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Research

Accuracy and influencing factors of Type B2 vessels in predicting the invasion depth of superficial esophageal squamous cell carcinoma under narrow-band imaging magnifying endoscopy

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Abstract

Objective To evaluate the accuracy of Type B2 based on narrow-band imaging-magnifying endoscopy (NBI-ME) in judging invasion depth of superficial esophageal squamous cell carcinoma (SESCC) and analyze potential influencing factors.

Method Data from 113 patients where Type B2 was observed by magnifying endoscopy and confirmed by postoperative pathology as SESCC at the First Affiliated Hospital of Fujian Medical University and Fujian Provincial Hospital from January 2015 to April 2024 were retrospectively analyzed. Patients were divided into correct prediction and incorrect prediction groups according to the postoperative pathological results, and the prediction accuracy was calculated. The incorrect prediction group was further divided into overestimation and underestimation groups to identify the influential factors for overprediction and underprediction, respectively. The independent influential factors for the prediction were assessed using multivariate Cox logistic regression analysis.

Results B2-narrow (Type B2 area ≤ 5 mm) ($p < 0.001$) and Type B2 around erosion ($p = 0.040$) were independent risk factors of overpredicting the invasion depth of SESCC based on Type B2. The presence of significant endoscopic features was an independent protective factor for overpredicting the invasion depth of SESCC ($p = 0.014$), whereas the presence of significant features under endoscopy was an independent risk factor for the underprediction ($p = 0.005$).

Conclusion B2-narrow (Type B2 area ≤ 5 mm), Type B2 vessels around erosion, and non- significant endoscopic features are closely related to overpredicting the invasion depth of SESCC based on Type B2, and the presence of significant endoscopic features is closely associated with underprediction.

1 Introduction

China has the highest esophageal squamous cell carcinoma incidence worldwide, with a mortality rate ranking fourth globally [1, 2]. The prognosis of esophageal cancer is closely associated with its staging. The overall five-year survival rate for mid- to late-stage esophageal cancer after treatment is less than 10%, while early-stage esophageal cancer can achieve a five-year survival rate of 90% with aggressive treatment. Therefore, early diagnosis and treatment are crucial for improving the survival rate of esophageal cancer [3, 4]. Superficial esophageal cancer is defined as the depth of cancer invasion confined to mucosal and submucosal layers, with or without lymph node metastasis. The distinction from early-stage esophageal cancer lies in the presence or absence of lymph node metastasis. For esophageal

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squamous cell carcinoma, predicting the depth of invasion is crucial in determining the indications for endoscopic resection, as the rate of lymph node metastasis gradually increases with the depth of cancer cell invasion [5].

Research has shown that lymph node metastasis is rarely observed when the infiltration depth of superficial esophageal squamous cell carcinoma (SESCC) is limited to the epithelium or lamina propria mucosae (EP/LPM) [6–8]. However, the rate of lymph node metastasis increases from 10 to 40% in SESCC when the infiltration depth developed from the muscularis mucosae or superficial submucosa (MM/SM1) to those infiltrating deeper into the deeper submucosa (SM2/SM3) [9]. Therefore, surgery and chemoradiotherapy can be used for SESCC with infiltration depth reaching the muscularis mucosae and deeper layers. According to the Japanese guidelines for the diagnosis and treatment of esophageal cancer, SESCC invading the epithelium or lamina propria mucosae is considered an absolute indication for endoscopic resection (ER), whereas SESCC invading the muscularis mucosae or superficial submucosa is considered a relative indication [10]. SESCC invading the deep submucosal layer is still under investigation [11]. Surgical esophagectomy has a high mortality and recurrence rate [12–14], with recent Japanese studies reporting a mortality rate of 3.4% and an overall postoperative recurrence rate of 41.9% [15, 16]. Surgical esophagectomy is currently the main curative treatment for SESCC invading the deep submucosal layer. Notably, endoscopic submucosal dissection (ESD) has shown good long-term efficacy for SESCC with submucosal infiltration depth < 200 μm (SM1) [17–19]. Whether additional surgical intervention and radiotherapy are necessary after ESD of SESCC invading the muscularis mucosae or superficial submucosa depends on the patient's age, horizontal margin status, and vascular invasion. Therefore, accurately distinguishing between infiltration in the epithelium or lamina propria and infiltration into the muscularis mucosae or deeper layers is also crucial.

Existing evidence has demonstrated a close correlation between microvascular morphology and the depth of invasion in esophageal squamous cell carcinoma [20–22]. The Japan Esophageal Society (JES) has proposed a simplified classification based on the irregularity of microvessels in the target lesion under narrow-band imaging-magnifying endoscopy (NBI-ME). This classification, particularly the Type B2 vessels, is easy to master and highly accurate [23]. Type B2 vessels suggest tumor infiltration into the mucosal and submucosal layers up to one-third from the top. However, studies have shown that the sensitivity and positive predictive value of Type B2 vessels in predicting invasion into the mucosal and submucosal layers up to one-third are 75–86% and 53–75%, respectively, with a relatively low positive predictive value [24]. Therefore, the present study retrospectively analyzed the accuracy of predicting the invasion depth of SESCC based on Type B2 vessels under NBI-ME and explored the potential influencing factors.

2 Materials and methods

2.1 Patients selection

A total of 113 patients with SESCC confirmed by postoperative pathology, who underwent NBI-ME to evaluate the invasion depth of esophageal tumor, were observed for Type B2 vessels, and subsequently underwent endoscopic or surgical treatment at the First Affiliated Hospital of Fujian Medical University and Fujian Provincial Hospital from January 2015 to April 2024, were included in the case–control study. The collection of data was performed in line with the principles of the Declaration of Helsinki, and approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (approval number: MTCA, ECFAH of FMU [2015]084–2). Informed consent was obtained from all individual participants included in the study.

The exclusion criteria were as follows: confirmed diagnosis of esophageal cancer before NBI-ME evaluation; a history of esophageal surgery; and incomplete clinical, endoscopic, and pathological data.

2.2 Review of endoscopic images

All endoscopic images were independently analyzed by two experienced endoscopists according to the JES classification. The two endoscopists were blinded to patients' clinical information. Consistent results were considered reliable. A blinded senior chief physician adjudicated all discrepancies.

2.3 Definitions

2.3.1 JES classification

The JES classification offers simplified criteria not only for characterization but also for prediction of the invasion depth of SESCC [25]. Diagnostic criteria of the JES classification are based on the degree of microvascular irregularity in the target lesion observed by magnifying endoscopy. Intrapapillary capillary loops (IPCL) are a basic unit of microvasculature in the squamous mucosal surface. The microvascular irregularity is assessed for the presence or absence of each of the following morphological factors: weaving (i.e., tortuosity), dilatation, irregular caliber, and different shapes (i.e., various shapes) [26, 27]. The JES classification system consists of the following two types: Type A: Normal IPCL or abnormal microvessels without severe irregularity. Type B: Abnormal microvessels with severe irregularity or highly dilated abnormal vessels. Type B1 is defined as Type B vessels with a loop-like formation. B1 is defined as Type B vessels that normally appear as dot-like microvessels in a target area (i.e., a brownish area) under NBI endoscopic observation with low or no magnification. B2 is defined as Type B vessels without a loop-like formation with a stretched and markedly elongated transformation. B2 vessels often show a multilayered arrangement or an irregularly branched/running pattern. B3 is defined as highly dilated abnormal vessels whose caliber appears to be more than three times that of the usual B2 vessels [24].

2.3.2 Diameter of avascular areas (AVA)

The diameter of AVA is related to the invasion depth of SESCC. AVA is classified into three types: AVA-small (long axis ≤ 0.5 mm), AVA-medium (long axis > 0.5 to < 3.0 mm), and AVA-large (long axis ≥ 3.0 mm), (Fig. 1). Any type of AVA surrounded by Type B1 vessels suggests tumor invasion into the epithelial layer/lamina propria. AVA-medium and AVA-large surrounded by B2 or B3 vessels indicate tumor invasion into the mucosal muscular/submucosal layer up to one-third or two-thirds or deeper [24].

2.3.3 B2 area diameter

A B2 area diameter ≤ 5 mm is defined as a B2-narrow area, while a B2 area diameter > 5 mm is defined as a B2-broad area.

2.3.4 Significant endoscopic features

Significant endoscopic features are defined as nodular type (diameter > 2–3 mm, height > 1 mm), thickened type (minimal change in lesion shape after insufflation and aspiration, indicating submucosal infiltration), markedly depressed type (marked depression with distinct borders even if the border is elevated) [28] (Fig. 2).

2.3.5 Type B2 vessels around *erosion*

Non-circular vessels are found in erosions or regenerating mucosa within the cancerous area, which have two major characteristics: dense vessel morphology and similarity in vessel diameters (Fig. 3).

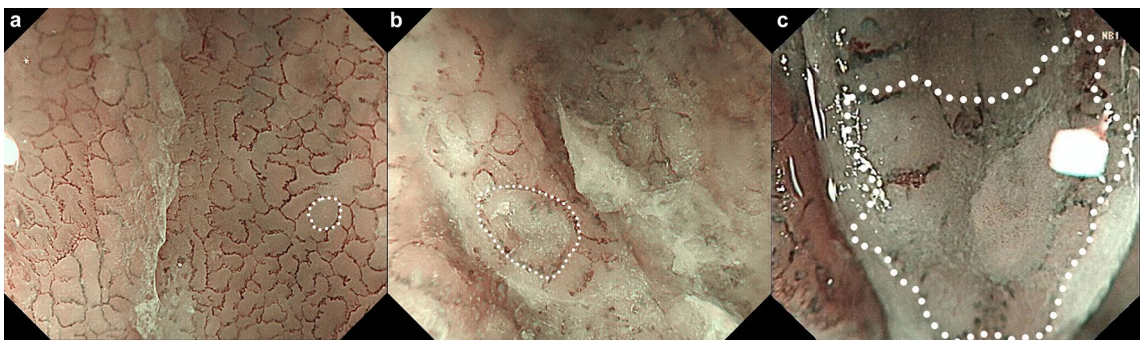

Fig. 1 Classification of avascular areas (AVA): **a** AVA-small (long axis ≤ 0.5 mm); **b** AVA-medium (long axis > 0.5 to < 3.0 mm); **c** AVA-large (long axis ≥ 3.0 mm)

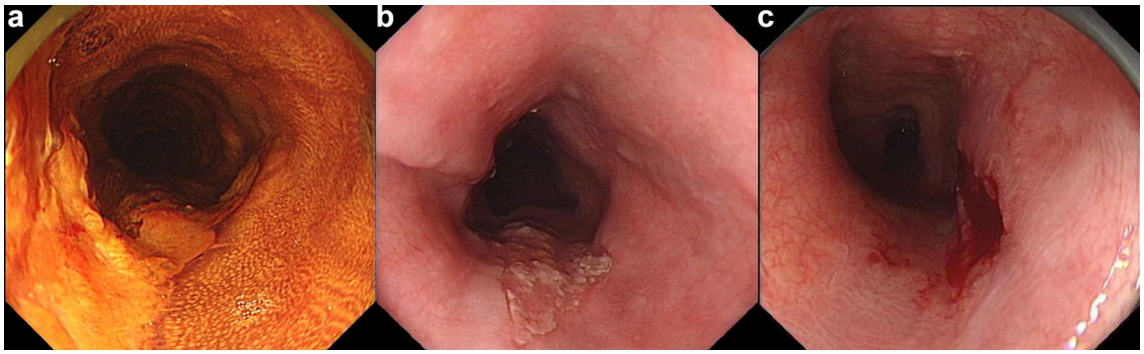

Fig. 2 Significant endoscopic features: **a** nodular type (diameter > 2–3 mm, height > 1 mm); **b** thickened type (minimal change in lesion shape after insufflation and aspiration, indicative of submucosal infiltration); **c** markedly depressed type (marked depression with distinct borders even if the border is elevated)

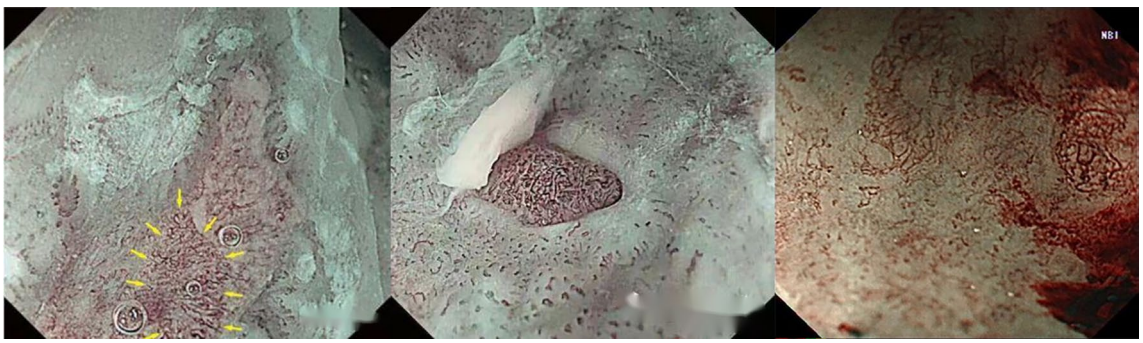

Fig. 3 Images of Type B2 vessels around erosion. Non-circular vessels are found in erosions or regenerating mucosa within the cancerous area, characterized by dense morphology and similar diameters of vessels

2.4 Data collection

The variables studied were demographic, clinical, imaging, pathological, and endoscopic data. Patient data, including gender, age, white-light endoscopy images, ME-NBI images, endoscope models, surgical records, and postoperative pathological reports, were collected.

2.5 Statistical analysis

Using a postoperative pathological diagnosis as the gold standard, patients were divided into two groups according to the prediction of the invasion depth of SESCC based on Type B2 vessels under NBI-ME: the correct prediction (pMM/SM1) group and the incorrect prediction group. The prediction accuracy was calculated. Furthermore, the incorrect prediction group was further divided into two subgroups: the overestimation (pEP/LPM) group and the underestimation (pSM2/SM3) group, and compared with the correct prediction group to identify the influential factors for overestimation and underestimation, respectively. Subsequently, multivariate Cox logistic regression analysis was conducted to explore their respective independent risk factors. Data were analyzed using SPSS 22.0 software. Count data were expressed as frequency (%), and intergroup comparisons were performed using the chi-square test or Fisher's exact probability method. Normally distributed measurement data were expressed as mean standard deviation ($\overline{x} \pm S$) and the t-test was utilized to compare differences between groups. Skewed measurement data were expressed as the median and interquartile range [M (IQR)], and compared using the rank-sum test. A P-value of < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

A total of 113 patients were enrolled, comprising 77 males and 36 females, with a median age of 61 (IQR: 13). There were 113 postoperative pathological diagnoses of SESCC lesions, with a median size of 40.0 (IQR: 20.0) mm. All lesions were classified as Type B2 vessels under ME-NBI (endoscopic examinations were performed using the Japanese Olympus GIF-H260Z gastroscope and NBI system). The majority of lesions (76.1%, 86/113) appeared as superficial flat type (0-IIb type) under endoscopy, with 86 lesions (76.1%) removed endoscopically and 27 lesions (23.9%) removed surgically. According to the postoperative pathological diagnosis (assessed by experienced pathologists), among the lesions predicted for invasion depth based on Type B2 vessels under ME-NBI, 31 lesions (27.43%, correct prediction group) were correctly predicted and 82 lesions (72.57%, prediction error group) were incorrectly predicted. Meanwhile, 66 lesions (58.41%, overestimation group) were overestimated, and 16 lesions (14.16%, underestimation group) were underestimated.

3.2 Analysis of overprediction factors based on Type B2 vessels

The results of univariate Cox regression analysis revealed no statistically significant differences between the overestimation group and the correct prediction group in terms of median age, gender ratio, lesion distribution, median size, circumference area composition, gross morphology composition, and AVA classification composition of the patients ($P > 0.05$). However, B2 area classification composition, presence of significant endoscopic features, and presence of inflammation erosion around B2 vessels were statistically significantly different between the two groups ($P < 0.05$, Table 1).

Table 1 Univariate Cox regression analysis of factors related to the overprediction of invasion depth in SESCC based on Type B2 vessels

Variable	Overprediction Group ($n=66$)	Correct-prediction Group ($n=31$)	Statistics	*P* value
Age [M^b(IQR^c)]	61(15)	61(11)	$z=0.030$	0.862
Sex, male/Female	40/26	25/6	$\chi^2=3.675$	0.055
Lesion location			$\chi^2=2.779$	0.096
Upper thoracic esophagus	5	0		
Middle thoracic esophagus	34	14		
Lower thoracic esophagus	27	17		
Lesion size[mm, *M*(IQR)]	33.5(17.75)	45(30)	$z=5.568$	0.018
Circumference of the lesion			$\chi^2=5.391$	0.02
< 1/2 circle	50	17		
1/2 ~ 3/4 circle	10	6		
≥ 3/4 circle to circumferential involvement	3	3		
Circumferential involvement	3	5		
Visual classification			$\chi^2=0.755$	0.385
0–IIa	3	8		
0–IIb	62	18		
0–IIc	1	5		
B2 area classification (narrow area/broad area)	63/3	12/19	$\chi^2=25.307$	< 0.001
AVA[a] classification			$\chi^2=1.716$	0.190
Non/Small	64	28		
Middle/Large	2	3		
Significant Endoscopic Features (positive/negative)	3/63	12/19	$\chi^2=13.773$	< 0.001
Type B2 vessels around erosion (positive/negative)	46/20	7/24	$\chi^2=16.641$	< 0.001

[a]AVA: avascular areas; [b]M: median; [c]IQR: interquartile range

Table 2 Multivariate Cox regression analysis of factors related to the overprediction of invasion depth in SESCC based on Type B2 vessels

Variable	Regression coefficients	Standard error	Wald χ^2	*P* Value	*OR*[a] (95%*CI*[b])
B2 area classification (narrow area/broad area)	4.208	0.995	17.895	< 0.001	67.238 (9.569–472.474)
Significant Endoscopic Features (positive/negative)	−2.571	1.046	6.040	0.014	0.076 (0.010–0.594)
Type B2 vessels around erosion (positive/negative)	1.756	0.856	4.203	0.040	5.789 (1.080–31.018)

[a]OR: odds ratio; [b]CI: confidence interval

Multivariate Cox logistic regression analysis results showed that a small area of B2 and the presence of inflammation erosion around B2 vessels were independent risk factors for overestimation of the invasion depth of SESCC based on Type B2 vessels. Conversely, the presence of significant endoscopic features was an independent protective factor for the overestimation of the invasion depth of SESCC based on Type B2 vessels (Table 2).

3.3 Analysis of underprediction factors based on Type B2 vessels

The results of univariate Cox regression analysis revealed no statistically significant differences between the underestimation group and the correct prediction group in terms of median age, gender ratio, lesion distribution, median size, circumferential area composition, gross morphology composition, B2 area composition, AVA classification composition, and whether inflammation erosion was present around B2 vessels (P > 0.05). However, the presence of significant endoscopic features was statistically significantly different between the two groups (P < 0.05, Table 3).

Table 3 Univariate Cox regression analysis of factors related to the underprediction of invasion depth in SESCC based on Type B2 vessels

Variable	Underprediction Group (*n* = 16)	Correct-prediction Group (*n* = 31)	Statistics	*P* Value
Age [*M*(IQR)]	62(17)	61(11)	*z* = 0.064	0.800
Sex, male/Female	12/4	25/6		0.357
Lesion location				0.200
Upper thoracic esophagus	3	0		
Middle thoracic esophagus	6	14		
Lower thoracic esophagus	7	17		
Lesion size [mm, *M*[b] (IQR[c])]	42.5(10)	45(30)	*z* = 0.067	0.795
Circumference of the lesion				0.991
< 1/2circle	10	17		
1/2 ~ 3/4 circle	1	6		
≥ 3/4 circle to circumferential involvement	1	3		
Circumferential involvement	4	5		
Visual classification				0.652
0–IIa	5	8		
0–IIb	6	18		
0–IIc	5	5		
B2 area classification (narrow area/broad area)	3/13	12/19	χ^2 = 3.123	0.077
AVA[a] classification			χ^2 = 0.755	0.385
Non/Small	13	28		
Middle/Large	3	3		
Significant Endoscopic Features(positive/negative)	15/1	12/19	χ^2 = 8.343	0.004
Type B2 vessels around erosion(positive/negative)	1/15	7/24	χ^2 = 1.741	0.187

[a]AVA: avascular areas; [b]M: median; [c]IQR: interquartile range

Multivariate Cox logistic regression analysis results showed that the presence of significant features under endoscopy was an independent risk factor for the underestimation of the invasion depth of SESCC based on Type B2 vessels (P = 0.027, odds ratio = 7.899, 95% confidence interval: 1.259–49.565).

4 Discussion

Previous studies have indicated that tumor invasion into the muscularis mucosa layer or deeper can disrupt the formation of intraepithelial capillary loops, which are defined as Type B2 vessels according to the JES classification [20–22]. However, whether these non-villous vascular structures are Type B2 vessels cannot be confirmed in clinical practice because inflammation has also been associated with abnormalities in these non-villous vascular structures. In the present study, we defined areas with more than 3 abnormal non-villous, non-dilated vessels observed in the target area as B2 vessel regions. A total of 113 lesions were classified as Type B2 vessels under NBI-ME and confirmed as esophageal squamous cell carcinoma by postoperative pathology. Among them, postoperative pathology suggested infiltration into the epithelium/lamina propria in 66 cases (58.41%), infiltration into the muscularis mucosae as well as upper 1/3 area of the submucosa in 31 cases (27.43%), and infiltration into the lower 2/3 area of the submucosa, i.e., SM2 and SM3, in 16 cases (14.16%). It can be seen that relying solely on the prediction of the depth of infiltration of esophageal squamous cell carcinoma based on Type B2 vessels observed under NBI-ME results in a low accuracy rate. In our study, the diagnostic accuracy of B2 vessels is lower than what has been reported in the literature [29, 30]. We argue this is due to differences in dietary habits, healthcare-seeking behaviors, and genetic variations among populations in different regions. These factors may lead to different physiological origin of Type B2 vessels. For instance, the high incidence of mucosal inflammation in our region might affect IPCL, resulting in a lower probability of muscularis mucosa and superficial submucosa invasion regarding same B2 vessel appearance compared to other regions.

Recent studies have demonstrated the feasibility and effectiveness of endoscopic treatment combined with selective radiotherapy and chemotherapy for early esophageal cancer patients with T1bN0M0 [31]. Underestimation of the tumor infiltration may delay further surgical or radiotherapy and chemotherapy treatment for patients, leading to an increased risk of lymph node metastasis in tumor patients. Conversely, overestimation of the tumor infiltration depth may result in unnecessary radiotherapy and chemotherapy treatments. Therefore, analyzing influencing factors can help reduce misjudgments of the depth of SESCC based on Type B2 vessels, thereby selecting the correct treatment modality, reducing unnecessary treatment, and preventing delays in subsequent treatment.

Pass study reported a significant correlation between the maximum diameter of VN-type (non-structured, showing no architectural features) pit patterns in the Kudo-Tsuruta classification and the depth of submucosal infiltration in patients with colorectal cancer [32]. Therefore, we hypothesized that the maximum diameter of B2 vascular areas in SESCC patients may also be related to the depth of submucosal infiltration. We divided B2 vascular areas into small and large regions based on the measurement of their maximum diameter. In clinical practice, the maximum magnification of the H260Z (Japanese Olympus) provides a field of view width of 4 mm, and combining this with caliper measurements of the specimen's B2 area diameter can roughly determine the size of the B2 area. Therefore, when the target area displays B2 vessels, if a single field of view provided by the H260Z accommodates the target area or if the measured B2 area is ≤ 5 mm using a caliper, then the target area displaying B2 vessels is defined as a small B2 region; otherwise, if the B2 vascular area exceeds the width of the field of view provided by the H260Z or if the measured B2 area is > 5 mm, it is defined as a large B2 region. The results of the multivariate Cox logistic regression analysis showed that a small B2 region was an independent risk factor for overestimating the infiltration depth of SESCC based on Type B2 vessels under NBI-ME.

Studies have shown that ME-NBI does not offer additional benefits over white light imaging in diagnosing the infiltration depth of SESCC[33]. White light endoscopic features help differentiate the infiltration depth in SESCC. By combining the endoscopic macroscopic classification, size, and surface features of lesions, an endoscopic prediction model can be established to predict SESCC infiltration beyond the SM1 layer [34]. It is suggested that the appearance of surface nodules, granular surface, surface irregularities, deep depressions, and mucosal thickening under endoscopy are independent factors associated with SESCC infiltration beyond the SM1 layer. The current study also retrospectively analyzed white-light endoscopic images of SESCC cases based on Type B2 vessels and found that nodular, thickened, and significantly depressed types had significant features under endoscopy. The results of the multivariate Cox logistic regression analysis showed that the presence of significant features under endoscopy was an independent protective factor for overestimating the infiltration depth of SESCC based on Type B2 vessels under NBI-ME and also an independent risk factor for underestimating the infiltration depth, indicating a closer relationship with diagnostic inadequacy.

Sato et al. [35] pointed out that mild infiltration into the mucosal muscle layer causes non-structured vessels, which are difficult to distinguish from tumors under endoscopy. Fujiwara et al. [36] found that vessels affected by inflammation were generally short and showed no significant changes in diameter. Approximately 18% of cases infiltrated into the epithelial layer/mucosal layer in Type B2 vessels, which were overestimated as infiltrating into the muscularis mucosae/submucosa upper 1/3, with 46% of cases having inflammation erosion around Type B2 vessels. Takahashi et al. [37] evaluated the pathological features of inflammatory vessels and found that they typically appeared as slender and high-density structures surrounded by inflammation. They define vessels with inflammation as B2-i, suggesting inflammation rather than invasion into the mucosal muscle layer or deeper layers of the tumor, thereby reducing overdiagnosis. the present study did not further subdivide the diameter and density of Type B2 vessels but rather subdivided non-structured vessels based on whether they were affected by tumor invasion or inflammation and included them in the multivariate Cox regression analysis. The results showed that inflammation erosion around B2 vessels was an independent risk factor for overestimating the infiltration depth of SESCC based on Type B2 vessels under NBI-ME.

Nevertheless, this study has several limitations. First, this is a retrospective study and may be susceptible to selection bias. Further prospective studies are needed to confirm the relationship between the diameter of Type B2 vessel areas and the infiltration depth of SESCC. Second, this study only used recorded endoscopic images to measure the maximum diameter of Type B2 vessel areas, which may affect the accuracy of measurements. Further precise measurements are needed under endoscopy. Third, the number of cases infiltrating into the lower 2/3 of the submucosa is small; thus, further studies are warranted to explore the relationship between Type B2 vessels and infiltration into the lower 2/3 of the submucosa. Finally, this is a single-center study and may not represent the overall population.

5 Conclusion

In summary, this study demonstrates that relying solely on the prediction of the infiltration depth of SESCC based on Type B2 vessels under NBI-ME has a low accuracy and is prone to overestimation. A small B2 region, inflammation erosion around B2 vessels, and the absence of nodular, thickened, or significantly depressed features under endoscopy are related to the overestimation of the infiltration depth, while the presence of nodular, thickened, or significantly depressed features under endoscopy are related to the underestimation of the infiltration depth.

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Author contribution Xu Lin designed this research. Xiaolu Lin, Wanyin Deng, Wei Liang and Wenming Liu processed the data. Xu Lin collected the images used in the research, analyzed data and wrote the manuscript. All authors read and approved the final version of the manuscript.

Availability of data and materials All data that support the findings of this study are available from the corresponding authors upon request.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (approval number: MTCA, ECFAH of FMU [2015]084–2). Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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