JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12246

ORIGINAL ARTICLE

Additional effect of magnifying narrow-band imaging on estimating the invasion depth of superficial esophageal cancer

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Key words
esophageal squamous cell carcinoma, invasion depth, magnifying narrow-band imaging, white light endoscopy.

Accepted for publication 31 July 2019.

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Declaration of conflict of interest: None.
Author contribution: Minoru Kato and Yoshito Hayashi contributed to conception and design. Minoru Kato, Yoshito Hayashi, Ryotaro Uema, Takanori Inoue, Shunsuke Yoshii, and Yoshiki Tsujii contributed to the conduction of the study. Minoru Kato and Yoshito Hayashi contributed to the analysis and interpretation of the data. Minoru Kato and Yoshito Hayashi contributed to the drafting of the article. Hideki Iijima and Tetsuo Takehara contributed to critical revision. The article was approved finally by all authors.

Abstract

Background and Aim: To investigate whether assessment by magnifying narrow-band imaging (M-NBI) based on the classification of the Japan Esophageal Society provides additional value to the estimation of the invasion depth of superficial esophageal squamous cell carcinoma (SCC) compared with assessment by white light endoscopy (WLE) alone.
Methods: Endoscopic images of 211 consecutive superficial esophageal SCCs resected by endoscopic submucosal dissection were separated into WLE and M-NBI images. Depth estimation was performed independently by five evaluators using the numerical depth estimation scale (0 = epithelium (EP)/lamina propria (LPM), 1 = EP/LPM > muscularis mucosa (MM)/shallow submucosa (SM1), 2 = MM/SM1 > EP/LPM, 3 = MM/SM1, 4 = MM/SM1 > deep submucosa (SM2), 5 = SM2 > MM/SM1, 6 = SM2), using primarily WLE images (step 1), and subsequently both WLE and M-NBI images (step 2). The discordance scores, determined by the average of the five evaluators' difference between the estimated score (from 0 to 6) and pathological score (0 for histologically proven EP/LPM, 3 for MM/SM1, and 6 for SM2), were analyzed in steps 1 and 2.
Results: The discordance scores significantly decreased in step 2 (0.53 ± 0.06) compared with those in step 1 (0.79 ± 0.07) ($P < 0.001$). When the discordance score < 1.5 was regarded as a clinically correct diagnosis, the rate of the clinically correct diagnosis significantly increased in step 2 compared with that in step 1 (81% to 91%, $P < 0.001$).
Conclusion: M-NBI has an additive value for estimating the invasion depth of superficial esophageal SCCs.

Introduction

The depth of tumor invasion is closely associated with metastasis and survival rates in superficial esophageal squamous cell carcinoma (SCC),[1–6] and accurate estimation of its invasion depth is essential in deciding the optimal therapeutic strategy. Endoscopic diagnosis of invasion depth is usually classified into three categories in Japan: tumor limited to the epithelium or lamina propria mucosa (EP/LPM), tumor invading the muscularis mucosae or submucosa to a depth of 200 μm or less from the muscularis mucosae (MM/SM1), and tumor invading the submucosa to a depth of more than 200 μm (SM2), because these categories correspond well with the risk of metastasis.[7]

The invasion depth of superficial esophageal SCCs is usually estimated by the macroscopic appearance of the lesion using white light endoscopy (WLE) as follows: EP/LPM, flat lesion with no irregularity on its surface; MM/SM1, slightly elevated/depressed lesion with irregularity on its surface; and SM2, lesion with protrusion or deep depression.[1,8,9] However, magnifying narrow-band imaging (M-NBI) has provided another approach to predict tumor depth through the visualization of the microvessels of the tumor, whose morphological patterns are known to have a close relationship with the tumor depth.[10] In 2012, the Japan Esophageal Society (JES) established a simple classification of M-NBI findings to differentiate the invasion depth of superficial esophageal SCCs.[11] In this classification, abnormal microvessels observed on the surface of the tumor are called type B vessels and are classified into B1, B2, and B3 based on their morphology. If a tumor has only type B1 vessels, the invasion depth is suggested to be EP/LPM. Moreover, types B2 and B3 vessels are the indicators of MM/SM1 and SM2 cancers, respectively. One prospective study reported that the JES classification had an overall accuracy of 90.5%[12]; however, the

trial was conducted by the committee members of JES, who were already familiar with the classification, which may raise some concerns about the results' generalizability. Moreover, in that trial, the diagnosis of the invasion depth was conducted only with M-NBI findings; however, in our clinical practice, the diagnosis is usually made by the combined use of WLE and M-NBI.[8,9,13]

Whether M-NBI findings actually provide an additional value to estimate the invasion depth compared with WLE alone still remains controversial.[8,9,13] Therefore, we planned a study to elucidate the contribution of M-NBI to the improvement in estimating the invasion depth of superficial esophageal SCCs compared with that of WLE alone.

Methods

Study design and materials. This was a retrospective study, where five evaluators independently reviewed the previously recorded endoscopic images of superficial esophageal SCCs. The study was approved by the ethics committee of Osaka University.

We identified consecutive esophageal lesions treated by endoscopic submucosal dissection (ESD) between January 2012 and March 2019 from our prospectively collected database and included them in this study. The exclusion criteria were as follows: (i) no confirmation of SCC in the resected specimen, (ii) prior chemotherapy and/or radiotherapy for esophageal cancer, and (iii) pretreatment endoscopic images of either WLE or M-NBI judged as not having enough quality for assessing the invasion depth.

All lesions were generally examined using a magnifying endoscope with NBI (GIF-Q240Z, GIF-H260Z or GIF-H290Z; Olympus Medical Systems, Tokyo, Japan) before ESD. The tumor invasion depth was judged by pathologists after ESD and classified into three groups: EP/LPM, MM/SM1, and SM2.

One investigator (M.K.) collected all pretreatment endoscopic images of the eligible superficial esophageal SCCs from the database, and all images of the lesions blinded for patient names and examination dates were divided into WLE and M-NBI images. To avoid the intentional selection of the images that may lead evaluators to correctly predict the invasion depth, all the WLE and M-NBI images capturing the target lesion were used. Thus, an endoscopic image library of the superficial esophageal SCCs containing either all WLE images or all M-NBI images was prepared.

Numerical depth estimation scale. In clinical practice, there are many lesions exhibiting ambiguous endoscopic findings, and it is not always easy to clearly differentiate the tumor depth into three groups (i.e. EP/LPM, MM/SM1, SM2). Therefore, we developed a 0–6 numerical depth estimation scale in an attempt to express both conclusive and inconclusive estimation:

0 = Depth of tumor can be certainly distinguished as EP/LPM (EP/LPM).

1 = Depth of tumor is assumed to be EP/LPM, but the possibility of MM/SM1 cannot be ruled out (EP/LPM > MM/SM1).

2 = Depth of tumor is assumed to be MM/SM1, but the possibility of EP/LPM cannot be ruled out (MM/SM1 > EP/LPM).

3 = Depth of tumor can be certainly distinguished as MM/SM1 (MM/SM1).

4 = Depth of tumor is assumed to be MM/SM1, but the possibility of SM2 cannot be ruled out (MM/SM1 > SM2).

5 = Depth of tumor is assumed to be SM2, but the possibility of MM/SM1 cannot be ruled out (SM2 > MM/SM1).

6 = Depth of tumor can be certainly distinguished as SM2 (SM2).

Scores of 0 (EP/LPM), 3 (MM/SM1), and 6 (SM2) indicated conclusive estimation (i.e. high confident estimation), whereas scores of 1 (EP/LPM > MM/SM1), 2 (MM/SM1 > EP/LPM), 4 (MM/SM1 > SM2), and 5 (SM2 > MM/SM1) indicated inconclusive estimation (i.e. low confident estimation).

Evaluation procedure. Five evaluators (A, B, C, D, and E), who had 6, 7, 9, 14, and 16 years of experience in endoscopy, respectively, independently evaluated the prepared endoscopic image library. All evaluators were blinded to the pathological invasion depth of the lesions.

The evaluation procedure for each case consisted of two steps using the aforementioned 0–6 numerical depth estimation scale: step 1, the evaluators viewed only WLE images of a target lesion and selected a score from 0 to 6 that best described their judgment, and the score was recorded on a case report form; step 2, they were allowed to view M-NBI images of the same lesion and once again scored the lesion from 0 to 6 by comprehensively assessing both WLE and M-NBI images, and the score was also recorded on a case report form. In each step, if the evaluators were confident in their depth estimation, they scored 0 (EP/LPM), 3 (MM/SM1), or 6 (SM2), whereas if the evaluators were not confident in classifying the invasion depth into those three groups because of the lesion's ambiguous macroscopic appearance and/or microvessel morphology, they chose the remaining intermediate scores (i.e. 1, 2, 4, 5). We defined the score evaluated by viewing endoscopic images as the "estimated score."

In step 2, evaluators were also asked to classify the abnormal microvessels observed on a target lesion into three groups according to the JES classification (i.e. type B1, B2, or B3).

Before starting the actual evaluation process, the commonly known diagnostic criteria for predicting the invasion depth of the superficial esophageal SCCs using WLE[1,8,9] and the JES classification for M-NBI[11,12] were explained by the primary investigator (M.K.) to all evaluators using representative endoscopic images to control the estimation quality.

Measured outcomes. We defined the "pathological score" for each case, such as 0 for histologically confirmed EP/LPM cancer, 3 for MM/SM1 cancer, and 6 for SM2 cancer. If the "estimated score (X = 0–6)" becomes closer to the "pathological score (Y =0, 3, or 6)," it can be interpreted that depth estimation has become more accurate and conclusive. Therefore, we calculated an absolute value of the difference ($|X - Y|$) in each case.

In addition, the overall interobserver agreement of type B vessels between all five evaluators was also investigated to assess the reproducibility of the JES classification.

Statistical analysis. For each case, the mean value of the five evaluators' difference between the estimated and pathological scores ($|X - Y|$) was determined and termed as the discordance score. A paired t-test was used to compare the discordance scores between steps 1 and 2. In each case, if the discordance score was lower than 1.5, we regarded it as a clinically correct diagnosis, and its ratio was compared in steps 1 and 2 using the McNemar test. The paired t-test was used for comparison of the mean values ($|X - Y|$) in steps 1 and 2 for each evaluator. A *P*-value <0.05 was considered statistically significant.

Fleiss's κ coefficient was calculated to assess the overall interobserver agreement of type B vessels among all five evaluators. Agreement was classified as excellent for a value ≥0.8, substantial for <0.8 to ≥0.6, moderate for <0.6 to ≥0.4, and fair for <0.4.

We used the Online Kappa Calculator software (retrieved from http://justus.randolph.name/kappa) for kappa statistics. All other analyses were performed using JMP Pro version 13 (SAS Institute, Cary, NC, USA).

Results

Eligible lesions. A total of 322 superficial esophageal lesions were treated by ESD at Osaka University Hospital between January 2012 and March 2019. Among them, 23 lesions with no confirmation of SCC after ESD (2, no neoplasm; 16, adenocarcinoma; 5, low-grade intraepithelial neoplasia), 47 lesions that developed in patients who had a history of chemotherapy and/or radiotherapy for esophageal cancer, and 41 lesions with pretreatment endoscopic images of either WLE or M-NBI that cannot be assessed were excluded. The remaining 211 lesions were included in this study (Fig. 1). The median number of WLE and M-NBI images for each lesion were 6 (range, 1–34) and 18 (range, 2–89), respectively.

The characteristics of the 211 superficial esophageal SCCs are presented in Table 1. The median size of the lesions was 19 mm (range, 2–124), and the luminal circumference was <1/2 in most of the lesions (83%). Histologically, the depth of invasion was EP/LPM (pathological score = 0) in 171 lesions, MM/SM1 (pathological score = 3) in 31 lesions, and SM2 (pathological score = 6) in 9 lesions.

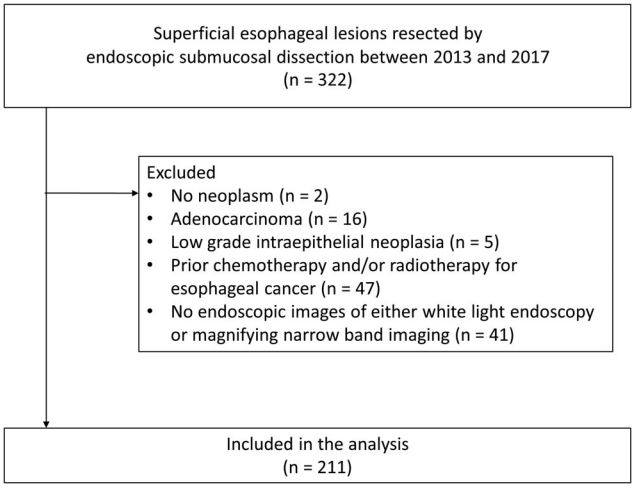


Figure 1 Flow chart of the eligible lesions.

Table 1 Lesion characteristics

Location, *n*	
Upper third	35
Middle third	119
Lower third	57
Morphology, *n*	
Elevated	14
Flat	31
Depressed	151
Mixed	15
Lesion size, median (range), mm	19 (2–124)
Circumference of the lesion, *n*	
<1/2	175
≥1/2–<2/3	29
≥2/3	7
Histological depth of the tumor, *n*	
EP/LPM	171
MM/SM1	31
SM2	9

EP, epithelium; LPM, lamina propria; MM, muscularis mucosa; SM, submucosa.

Study outcomes. The average (±standard error [SE]) of the discordance scores of all 211 cases was significantly lower in step 2 (0.53 ± 0.06) compared with that in step 1 (0.79 ± 0.07) ($P < 0.001$) (Fig. 2a). In detail, the discordance scores decreased in 123 cases (58%), unchanged in 60 cases (29%), and increased in 28 cases (13%) (Fig. 2b). The proportion of having a clinically correct diagnosis significantly increased in step 2 compared with that in step 1 (91 *vs* 81%, $P < 0.001$) (Fig. 2c).

All five evaluators showed significantly lower values ($|X - Y|$) in step 2 compared with those in step 1 (A, 1.03 in step 1 and 0.63 in step 2, $P < 0.001$; B, 0.83 and 0.56, $P < 0.001$; C, 0.72 and 0.50, $P < 0.001$; D, 0.82 and 0.62, $P < 0.001$; E, 0.55 and 0.34, $P < 0.001$) (Fig. 3).

In a subgroup analysis, M-NBI significantly reduced the average (±SE) of discordance scores between steps 1 and 2 in all three subgroups of tumor depth (EP/LPM, 0.47 ± 0.04 to 0.27 ± 0.03, $P < 0.001$; MM/SM1, 1.72 ± 0.11 to 1.36 ± 0.15, $P = 0.0009$; SM2, 3.62 ± 0.55 to 2.51 ± 0.63, $P = 0.0067$). Type B3 vessels, which obtained agreement from more than four evaluators, were detected in three (33%) of nine SM2 cancers.

As shown in Figure 4, distribution of the five evaluators' estimated score shifted close to the pathological score in step 2 from that of step 1 in all three subgroups of tumor depth.

Representative cases. Figure 5 (case 1) and Figure 6 (case 2) show the representative cases in which the estimated score became closer to the pathological score in step 2.

Case 1 was an MM/SM1 cancer (pathological score = 3). Although four evaluators (A, B, C, and D) scored the lesion as

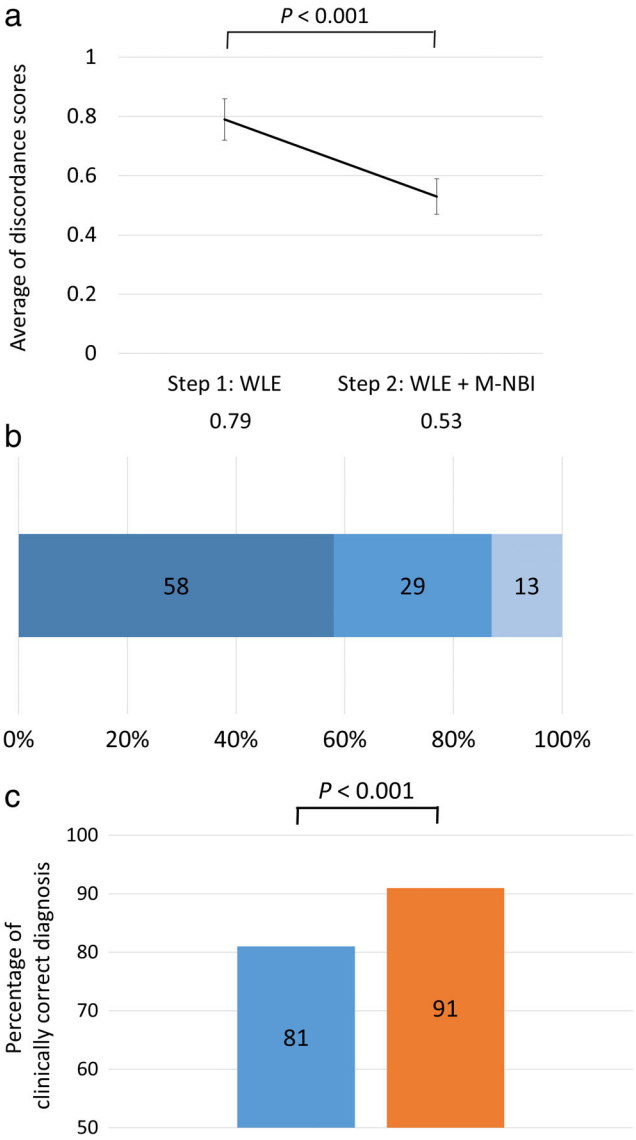
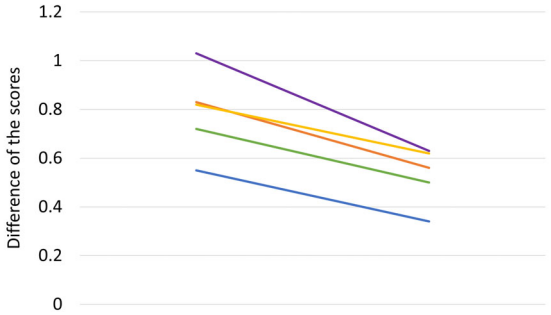


Figure 2 (a) The average (±standard error) of discordance scores of all 211 cases in steps 1 and 2. The value was significantly smaller in step 2 (0.53 ± 0.06) compared with that in step 1 (0.79 ± 0.07) ($P < 0.001$). (b) The ratio of how the discordance score changed from steps 1 to 2. The discordance scores decreased in 123 cases (58%), were unchanged in 60 cases (29%), and increased in 28 cases (13%). (■), Decreased; (■), Unchanged; (■), Increased. (c) The ratio of having a clinically correct diagnosis in steps 1 and 2. A discordance score < 1.5 was set as a clinically correct diagnosis. The ratio was significantly increased in step 2 compared with that in step 1 (81 and 91%, $P < 0.001$). (■), Step 1: white light endoscopy (WLE); (■), Step 2: WLE + magnifying narrow-band imaging (M-NBI).



	Step 1: WLE	Step 2: WLE+M-NBI	*P* - value
Evaluator A	1.03	0.63	< 0.001
Evaluator B	0.83	0.56	< 0.001
Evaluator C	0.72	0.50	< 0.001
Evaluator D	0.82	0.62	< 0.001
Evaluator E	0.55	0.34	< 0.001

Figure 3 The changes in the mean difference of the estimated and pathological scores in each evaluator between steps 1 and 2. All evaluators showed significantly smaller differences in step 2 compared with those in step 1 (A, 1.03 and 0.63, $P < 0.001$; B, 0.83 and 0.56, $P < 0.001$; C, 0.72 and 0.50, $P < 0.001$; D, 0.82 and 0.62, $P < 0.001$; E, 0.55 and 0.34, $P < 0.001$). WLE, white light endoscopy; M-NBI, magnifying narrow-band imaging.

1 (EP/LPM > MM/SM1) in step 1, these evaluators changed the scores to 3 (MM/SM1) in step 2 because M-NBI indicated type B2 vessels on the lesion.

Case 2 was an EP/LPM cancer (pathological score = 0). In step 1, two evaluators (A and B) scored the lesion as 1 (EP/LPM > MM/SM1), while three evaluators (C, D, and E) scored it as 2 (MM/SM1 > EP/LPM). In step 2, where M-NBI showed only type B1 vessels, three evaluators (A, B, and E) properly scored the lesion as 0 (EP/LPM). The scores of the remaining two evaluators (C and D) also became closer to the pathological score (from 2 to 1).

Reproducibility of the JES classification. Interobserver agreement in all five evaluators for the type B vessels had a κ coefficient (95% confidence interval) of 0.58 (0.49–0.67), which indicated moderate agreement.

Discussion

The current study clearly demonstrated the positive effects of using M-NBI assessment in estimating the invasion depth of superficial esophageal SCCs compared with that of WLE alone. Using the numerical depth estimation scale, we have shown that the difference between "estimated" and "pathological" scores significantly decreased after incorporating the assessment of M-NBI images. This result indicates that the assessment of M-NBI findings of superficial esophageal SCCs according to the JES classification leads to a more accurate and conclusive depth estimation.

As we have shown in Figure 2a, the difference between estimated and pathological scores in step 1 was <1.0 on average, which indicates that WLE alone had considerable power to provide the correct clinical diagnosis in most cases. Moreover, the actual reduced value of the difference by M-NBI was only 0.26 in step 2. Taking these results into account, clinically, the main role of using M-NBI in diagnosing the invasion depth of superficial esophageal SCCs is to make the diagnosis more conclusive or self-confident rather than change the diagnosis fundamentally. In line with this speculation, the improvement in the ratio of a clinically correct diagnosis provided by M-NBI was suboptimal

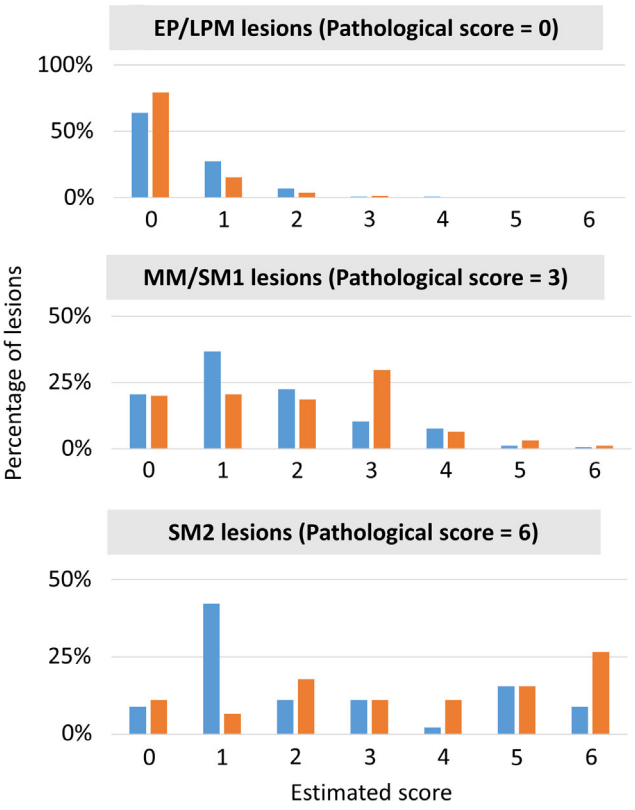


Figure 4 Distributions of all five evaluators' estimated scores in each subgroup of the invasion depth. EP/LPM, tumor limited to the epithelium or lamina propria mucosa; MM/SM1, tumor invading the muscularis mucosae or submucosa to a depth of 200 μm or less from the muscularis mucosae; SM2, tumor invading the submucosa to a depth of more than 200 μm. (▬), Step 1: white light endoscopy (WLE); (▬), Step 2: WLE + magnifying narrow-band imaging.

(10% improvement, Fig. 2c). However, because there are almost no disadvantages in using M-NBI during endoscopic examination, we deem that the routine use of M-NBI is reasonable. One of the problems in evaluating the invasion depth using only WLE findings is the lack of standardized criteria and objectivity, which sometimes leads to doubtful judgment. In contrast, the assessment of M-NBI findings according to the JES classification provides a rather objective indicator of invasion depth, which may improve the sureness of our judgment.

Currently, there are only three articles written in English regarding the additional effect of M-NBI on WLE in estimating the invasion depth of superficial esophageal SCCs.[8,9,13] Ebi *et al.* conducted a prospective trial, in which the diagnostic accuracy of tumor depth assessed by WLE alone and both WLE and M-NBI were 71 and 65% ($P = 0.38$), respectively, suggesting that M-NBI had no positive effect.[8] However, the study was conducted using Inoue's classification for M-NBI,[10] which is more complicated than the JES classification. In addition, although the data were prospectively collected, the sample size of the trial was smaller (49 lesions) than that of our study (211 lesions). The study conducted by Wang *et al.* also could not show the additional benefit of M-NBI.[9] Diagnostic accuracy of the invasion depth was 53% for WLE alone and 57% for WLE with M-NBI ($P > 0.05$). Although their study used JES classification, half of the invited evaluators were inexperienced endoscopists, who might not have been fully accustomed to the classification. In the study conducted by Katada *et al.*, the accuracy of WLE combined with M-NBI (84%) for depth estimation was higher than that of WLE alone (78%); however, their results were not statistically analyzed.[13] In this context, we consider that our results provide new and important information about the efficacy of M-NBI diagnosis.

In the subgroup analysis, although the difference between estimated and pathological scores was significantly reduced by M-NBI observation in SM2 cancers (3.62 to 2.51, $P = 0.0067$), the difference was still rather big in step 2. The invasion depth of SM2 cancers tended to be underestimated (Fig. 4). This may be attributable to the low incidence of type B3 vessels in SM2 cancers (3/9, 33%), which had also been reported in a previous study.[12] However, such an underestimation might be acceptable because these lesions would undergo endoscopic resection first, and subsequent histological examination would indicate the necessity for further treatment, with no drawbacks regarding patients' prognosis.[14,15]

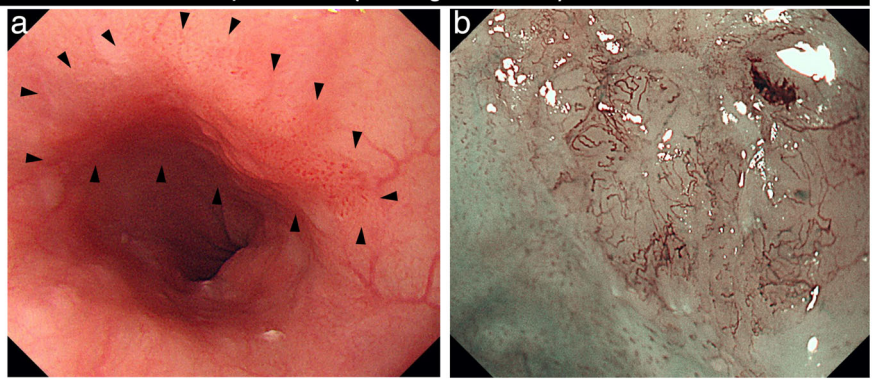
In this study, although the interobserver agreement (κ value) regarding the JES classification among all five evaluators was acceptable (0.58), it did not reach the substantial level. To further increase the agreement, the development of an objective method to assess abnormal microvessels, such as an artificial intelligence diagnosis system, is expected.

We consider that the numerical depth estimation scale used in this study, which distinguished conclusive and inconclusive endoscopic estimation, well reflected our actual clinical practice in the sense that we cannot always make a clear-cut judgment. Using this scale, we could show the additional benefit of M-NBI of not only improving the accuracy of depth estimation but also increasing its conclusiveness, which we emphasize as a unique point of this study.

The present study has several limitations because this was a retrospective study conducted in a single institution. First, there was a spectrum bias as only the tumors treated by ESD were included in the analysis, and hence, the number of MM/SM1 and SM2 tumors was relatively small; however, this information was not disclosed to all evaluators to avoid their evaluation being affected by this bias. Second, the depth estimation was performed by the recorded images, which might be different from the real-time evaluation. Third, the evaluators invited to this study were all dedicated to the magnifying endoscopic diagnosis of early gastrointestinal cancer in their daily practice; thus, it is not clear whether our results are applicable to general gastroenterologists. However, considering the fact that all five evaluators, regardless of their years of experience in endoscopy, showed similar improvement in depth estimation, we believe that our results are also applicable to general endoscopists if they acquire certain knowledge of M-NBI diagnosis.

In conclusion, although the assessment of M-NBI findings based on the JES classification had a relatively low impact on changing the clinical diagnosis made by WLE alone, it provided a more conclusive depth estimation. Routine use of M-NBI is reasonable in pretreatment endoscopic examination for superficial esophageal SCCs.

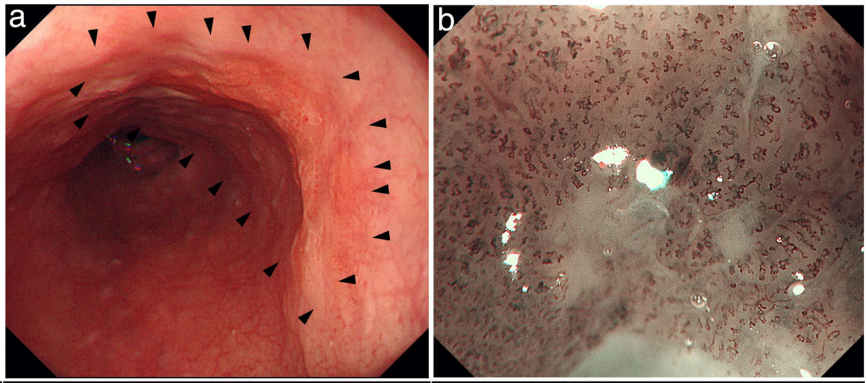
MM/SM1 cancer (Pathological score = 3)



Evaluator	Estimated Score in step 1 (WLE)	Estimated Score in step 2 (WLE+NBI)
A	1 (EP/LPM > MM/SM1)	3 (MM/SM1)
B	1 (EP/LPM > MM/SM1)	3 (MM/SM1)
C	1 (EP/LPM > MM/SM1)	3 (MM/SM1)
D	1 (EP/LPM > MM/SM1)	3 (MM/SM1)
E	3 (MM/SM1)	3 (MM/SM1)

Figure 5 Endoscopic images of case 1 (MM/SM1 cancer) and the scoring results of five evaluators. The left image is the macroscopic appearance of the lesion recorded by white light endoscopy (black arrowhead). The right image is part of the same lesion observed by magnifying narrow-band imaging, which indicated type B2 vessels. EP/LPM, tumor limited to the epithelium or lamina propria mucosa; MM/SM1, tumor invading the muscularis mucosae or submucosa to a depth of 200 μm or less from the muscularis mucosae.

EP/LPM cancer (Pathological score = 0)



Evaluator	Estimated Score in step 1 (WLE)	Estimated Score in step 2 (WLE+NBI)
A	1 (EP/LPM > MM/SM1)	0 (EP/LPM)
B	1 (EP/LPM > MM/SM1)	0 (EP/LPM)
C	2 (MM/SM1 > EP/LPM)	1 (EP/LPM > MM/SM1)
D	2 (MM/SM1 > EP/LPM)	1 (EP/LPM > MM/SM1)
E	2 (MM/SM1 > EP/LPM)	0 (EP/LPM)

Figure 6 Endoscopic images of case 2 (EP/LPM cancer) and the scoring results of five evaluators. The left image is the macroscopic appearance of the lesion recorded by white light endoscopy (black arrowhead). Magnifying narrow-band imaging demonstrated only type B1 vessels on the surface of the same lesion (right image). EP/LPM, tumor limited to the epithelium or lamina propria mucosa; MM/SM1, tumor invading the muscularis mucosae or submucosa to a depth of 200 μm or less from the muscularis mucosae.

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