-IIa/0-IIb/0-IIc)	43/281/14
Vessel type (B1/B2/B3)	274/57/7
AVA (negative/small/middle/large)	279/55/4/0
Invasion depth (EP/LPM/MM/SM1/SM2)	235/34/28/27/14
Tumor classification (LGIN/HGIN/SCC)	63/110/165

AVA, avascular area; EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM1, invasion within 200 μ m or not exceeding the upper third of the submucosa; SM2, invasion beyond 200 μ m or exceeding the upper third of the submucosa; LGIN, low-grade intraepithelial neoplasia; HGIN, high-grade intraepithelial neoplasia; SCC, squamous cell carcinoma.

tified as AVA-small, 4 as AVA-middle, and none as AVA-large. Regarding the depth of invasion, 235 cases exhibited EP involvement, 34 LPM, 28 MM, 27 SM1, and 14 SM2. Among these, 63 were diagnosed as LGIN, 110 as HGIN, and 165 as SCC (Table 1).

Diagnostic Accuracy of Type B IPCL

The invasion depths for each subtype of type B IPCL are shown in Table 2. In the B1 subtype, EP (75.2%) and LPM (10.2%) were predominant. In the B2 subtype, neither MM (10.5%) nor SM1 (24.6%) was predominant. Conversely, the B3 subtype exhibited predominant invasion into SM2 (42.9%) (Table 2).

Diagnostic Accuracy of AVA

The invasion depths for each AVA subtype are presented in Table 3. In the AVA-small category, EP/LPM (8, 42.1%) was comparable to MM/SM1 (9, 47.4%). For AVA-middle, only 2 lesions were observed, with one case exhibiting EP and one showing SM1 involvement.

Furthermore, the diagnostic accuracy of AVA was found to be 21.1%. Specifically, AVA-small showed a diagnostic accuracy of 42.9%, with a sensitivity of 88.9%, specificity of 8.3%, PPV of 42.1%, and NPV of 50.0%. For AVA-middle, the diagnostic accuracy was 57.1%, with a sensitivity of 10.0%, specificity of 91.7%, PPV of 50.0%, and NPV of 61.1% (Table 4).

Suitable for ESD

If lesions involving EP to SM1 are all categorized as “suitable for ESD” (type B1 or B2 IPCL), the overall accuracy of the JES classification is 95.6%, with a sensitivity of 98.8%, specificity of 21.4%, PPV of 96.7%, and NPV of 42.9% (Table 4).

Discussion

At the 65th JES Annual Meeting in Sendai, Japan, in 2011, simplified criteria were established for diagnosing the invasion depth of SESCC using NBI-ME [11, 13]. In a subsequent prospective study involving 211 SESCC patients treated with ESD, the JES classification demonstrated an excellent overall accuracy of 90.5% [6]. However, our results indicated that the overall accuracy in real clinical settings was 76.0%, which is lower than the prospective study results. Prospective clinical trials have relatively strict design and implementation processes, which can lead to more ideal outcomes. Conversely, the diagnostic performance of the same method may decline to some extent in the complex and variable nature of clinical environment. The main reason for this discrepancy may be that prospective studies can ensure the standardization of NBI-ME procedures and consistency in image interpretation through comprehensive training of the operators.

Additionally, as a simplified classification standard, the JES classification may result in difficulties in classifying certain lesions, especially the highly variable B2 subtype. In prospective studies, a unified research team can discuss and resolve any controversy. Similarly, some retrospective studies also reevaluate previous NBI-ME images, potentially overestimating the diagnostic performance of the JES classification. For example, the study by Mizumoto *et al.* [14] demonstrated an overall diagnostic accuracy of 78.9% for the JES classification, while Kim *et al.* [15] reported 78.6%.

The data for this study were entirely sourced from the electronic medical record system, including patients who underwent ESD and esophagectomy treatments, better representing the actual clinical environment. Liu *et al.* [16] evaluated the JES classification using a similar method to our study. Their study included 834 cases of NBI-ME from 2014 to 2019, and they observed the overall accuracy of the JES classification to be 76.8%, which is close to the result of our study (76.0%). Although the diagnostic performance of the JES classification demonstrates a slight decrease, the advantages of its various subtypes are retained. For example, our results reveal that B1's high sensitivity (87.0%) and the high specificity of B2 (86.9%) and B3 (98.8%) are consistent with the prospective results (97.5%, 96.2%, and 100%), with only slight reductions. However, the specificity of B1 (42.0%) and the sensitivity of B2 (36.4%) and B3 (21.4%) are significantly lower than those in the prospective study (72.9%, 75.0%, and 55.0%) [6]. This characteristic can also be observed in the results of Liu *et al.* [16], where the specificity of B1 was 35.0%, and the sensitivity of B2 and B3 was 23.3% and 17.5%, respectively. Therefore, in practical application, while the advantages of the JES classification can be retained, its disadvantages may become more evident. This could explain why its overall diagnostic performance is lower than the results of prospective studies.

Table 2. Distribution characteristics of invasion depth with different vascular types.

Vessel type	Invasion depth (n)					Total
	EP	LPM	MM	SM1	SM2	
B1	206 (75.2%)	28 (10.2%)	21 (7.7%)	13 (4.7%)	6 (2.2%)	274
B2	27 (47.4%)	5 (8.8%)	6 (10.5%)	14 (24.6%)	5 (8.8%)	57
B3	2 (28.6%)	1 (14.3%)	1 (14.3%)	0	3 (42.9%)	7
Total	235 (69.5%)	34 (10.1%)	28 (8.3%)	27 (8.0%)	14 (4.1%)	338

EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM1, invasion within 200 μ m or not exceeding the upper third of the submucosa; SM2, invasion beyond 200 μ m or exceeding the upper third of the submucosa.

Table 3. Distribution characteristics of invasion depth with different AVA sizes.

AVA	Invasion depth (n)					Total
	EP	LPM	MM	SM1	SM2	
Negative	21 (58.3%)	2 (5.6%)	2 (5.6%)	8 (22.2%)	3 (8.3%)	36
Small	5 (26.3%)	3 (15.8%)	4 (21.1%)	5 (26.3%)	2 (10.5%)	19
Middle	1 (50.0%)	0	0	1 (50.0%)	0	2
Large	0	0	0	0	0	0
Total	27 (47.4%)	5 (8.8%)	6 (10.5%)	14 (24.6%)	5 (8.8%)	57

AVA, avascular area; EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM1, invasion within 200 μ m or not exceeding the upper third of the submucosa; SM2, invasion beyond 200 μ m or exceeding the upper third of the submucosa.

In the studies mentioned above, type 0-I and type 0-III SESCC were not excluded. Since the submucosal invasion probabilities for these two forms of SESCC are as high as 79% and 84%, respectively [12], the JES classification primarily focuses on evaluating infiltration depth for type 0-II SESCC. When observing type 0-I/0-III lesions under white light endoscopy, SM1 or deeper invasion is usually assumed. Furthermore, the high degree of tissue atypia in type 0-I and type 0-III SESCC may make them unsuitable for observation using the NBI-ME mode. Future research should focus on developing early diagnostic methods for assessing the infiltration depth of type 0-II SESCC.

Although the overall diagnostic performance of the JES classification is reduced in practical application compared to its ideal state, it remains valuable, especially for B1 or B3 subtypes. The sensitivity (87.0%) and PPV (85.4%) of the B1 subtype are relatively high, providing endoscopists with considerable diagnostic confidence. Similarly, the specificity (98.8%) and NPV (96.8%) of the B3 subtype are also high, which is beneficial for accurately identifying lesions with deeper infiltration. However, managing lesions associated with the B2 IPCL subtype can be more challenging [17]. Since the predicted depth for the B2 subtype includes both MM and SM1, corresponding to the T1a and T1b stages. According to the latest guidelines, ESD is weakly recommended as a first-line treatment for cT1a-MM/T1b-SM1 (N0M0) SESCC [18]. For pT1a-MM, additional treatment may not be necessary, while for pT1b-SM1, further treatment is strongly recommended. Therefore, distinguishing between MM and SM1 in the preoperative diag-

nosis is crucial to maximize patient benefits. For patients at the T1a-MM stage, diagnostic ER can be performed, and if postoperative pathology indicates no lymph-vascular invasion, follow-up observation may suffice. For patients at the T1b-SM1 stage, additional ESD treatment would increase the burden on patients. Nevertheless, NBI-ME cannot precisely differentiate MM and SM1 preoperatively [18].

The abovementioned issue may result from the complex and variable vascular morphology of the B2 subtype, which includes lesions with different infiltration depths (Table 2). The term “atypical capillaries without loops” does not adequately describe the morphology of B2 vessels. Oyama *et al.* [6] attempted to identify non-neoplastic lesions using a similarly non-looped reticular pattern (Type R) vascular. Moreover, a prospective study exploring the relationship between the size of the B2 vascular region and the invasion depth of SESCC (Japan BEES study) is currently underway [17]. Based on the results of this study, we believe that endoscopists should adopt a cautious approach when encountering B2 vessels and use as many methods as possible, including assessing the gross morphology under white light endoscopy and endoscopic ultrasound, to evaluate the invasion depth of the lesions. Further investigation into B2 vessels is warranted.

From a different perspective, if MM/SM1 stages are included within the scope of ESD treatment, the overall accuracy of JES classification (based on vascular types) would increase to 95.6%. Additionally, the sensitivity (98.8%) and positive predictive value (PPV) (96.7%) would remain high. In this regard, the JES classification is appropriate

Table 4. Diagnostic accuracy of vessel type, AVA size and “suitable for ESD”.

ME-NBI diagnose		Accuracy	Sensitivity	Specificity	PPV	NPV
Vessel Type	B1	77.8%	87.0%	42.0%	85.4%	45.3%
	B2	78.7%	36.4%	86.9%	35.1%	87.5%
	B3	95.6%	21.4%	98.8%	42.9%	96.8%
AVA	small	42.9%	88.9%	8.3%	42.1%	50.0%
	middle	57.1%	10.0%	91.7%	50.0%	61.1%
Suitable for ESD		95.6%	98.8%	21.4%	96.7%	42.9%

ESD, endoscopic submucosal dissection; NBI-ME, narrow-band imaging magnifying endoscopy; AVA, avascular area; PPV, positive predictive value; NPV, negative predictive value.

for assessing whether an SESCC lesion is suitable for ESD treatment. Patients can still receive additional treatment if the invasion depth is underestimated before ESD. However, if the invasion depth is overestimated, it may cause irreversible damage to the patient [18].

The JES classification also includes AVA as an auxiliary diagnostic tool [11]. However, this study’s results show that AVA’s contribution is limited, with an overall accuracy of 21.1%. Firstly, if AVA-small is identified, it only suggests that the invasion depth in that area is limited to EP/LPM, while other B2 areas may have a deeper invasion. Secondly, if AVA-middle is detected, it can be treated similarly to B2 IPCL. Therefore, only AVA-large has a relatively good indicative effect, but its occurrence is infrequent [6]. Furthermore, the original intention of the JES classification was to simplify practical use, mainly through a more intuitive judgment of the IPCL. Introducing the assessment dimension of AVA increases the practical difficulty, particularly since it needs to be measured in terms of the size of AVA.

This study still has some limitations. First, the area where our center is located, the southern region of Jiangsu province, has a relatively low incidence of esophageal cancer. Although our center treats many patients from high-incidence areas for esophageal SCC (such as Anhui and northern Jiangsu) [19], the single-center study design may still introduce selection bias. Second, the sample size in this study is relatively limited. A larger sample size would yield more reliable conclusions in this retrospective study based on real-world data. However, we provided detailed presentations of tumor infiltration depths corresponding to various diagnostic indicators in the results section. Other researchers can combine these with data from their centers and perform simple calculations to obtain diagnostic test evaluation results. Lastly, the study spans 5 years and includes two generations of magnifying endoscopes (GIF-H260Z and GIF-H290Z). Advances in endoscopic technology may also influence the identification of lesions by endoscopists.

Conclusions

In the actual clinical setting, the diagnostic performance of the JES classification for evaluating the invasion depth of

type 0-II SESCC has decreased. While the diagnostic efficacy of each subtype has retained its original characteristics, the drawbacks have been magnified. The primary issue lies in the high variability of the B2 subtype, suggesting that further research on this subtype could enhance the application value of the JES classification. Despite increasing the complexity of the classification system, the inclusion of AVA has not significantly improved the diagnostic efficacy of the JES classification. Finally, the JES classification demonstrates good diagnostic performance in determining whether a type 0-II SESCC lesion is suitable for ESD.

Availability of Data and Materials

The datasets utilized or analyzed in this study are available from the corresponding authors upon reasonable request.

Author Contributions

SZ and HP designed the study. SZ, YL and HL performed literature search, data collation. SZ, ZH and RL made the statistical analysis. SZ wrote the manuscript. RL revised and reviewed the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All patients signed informed consent forms before undergoing the NBI-ME examination or subsequent treatment. The study design adhered to the Declaration of Helsinki, and all data were obtained from routine clinical procedures without involving patient privacy. The Ethics Committee of the First Affiliated Hospital of Soochow University approved this study (Approval No. 2024-362).

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Conflict of Interest

The authors declare no conflict of interest.

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