

# Effect of adding magnifying BLI, magnifying NBI, and iodine staining to white light imaging in diagnosis of early esophageal cancer



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## ABSTRACT

**Background and study aims** We investigated the effect of adding magnifying blue laser imaging (BLI), magnifying narrow-band imaging (NBI), and iodine staining to white light imaging in diagnosis of early esophageal squamous cell carcinoma (EESCC) in high-risk patients.

**Patients and methods** Between May 2013 and March 2016, two parallel prospective cohorts of patients received either primary WLI followed by NBI-magnifying endoscopy (ME) or primary WLI followed by BLI-ME, were studied. At the end of screening, both groups underwent iodine staining. The percentage of patients with newly detected esophageal malignant lesions in each group and the diagnostic ability of image-enhanced endoscopy (IEE)-ME were evaluated.

**Results** There are 258 patients assigned to the NBI-ME group and 254 patients assigned to the BLI-ME group. The percentage of patients with one or more malignant lesions detected in the WLI + NBI-ME examination was similar in the WLI + BLI-ME examination (15 of 258 patients or 5.81% vs. 14 of 254 patients or 5.51%). However, four of 19 lesions in the NBI-ME group and six of 21 lesions in the BLI-ME group were overlooked and were detected by iodine staining. NBI-ME and BLI-ME showed similar accuracy in differentiation of cancerous lesions from non-cancerous lesions in diagnosis of EESCC (NBI/BLI: sensitivity, 87.5/89.5; specificity, 78.9/76.6; accuracy, 80.8/79.5; positive predictive value, 53.8/53.1; negative predictive value, 95.7/96.1).

**Conclusions** Both NBI and BLI were useful for detection of EESCC. However, because some lesions were overlooked by even NBI and BLI, high-risk patients may benefit from use of iodine staining during endoscopic screening of EESCC (UMIN000023596).

## Introduction

Narrow-band imaging (NBI) (Olympus, Tokyo, Japan), a novel image-enhanced endoscopy (IEE) method, is based on narrowing the bandwidth of spectral transmittance of the optical filters used in the frame sequential imaging method to create vid-

eo endoscopy images. This method was first described in 2003 [1]. It can highlight the surface microvasculature of lesions, because the central wavelengths of the NBI filter are 415 and 540 nm, which are well absorbed by hemoglobin. NBI also facilitates detection of early esophageal squamous cell carcinoma

(EESCC), which should be considered when a well-demarcated brownish area is observed [2, 3].

Recent advances in endoscopic magnification have enabled the observation of alterations in intraepithelial papillary capillary loops (IPCL) in the esophageal region, such that cancerous lesions can be differentiated from inflammatory changes [4, 5]. Moreover, NBI has improved the accuracy of magnifying endoscopy (ME) in assessment of esophageal lesions [6]. Muto et al. reported that NBI improves the rate of EESCC detection [7]. NBI, which is the most commonly performed IEE technique, enhances the relief of the mucosa and the underlying vascular pattern and provides greater convenience without the risks inherent to methods using vital dye [8].

A new endoscopic system named “LASEREO” was developed by FUJIFILM Corporation (Tokyo, Japan) in 2012. The LASEREO system combines two types of laser light with phosphors to allow NBI observation as blue laser imaging (BLI). One of the laser lights, with a wavelength of 450 nm, stimulates the phosphor to achieve a white illumination similar to that obtained with a xenon lamp. The other laser, with a wavelength of 410 nm, is used to enhance the blood vessels at a shallow depth in a distant view [9, 10]. Tomie et al. reported that BLI-bright visualizes EESCC better than other methods (WLI and NBI) [11]. It has been reported that BLI-bright is useful for detecting gastric cancer in the distant view [12]. Similar to NBI-ME, magnifying endoscopy with BLI and BLI-bright provides excellent visualization of the microstructures and microvessels for the diagnosis of early gastric cancer [13]. BLI-ME is also useful for determining the tumor depth of superficial esophageal squamous cell carcinoma [14, 15].

Iodine staining has been used for the endoscopic screening of patients at high risk for EESCC, however, it has low specificity and multiple biopsy specimens are required [16, 17]. In addition, it causes heartburn and severe discomfort. Several studies

have also demonstrated that the detection rate for EESCC with NBI-ME could be comparable to that of iodine staining [7, 18].

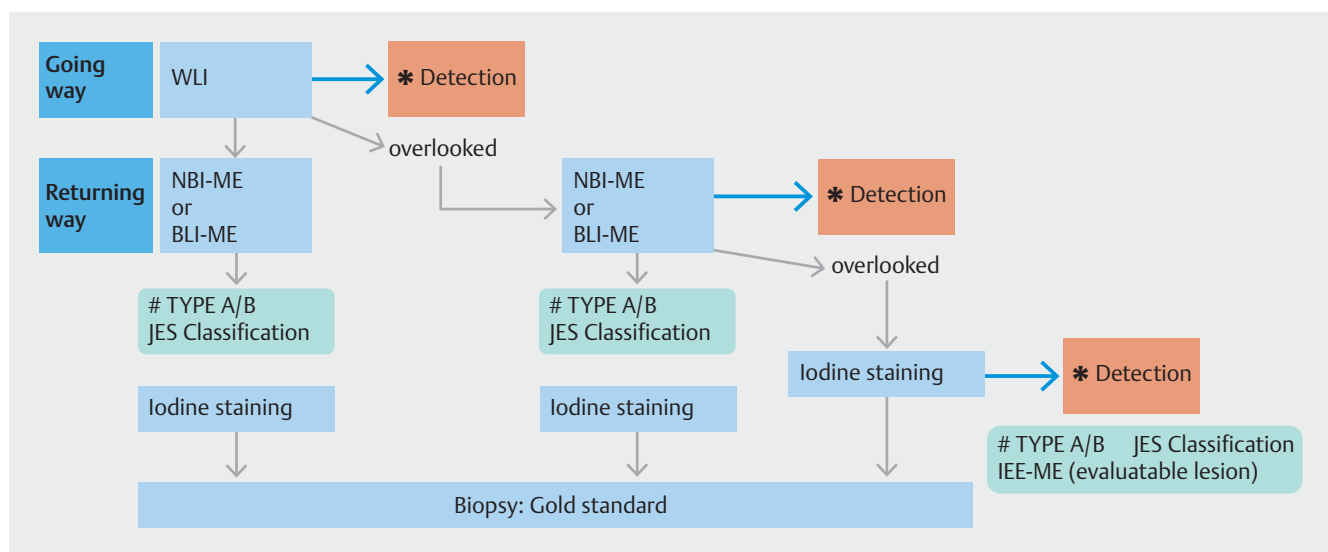
The diagnostic ability of BLI-ME was reported to be similar to that of NBI-ME for EESCC in high-risk patients at a single center [19]. However, we do not know if it is reasonable to omit iodine staining to detect EESCC in routine screening examinations. Accordingly, we conducted a multicenter prospective trial to investigate the effect of adding NBI-ME, BLI-ME and iodine staining to WLI in diagnosis of early EESCC in high-risk patients.

## Patients and methods

### Study design

This study was performed at two university hospitals and one academic center in Japan from May 2013 to March 2016. The study was initially designed as a randomized controlled trial, but it was analyzed as two separate prospective cohort studies because of methodological reasons. This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the medical ethics committees at each center. This study was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN 000023596).

Single-blinded participants were enrolled in this study. The patients were randomly assigned to receive primary white light imaging (WLI) followed by magnifying endoscopy with NBI (NBI-ME group) or primary WLI followed by magnifying endoscopy with BLI (BLI-ME group). At the end of screening, both groups underwent iodine staining. We checked the detection rates of these techniques (► Fig. 1), which was the percentage of patients with one or more malignant lesions found during the examination. We also investigated the diagnostic ability to differentiate cancerous lesions from non-cancerous lesions using NBI-ME and BLI-ME when microvessels on the mucosa could be properly evaluated (► Fig. 1). Randomization was carried out using numbered sealed envelopes.



► Fig. 1 Overview of study design.

## Patients

Head and neck cancer patients frequently had coexisting superficial esophageal squamous cell carcinoma, and esophageal cancer patients develop second primary esophageal cancer; thus, they provide a good cancer screening model.

We enrolled patients  $\geq 20$  years of age who had been treated for early esophageal cancer by endoscopic resection more than 6 months previously, or who had current or previous head and neck cancer. The exclusion criteria were as follows: 1) previous surgical resection or radiotherapy, or chemoradiotherapy for esophageal squamous cell carcinoma; 2) allergy to iodine staining; 3) cases in which biopsy specimens could not be obtained due to the use of antithrombotic or anticoagulant drugs; 4) esophageal adenocarcinoma; and 5) patients who were judged as inappropriate (severe esophagitis, or esophageal stricture). Written informed consent was obtained from all participants.

## Equipment

A video endoscopy system (LASEREO, Fujifilm Corporation, Tokyo, Japan) and high-definition upper gastrointestinal endoscope (EG-L590ZW; Fujifilm Corporation, Tokyo, Japan) were used for WLI and BLI in the BLI-ME group. The structure enhancement of the endoscopic video processor was set to A-mode level 6 or B-mode level 8 for BLI. The color mode was fixed to level C1. A video endoscope system (EVIS ELITE, LUCERA SPECTRUM system, Olympus Co, Tokyo, Japan) and high-resolution upper gastrointestinal endoscope-GIF-H260Z, Olympus Co, Tokyo Japan) were used in the NBI group. The structure enhancement function of the endoscopic video processor was set to A-mode level 8 for WLI and B-mode level 8 for NBI. The color mode was fixed to level 1 for NBI.

## Endoscopic examination

Endoscopic examinations were performed by an expert who had specialist qualifications from the Japan Gastroenterological Endoscopy Society. Each of the endoscopists had more than 6 months experience in performing NBI and BLI. Before the study started, all participating endoscopists reached a common consensus at a meeting on detecting different IEE abnormalities.

Surveillance endoscopy was performed thoroughly with or without conscious sedation using intravenous midazolam. At the beginning of screening, the endoscope was inserted from the cervical esophagus into the abdominal esophagus under WLI (► Fig. 2a). After observing the stomach and duodenum, the endoscope was withdrawn from the abdominal esophagus to the cervical esophagus under NBI or BLI. All lesions were observed by IEE-ME, to determine whether or not they were malignant.

The endoscopic findings, macroscopic appearance of the esophageal lesion, location, direction, and size of the lesion were recorded on a case report form after the examination. On endoscopy, esophageal neoplasia was suspected based on the presence of reddish color change, the loss of the normal vascular network, and the presence of a brownish area on BLI (► Fig. 2b) or NBI (► Fig. 3).

## Classification

The diagnostic criteria for lesions observed by NBI-ME or BLI-ME were based on the Japan Esophageal Society (JES) classification [20] of AB types (► Fig. 4, type A; ► Fig. 2c, type B), according to the microvascular changes in the mucosal surface, which was based on the classifications proposed by Inoue et al. [4, 5] and Arima et al. [21]. After the detection of the abnormal esophageal area, the determination of whether or not it was cancerous was made by magnifying endoscopy with NBI or BLI using the JES classification. In this study, type A was defined as a non-cancerous lesion, while type B was defined as a cancerous lesion. In the present study a “non-cancerous lesion” was defined as a normal epithelium with inflammation or low-grade intraepithelial neoplasia, while a “cancerous lesion” was defined as high grade intraepithelial neoplasia, carcinoma in situ, or invasive SCC.

## Iodine staining

After IEE-ME, the endoscopist returned to WLI and then sprayed 20 mL of 0.5% iodine solution uniformly over the esophageal mucosa (► Fig. 2d). IEE-ME was performed after spraying iodine in some cases, and then the microvascular pattern was examined. Biopsy specimens were also obtained from well-demarcated lesions with an unstained area  $\geq 5$  mm in diameter. After iodine staining, at least one biopsy specimen was obtained from the target lesion. The pink-color sign [22] was not considered when the biopsy specimen was obtained, because it was difficult to observe the pink-color sign in the presence of 0.5% iodine staining.

## Histological evaluation

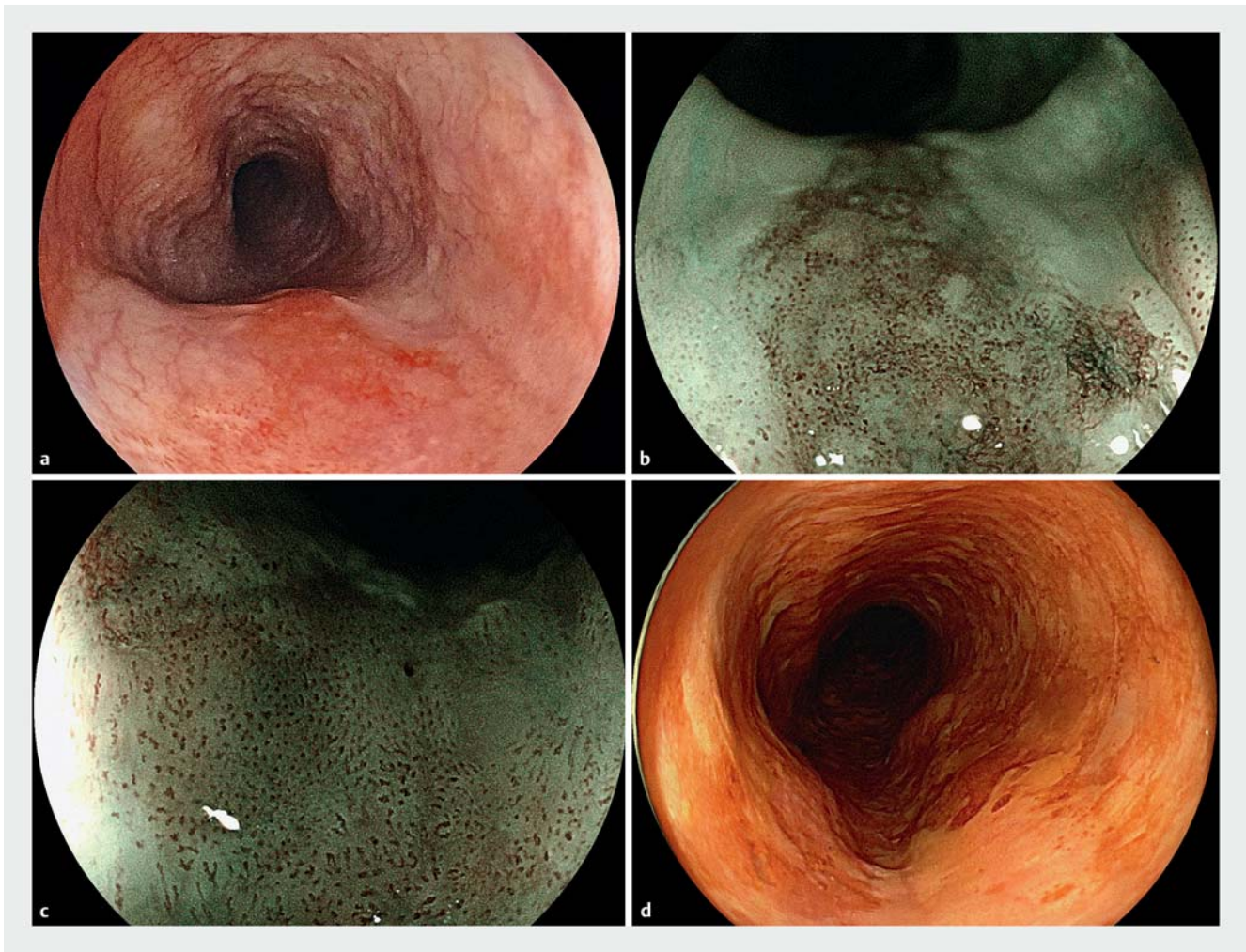
The gold standard for diagnosis of all lesions was determined based on pathological evaluations. Biopsy specimens were examined by experienced pathologists who were blinded to the endoscopic findings in each institution. When an early malignant lesion was recognized, endoscopic treatment was performed, and the specimen was examined histopathologically. The criteria proposed by the 10<sup>th</sup> edition of Japanese classification of esophageal cancer were used for the diagnosis of intraepithelial neoplasia and cancer as follows: low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN), carcinoma in situ, and invasive squamous cell carcinoma [23].

## Endpoints

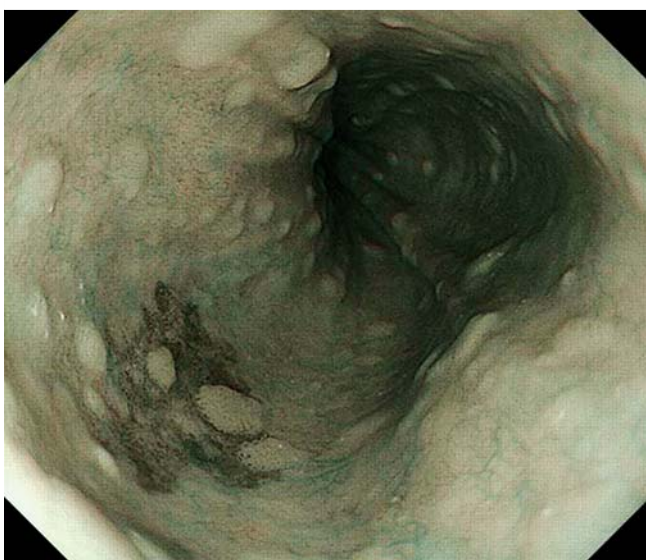
We investigated the following clinical data: 1) abnormal lesions detected by WLI in the NBI-ME and BLI-ME groups; 2) newly diagnosed lesions detected by NBI and BLI; 3) the accuracy of NBI-ME in diagnosis of cancerous or noncancerous lesions; 4) the accuracy of BLI-ME in diagnosis of cancerous or noncancerous lesions; and 5) newly diagnosed lesions detected by iodine staining that were overlooked by WLI and IEE.

The primary endpoint of this study was to investigate the effect of adding IEE-ME and iodine staining to WLI in detection of EESCC in each arm. The secondary endpoint was to investigate the diagnostic accuracy in differentiating cancerous lesions





► **Fig. 2** Early esophageal squamous cell carcinoma detected by BLI-ME endoscopy. **a** WLI. **b** BLI (brownish area). **c** Type B. **d** 0.5% iodine staining.



► **Fig. 3** Brownish area (NBI).

from non-cancerous lesions between NBI-ME and BLI-ME. We investigated the diagnostic accuracy of magnifying endoscopy only for lesions in which microvessels on the mucosa could be properly evaluated.

### Statistical analysis

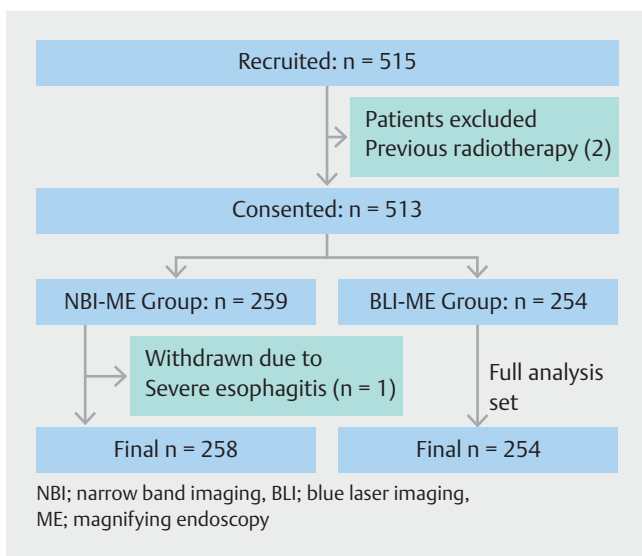
The characteristics of the enrolled patients are presented as the median or percentage, and diagnostic yields were examined using Fisher's test. The variables are expressed as the mean  $\pm$  SD. All statistical analyses were performed using the EZR software program [24].

### Results

Five hundred fifteen patients who were treated between May 2013 and March 2016 were enrolled in the present study. Two patients did not meet the inclusion criteria. The remaining 513 patients were randomized to two groups: 259 patients who underwent primary WLI followed by NBI-ME were assigned to the NBI-ME group, and 254 patients who underwent primary WLI followed by BLI-ME were assigned to the BLI-ME group. One pa-



► **Fig. 4** Magnifying endoscopic image with NBI. A Type A lesion is shown.



► **Fig. 5** Trial profile.

tient in the NBI-ME group who had severe esophagitis was excluded. Therefore, 258 patients were examined in the NBI-ME group (► **Fig. 5**).

The characteristics of the two groups are listed in ► **Table 1**. The two groups showed no significant differences with regard to age, sex, history of esophageal cancer treatment, current head and neck cancer, prior head and neck cancer, prior gastrectomy. Furthermore, there was no significant difference in the number of patients with  $\geq 10$  iodine unstained areas on iodine staining per endoscopic view. The diagnostic yields of NBI-ME group and BLI-ME group in the detection of EESCC using are summarized in ► **Table 2**.

Among the 107 biopsied lesions in the NBI-ME group (WLI, n = 25; NBI-ME, n = 25; and iodine staining, n = 57), a total of 19

► **Table 1** Baseline characteristics of study subjects.

	NBI-ME group	BLI-ME group
Patients, n	259	254
Male, n (%)	230 (88.8)	220 (86.6)
Age, (median $\pm$ SD min-max)	71.6 $\pm$ 8.03 (48–89)	71.6 $\pm$ 7.36 (49–87)
HNC current, n (%)	29 (11.2)	28 (11.2)
HNC prior, n (%)	72 (27.8)	69 (27.2)
EC prior ER, n (%)	207 (79.9)	208 (81.9)
Prior gastrectomy, n(%)	17 (6.6)	19 (7.5)
$\geq 10$ iodine unstained areas, n (%)	81 (31.3)	73 (28.7)

HNC, head and neck cancer; EC, esophageal cancer; ER, endoscopic resection.

lesions of early esophageal cancer were detected in 19 patients (7.36%).

Among the 106 biopsied lesions in the BLI-ME group (WLI, n = 36; BLI-ME, n = 29; and iodine staining, n = 41), a total of 21 lesions of early esophageal cancer were detected in 19 patients (7.48%). The detection rate was 3.87% (10/258) when using WLI (NBI-ME group), and 3.94% (10/254) when using WLI (BLI-ME group). The detection rates of primary WLI and secondary NBI-ME, and primary WLI and secondary BLI-ME were 5.81% (15/258) and 5.51% (14/254) (► **Table 2**). Both NBI and BLI had an additional effect to WLI in the detection of EESCC. Moreover, 4 of 19 lesions (21.0%) in the NBI-ME group and six of 21 lesions (28.5%) in the BLI-ME group were overlooked but were detected by iodine staining. The location, size, direction, and depth of tumor invasion of the overlooked lesions are shown in ► **Table 3**. Among 10 lesions, and nine cases that were detected by iodine staining, five cases arose from cases with  $\geq 10$  iodine-unstained areas in the background esophageal mucosa. Lesions were most often overlooked on the anterior wall of the lower thoracic esophagus. A typical case is shown in ► **Fig. 6**. The sizes of all newly detected EESCCs in both groups are shown in ► **Fig. 7**. The median size of squamous cell carcinoma tumors in the BLI-ME group was 10mm (range 4–29mm). On the other hand, that in the NBI-ME group was 15mm (range 3–50mm). There was no statistically significant difference between the two groups ( $P=0.49$ ). Endoscopic resection was performed within six months after detection for 14 lesions in the NBI-ME group, and 15 lesions in the BLI-ME group. The remaining cases were followed up due to the presence of advanced head and neck cancer. In both groups, all of the resected cases involved mucosal cancers.

We also evaluated the diagnostic accuracy for differentiation of cancerous lesions from non-cancerous lesions between NBI-ME and BLI-ME. We were not able to obtain a clear view of some lesions; thus, the microvascular patterns were not evaluated. Evaluable magnified images were obtained for 73 lesions in the NBI-ME group, and 83 lesions in the BLI-ME group.

► **Table 2** Detection of early esophageal squamous cell carcinoma.

	NBI-ME group (258)	BLI-ME group (254)
Number of detected lesions (patients)	19 (19)	21 (19)
Number of lesions per patient		
▪ 1	19	17
▪ 2	0	2
Number of lesions (patients) detected by primary WLI	10 (10)	11 (10)
Number of lesions (patients) detected by secondary IEE-ME	5 (5)	4 (4)
Number of lesions (patients) Detected by iodine staining	4 (4)	6 (5)
Detection rate (WLI)	3.87% (10/258)	3.94% (10/254)
Detection rate (WLI + IEE-ME)	5.81% (15/258)	5.51% (14/254)
Detection rate (WLI + IEE-ME + iodine staining)	7.36% (19/258)	7.48% (19/254)

NBI-ME, narrow-band imaging plus magnifying endoscopy; BLI-ME, blue-light imaging plus magnifying endoscopy; IEE-ME, image-enhance endoscopy plus magnifying endoscopy; WLI, white-light imaging.

► **Table 3** Lesions overlooked by WLI and IEE-ME, but detected by iodine staining.

Case	Location	Direction	Size (mm)	≥ 10 iodine unstained areas	Depth of invasion
NBI-1	Mt	PW	15	Negative	T1a-LPM
NBI-2	Lt	PW	25	Negative	F/U
NBI-3	Lt	AW	16	Positive	T1a-LPM
NBI-4	Ut	RW	5	Positive	T1a-EP
BLI-1-1	Mt	LW	10	Negative	T1a-EP
BLI-1-2	Lt	AW	10	–	F/U
BLI-2	Lt	AW	10	Positive	T1a-LPM
BLI-3	Lt	LW	12	Negative	T1a-LPM
BLI-4	Lt	LW	5	Positive	T1a-LPM
BLI-5	Mt	PW	15	Positive	T1a-EP

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; PW, posterior wall; AW, anterior wall; RW, right wall; LW, left wall; F/U, followed up; T1a-EP, carcinoma in situ; T1a-LPM, invaded to the lamina propria.

The characteristics of the target lesions in both groups are shown in ► **Table 4**.

The median size of the target lesions was 5 mm in both groups.

► **Table 5** summarizes the diagnostic performance for differentiation of cancerous lesions from non-cancerous lesions in both groups. In the NBI-ME group, 47 lesions were diagnosed as type A; 45 were non-cancerous lesions. Twenty-six lesions were diagnosed as type B; 14 were cancerous lesions.

In the BLI-ME group, 51 lesions were diagnosed as type A; 49 were non-cancerous lesions. Thirty-two lesions were diagnosed as type B; 17 were cancerous lesions. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the two imaging techniques showed similar accuracy in differentiation of cancerous lesion from cancerous lesions (NBI/BLI: sensitivity, 87.5/89.5; specificity, 78.9/76.6;

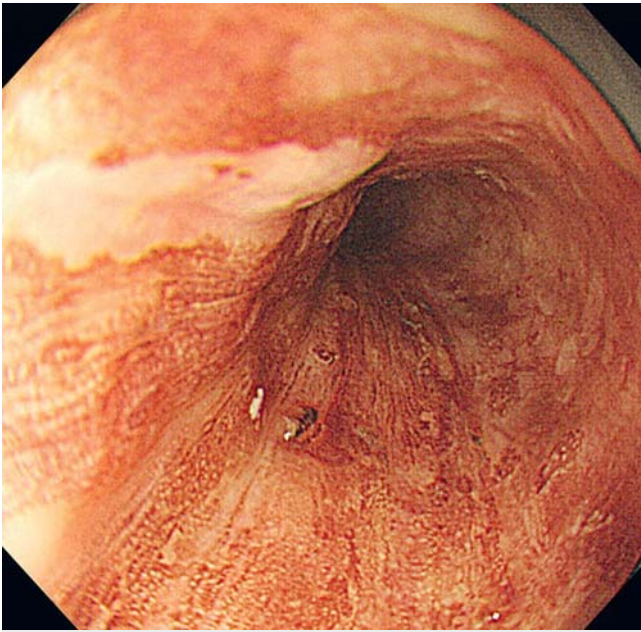
accuracy 80.8/79.5; PPV, 53.8/53.1; NPV, 95.7/96.1) (► **Table 6**). No serious adverse events were observed in either group.

## Discussion

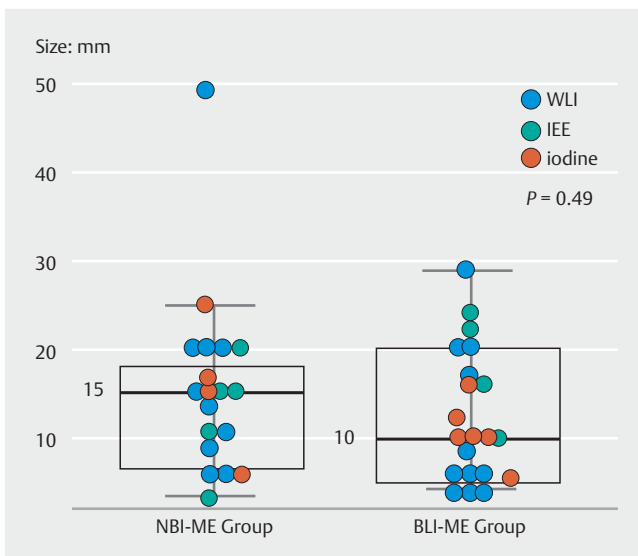
This study was initially designed as a randomized controlled trial to compare the diagnostic ability for EESCC between NBI-ME and BLI-ME, but it was analyzed as two separate prospective cohort studies for methodological reasons. In the past, the esophageal mucosa first was examined using WLI, followed by iodine staining in the screening of high-risk esophageal cancer patients. However, since the development of image enhanced endoscopy (NBI or BLI), iodine staining is sometimes omitted.

Therefore, we investigated the effect of adding magnifying BLI, magnifying NBI, and iodine staining to WLI in diagnosis of early esophageal cancer.





► **Fig. 6** A case of EESCC detected by iodine staining.



► **Fig. 7** Size of superficial cancer.

This report reveals that both NBI-ME and BLI-ME improve the real-time detection rate for EESCC during surveillance of high-risk patients with WLI. However, some lesions were overlooked and detected with iodine staining.

The primary endpoint of this study was to investigate the effect of adding IEE-ME and iodine staining to WLI in detection of EESCC in each arm. The detection rates were 3.87% (10/258) when using WLI (NBI-ME group), and 3.94% (10/254) when using WLI (BLI-ME group). The detection rates for primary WLI and secondary NBI-ME, and primary WLI and secondary BLI-ME were 5.81% (15/258) and 5.51% (14/254). Both BLI and NBI had an additive effect on WLI in detection of EESCC. However,

► **Table 4** Characteristics of target lesions that were evaluable by magnifying endoscopy.

	NBI-ME (n=73)	BLI-ME (n=83)
Location		
▪ Cervical esophagus	1	
▪ Upper thoracic esophagus	15	5
▪ Middle thoracic esophagus	34	40
▪ Lower thoracic esophagus	20	34
▪ Abdominal esophagus	3	4
Size		
▪ ~ 5 mm	39	44
▪ 6–10 mm	16	19
▪ 11–20 mm	16	28
▪ ≥21 mm	2	4
▪ Median±SD	56.52	5 ± 7.58
Direction		
▪ Left wall	22	19
▪ Right wall	23	20
▪ Anterior wall	10	16
▪ Posterior wall	18	28
NBI-ME, narrow-band imaging plus magnifying endoscopy; BLI-ME, blue-light imaging plus magnifying endoscopy.		

four of 19 lesions in the NBI-ME group and six of 21 lesions in the BLI-ME group were overlooked and were detected by iodine staining. The miss rate of WLI in the NBI-ME group was 47.4% (9/19), while that in the BLI-ME group was 47.6% (10/21).

The secondary endpoint of this study was to compare the diagnostic ability for differentiation of cancerous lesions from non-cancerous lesions using NBI-ME and BLI-ME in which microvessels on the mucosa could be properly evaluated. The sensitivity, specificity, accuracy, PPV, and NPV of BLI-ME were not statistically significantly different from NBI-ME. By adding IEE-ME to WLI, more detailed micro-vessel observation was possible. However, this resulted in detection small lesions ≤5 mm in size, and the PPV was lower in previous reports (PPV=62.5–94.1) [7, 16, 25]. In this study, we excluded the patients with current EESCC, and newly detected lesions that were suspicious for EESCC were analyzed. It was difficult to distinguish between type A and B microvascular patterns in such small lesions.

Diao et al. reported examining 153 lesions (cancer, n=75; non-cancer, n=78) with NBI-ME, BLI-ME, and 1.25% iodine chromoendoscopy [19]. The sensitivity, specificity, and accuracy of the three modalities were as follows: NBI-ME, 95.2%, 92.8%, and 85.7%, respectively; BLI-ME, 95.2%, 91.9%, 85.7%; and iodine chromoendoscopy, 95.2%, 94.6%, 91.3%.

In this study, 34 lesions in the NBI-ME group and 23 lesions in the BLI-ME group were not evaluated with IEE-ME. We examined 73 lesions (cancerous lesions, n=16; non-cancerous le-

► **Table 5** Correlation between histological diagnosis (cancerous or non-cancerous) and endoscopic diagnosis based on JES classification in both groups.

Histological diagnosis				
		Non-cancerous lesion	Cancerous lesion	SUM
NBI-ME JES classification	Type A	45	2	47
	Type B	12	14	26
	Total	57	16	73
BLI-ME JES classification	Type A	49	2	51
	Type B	15	17	32
	Total	64	19	83

NBI-ME, narrow-band imaging plus magnifying endoscopy; BLI-ME, blue-light imaging plus magnifying endoscopy.

► **Table 6** Comparison of diagnostic performance of NBI-ME and BLI-ME.

	NBI-ME (73 lesions)	BLI-ME (83 lesions)
Sensitivity	87.5 (61.7–98.4)	89.5 (66.9–98.7)
Specificity	78.9 (66.1–88.6)	76.6 (64.3–86.2)
Accuracy	80.8 (69.9–89.1)	79.5 (69.2–87.6)
Positive predictive value	53.8 (33.4–73.4)	53.1 (34.7–70.9)
Negative predictive value	95.7 (85.5–99.5)	96.1 (86.5–99.5)

NBI-ME, narrow-band imaging plus magnifying endoscopy; BLI-ME, blue-light imaging plus magnifying endoscopy.

sions, n = 57) in the NBI-ME group, and 83 lesions (cancerous lesions, n = 19; non-cancerous lesions, n = 64) in the BLI-ME group. Due to the low proportion of cancer in the subjects, the PPV in both groups was low. If we included patients with current ESCC, this result may have been good. In contrast, the NPV was very high in both groups. Biopsy may be omitted for cases diagnosed as non-cancerous.

A previous study suggested that the diagnostic accuracy of iodine staining in the detection of EESCC was remarkably improved by the additional assessment of a pink color change, the so-called “pink-color sign” [22]. Ishihara et al. reported that the pink-color sign was associated with the absence of the keratinous layer of the esophageal mucosa [26]. We did not consider the pink-color sign when the biopsy was taken, we biopsied lesions > 5 mm in size. Because we used 0.5% iodine, it was difficult to observe the pink-color sign clearly.

However, staining patterns show wide variation, and iodine staining has a high false-positive rate that leads to unnecessary biopsies. To reduce unnecessary biopsies, we should consider the pink-color sign. Goda et al. performed a randomized non-inferiority trial between NBI-ME and the pink-color sign, and found that none of the diagnostic values of the two techniques differed to a statistically significant extent [27]. Nagami et al. performed a prospective comparative study between non-magnifying NBI with iodine staining in EESCC screening. They reported that the accuracy and specificity of non-magnifying

NBI were superior to iodine staining, and the sensitivity of the two groups was not statistically significantly different [28].

The mechanism of BLI differs from NBI systems with regard to its emphasizing of the mucosal surface and micro-vessels. However, the images obtained in both groups were similar and there were no major differences. As a result, the detection rates of both groups were similar in screening for EESCC.

Although IEE-ME is considered to be a substitute for iodine staining, some lesions were picked up by iodine in this study. The utility of using 1% iodine to reduce iodine-related irritation also has been reported [29]. Further studies should be performed to determine the appropriate concentration of iodine in screening for EESCC.

The present study was associated with some limitations. The study design was probably not suitable for comparing the diagnostic yield of NBI and BLI, because these two modalities are used after WLI observation.

A crossover study would be appropriate; however, NBI and BLI systems are produced by different manufacturers and cannot be compared in real time. This study had no stratification factors at the time of randomization. Originally, automatic sorting by computer was necessary, and the number of research subjects became larger than necessary. Furthermore, we did not have a central histopathological diagnosis. Multiple experienced pathologists should perform histological evaluations with a central review. In this study, six experts in upper gastrointestinal endoscopy examined a population of patients



who were considered to have a high risk of developing esophageal neoplasms. Therefore, it is unclear whether similar results would be obtained if these examinations were performed by general clinicians with patients in the general population.

## Conclusions

Both NBI and BLI were useful for detection of EESCC. The ability to make a differential diagnosis was similar for NBI-ME and BLI-ME. However, because some lesions were overlooked by even NBI and BLI, high-risk patients may benefit from the use of iodine staining during endoscopic screening of EESCC.

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## Competing interests

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