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Usefulness of Non-Magnifying Narrow-Band Imaging in Screening of Early Esophageal Squamous Cell Carcinoma: A Prospective Comparative Study Using Propensity Score Matching

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OBJECTIVES: **The usefulness of non-magnifying endoscopy with narrow-band imaging (NBI; NM-NBI) in the screening of early esophageal squamous cell carcinoma (SCC) and high-grade intraepithelial neoplasia (HGIN) remains unclear. Here, we aimed to compare NM-NBI and chromoendoscopy with iodine staining (CE-Iodine) in terms of the diagnostic performance, and to evaluate the usefulness of NM-NBI in detecting early esophageal SCC.**

METHODS: **We prospectively enrolled 202 consecutive patients (male/female = 180/22; median age, 67 years) with high-risk factors for esophageal SCC. All patients received endoscopic examination with NM-NBI and CE-Iodine to screen for early esophageal SCC or HGIN. We conducted the examinations sequentially, and calculated the accuracy, sensitivity, and specificity through a per-lesion-based analysis. A propensity score matching analysis was performed to reduce the effects of selection bias, and we compared the respective outcomes according to NM-NBI and CE-Iodine after matching.**

RESULTS: **The accuracy, sensitivity, and specificity of NM-NBI were 77.0, 88.3, and 75.2%, respectively, and those for unstained areas by CE-Iodine were 68.0, 94.2, and 64.0, respectively. The accuracy and specificity of NM-NBI were superior to those of CE-Iodine ($P=0.03$ and $P=0.01$, respectively). However, the sensitivity did not significantly differ between NM-NBI and CE-Iodine ($P=0.67$). The accuracy and specificity of NM-NBI before matching were superior to those of CE-Iodine after matching ($P=0.04$ and $P=0.03$).**

CONCLUSIONS: **NM-NBI was useful and reliable for the diagnosis of esophageal SCC and can be a promising screening strategy for early esophageal SCC.**

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INTRODUCTION

The prognosis of esophageal squamous cell carcinoma (SCC) is poor, and its 5-year survival rate is approximately 10–15% (1,2). Previous papers suggest a high incidence of esophageal SCC in patients with primary head and neck SCC (range, 10–15%) (3–8) and in patients with a previous history for endoscopic resection (ER; 14.6%) (9); thus, these patients seem to be a high-risk group for esophageal SCC occurrence. Therefore, the early detection of esophageal SCC is essential for achieving higher survival rates with curable surgical resection or ER (2,10–12), particularly in the above-mentioned high-risk populations. However, it is difficult to make an endoscopic diagnosis of esophageal SCC during the early stage

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in cases where white-light conventional endoscopy alone is used (8,13–19).

Chromoendoscopy with iodine staining (CE-Iodine) facilitates the detection of esophageal SCC. However, this modality may cause severe chest pain and discomfort owing to mucosal irritation (6,20–22) and requires the examination of many biopsy specimens to obtain a definite pathological diagnosis (4–8). Narrow-band imaging (NBI) also facilitates the detection of esophageal SCC that is considered when a well-demarcated brownish area (BA) is observed (13). Moreover, this imaging modality can be easily switched from the standard examination with white-light imaging (WLI) without causing discomfort to patients (23). Muto *et al.* (14) reported that NBI improves the detection rate of superficial esophageal SCC during the early stage. Several studies have also demonstrated that the detection rate of superficial esophageal SCC with magnifying NBI during the early stage could be comparable to that of CE-Iodine (15). However, only a few studies have reported the usefulness of non-magnifying endoscopy combined with NBI (NM-NBI) for the detection of superficial esophageal SCC (17,18) despite its frequent use in routine screening examinations. Therefore, our primary objective was to elucidate the usefulness of NM-NBI for the detection of superficial esophageal SCC.

In daily clinical examinations, NBI and iodine staining are usually sequentially performed during the same endoscopic session (15–19), particularly in the high-risk group. However, it is difficult to perform a random cross-over trial of these examinations, as these procedures cannot be performed in the reverse order owing to the following reasons: first, it is difficult to accurately detect the BA by NBI after iodine staining, as iodine causes microscopic injury to the esophageal surface mucosa even if a neutralizing and washing solution (sodium thiosulfate hydrate) is used; second, the use of iodine staining may cause retrosternal chest pain and discomfort with spasm before a detailed examination by NBI can be performed. Furthermore, a randomized study to compare the detection rate between NM-NBI and CE-Iodine in the general Japanese population would require a large number of patients owing to the low incidence of superficial esophageal SCC. Therefore, we conducted the present prospective comparative study using a propensity score matching technique in the high-risk population to prove our hypothesis that non-magnifying endoscopy is reliable for the detection and diagnosis of esophageal SCC in high-risk patients compared with CE-Iodine.

METHODS

Patients

As patients with a previous history of head and neck SCC or ER for superficial esophageal SCC are at a high risk for esophageal SCC, we included these parameters in the inclusion criteria for the present study. In this study, 205 patients were recruited from May 2008 to January 2011. The enrolled patients ($n = 202$) met the following inclusion criteria: (i) age >20 years; (ii) present in the high-risk population for esophageal SCC, including those with a previous history of head and neck SCC or ER for superficial esophageal SCC; and (iii) provision of written informed consent regarding study participation. The exclusion criteria were as follows: (i) confirmed diagnosis of esophageal SCC; (ii) esophageal and pharyngeal stricture; (iii) iodine allergy; (iv) previous surgical resection or chemotherapy, radiotherapy, or chemoradiotherapy for esophageal SCC (as these procedures may influence the mucosal surface condition that is important for detecting these lesions); (v) previous CE-Iodine procedure within 6 weeks before the start of this study; (vi) the presence of serious complications (liver, kidney, heart, blood, or metabolic disorders); and (vii) other reasons that made the subject ineligible to participate in this study, at the discretion of the chief investigator.

Study design

This study (UMIN000004404) was a nonrandomized prospective trial of tandem endoscopy with trimodal imaging, conducted in a single center, and propensity score matching analysis was performed as a sensitivity analysis for nonrandomization in the present study. It was conducted according to the ethical guidelines for clinical studies, while considering the patients' human rights and privacy. The protocol of this study was approved by the Institutional Review Board of the Osaka City University Graduate School of Medicine, and written informed consent was obtained from each patient who underwent surveillance or screening endoscopic examination with different modalities.

Sample size

In this prospective study, sample size calculation was based on the diagnostic rate in a previous report (94.4% in the NM-NBI group and 77.8% in the CE-Iodine group) (19). Power calculation ($\alpha = 0.05$; $\beta = 0.10$) indicated a required sample size of $N = 204$ ($n = 102$ vs $n = 102$) using a two-tailed χ^2-test.

Study protocol

Different modalities were used for the endoscopic examination of the enrolled patients (**Figure 1**). As main outcomes, we compared the accuracy, sensitivity, and specificity of NM-NBI with those of CE-Iodine for diagnosing esophageal SCC or high-grade intraepithelial neoplasia (HGIN) before and after propensity matching. To evaluate diagnostic performance, we used the histologic diagnosis from a biopsy specimen or ER specimen as the reference standard diagnosis.

Endoscopic examination

Endoscopic examination was performed by three endoscopists (YN, HM, and NK, with more than 7 years' experience with conventional endoscopy). They had experienced more than 5,000 esophagogastroduodenoscopies, and all of them had specialist qualifications from the Japan Gastroenterological Endoscopy Society. Each endoscopist had more than 1 year of experience with NBI, and had performed NBI in more than 150 cases. Before the study started, all the participating endoscopists reached a common consensus on detecting different NBI abnormalities, including atypical endoscopic features, during a daily conference at our hospital. All procedures were performed by using an EVIS LUCERA SPECTRUM System (Olympus, Tokyo, Japan), with a

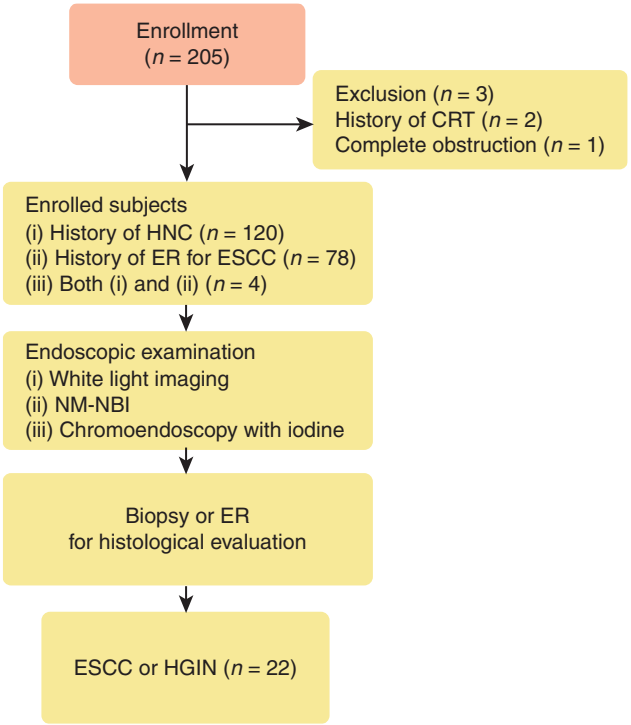

Figure 1. Diagram of the study design. CRT, chemoradiotherapy; ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; HGIN, high-grade intraepithelial neoplasia; HNC, head and neck carcinoma; NM-NBI, non-magnifying endoscopy with narrow-band imaging.

high-resolution upper gastrointestinal endoscope—GIF-H260Z or GIF-Q260 (Olympus). We used an NBI system according to the standard methods (13,23), and performed non-magnifying endoscopy by using GIF-H260Z. Surveillance endoscopy was performed thoroughly with or without conscious sedation using intravenous midazolam.

Before endoscopy, the esophageal surface muscosa was routinely washed with water, dimethicone (Gascon; Kissei Pharmaceutical, Nagano, Japan), and pronase (pronase MS; Kaken, Tokyo, Japan). After white-light evaluation, it was easily switched to NBI by pushing a button on the endoscope. CE-Iodine was then performed after a 1.5% iodine solution was sprayed over the entire mucosa of the esophagus. In all procedures, the endoscope was pulled back to view the area from the esophagogastric junction to the cervical esophagus. Endoscopic findings, such as the distance from the incisor teeth, circumferential location (anterior, posterior, right, or left wall), macroscopic appearance of the esophageal lesion, and size of the lesion (as determined using biopsy forceps as a marker), were recorded on a case report form after each respective endoscopic evaluation. We identified the lesions during respective endoscopic evaluations using this information. Endoscopically suspicious lesions for superficial esophageal SCC were commonly defined as follows: (i) the presence of reddish color change with the disappearance of the normal vascular network in WLI (**Figure 2a**); (ii) the presence of a well-demarcated BA in NM-NBI (**Figure 2b,c**) (13,14), wherein the reference points included scattered brown dots in the BA (**Figure 2c**) (24); and (iii) the presence of a well-demarcated unstained area of ≥5 mm in diameter (**Figure 2d**) after iodine staining, as a Lugol-voiding lesion is more likely to be neoplastic with increasing size (25).

After iodine staining, biopsy specimens were obtained from suspicious lesions, including well-demarcated unstained lesions with a diameter of <5 mm. If the BA was stained, we obtained biopsy specimens from lesions with a well-demarcated BA on NM-NBI after removing the staining with sodium thiosulfate solution. Thirteen lesions with typical endoscopic findings were treated with ER without prior biopsy (26). All of these lesions were treated with endoscopic submucosal dissection because endoscopic submucosal dissection is more efficient for achieving *en bloc* resection of the lesion (27).

Histological evaluation

The final diagnoses for all lesions were determined by pathological evaluations. Biopsy or ER specimens were prepared using standard procedures and evaluated by experienced pathologists who were blinded to the endoscopic findings. For the diagnosis of intraepithelial neoplasia and cancer, the criteria proposed by the World Health Organization and Vienna Classification were used as follows: low-grade intraepithelial neoplasia (LGIN), HGIN, invasive SCC (SCC), and the absence of neoplasia including chronic esophagitis (28,29). The accuracy, sensitivity, and specificity of NBI and CE-Iodine for diagnosing HGIN and SCC were evaluated according to the histology of lesions.

Image evaluation

To adjust for the selection bias during image analysis, we first confirmed the inter-observer and intra-observer agreement of the findings of NM-NBI through subclass analysis of 103 randomly chosen images (15). Two endoscopists assessed the presence of a well-demarcated BA as an indicator of superficial cancer in these images. The same images were reassessed after 20 months by one of the study endoscopists (YN).

Statistical analysis

Characteristic values of the enrolled patients are presented as medians or as percentages, and the diagnostic yields were examined using Fisher's test. The variables are expressed as the mean±s.d. The variables and the diagnostic performance of NBI were compared with those of CE-Iodine using unpaired *t*-tests for continuous values and Fisher's test for categorical values. Moreover, we performed propensity score matching to control and reduce selection bias in each case (30–32). A total of seven variables that could possibly influence the diagnosis of chromoendoscopy were used to generate a propensity score by logistic regression. These variables included the following: the endoscopist who performed the procedure; size of the lesion; distance from the incisor teeth; macroscopic appearance of the esophageal lesion; diagnosis by white light; and circumferential location of the esophageal lesion. We created a propensity score-matched cohort by attempting to match a patient who was diagnosed as BA positive by NBI with a patient who was diagnosed as BA negative by NBI (a 1:1 match) by using

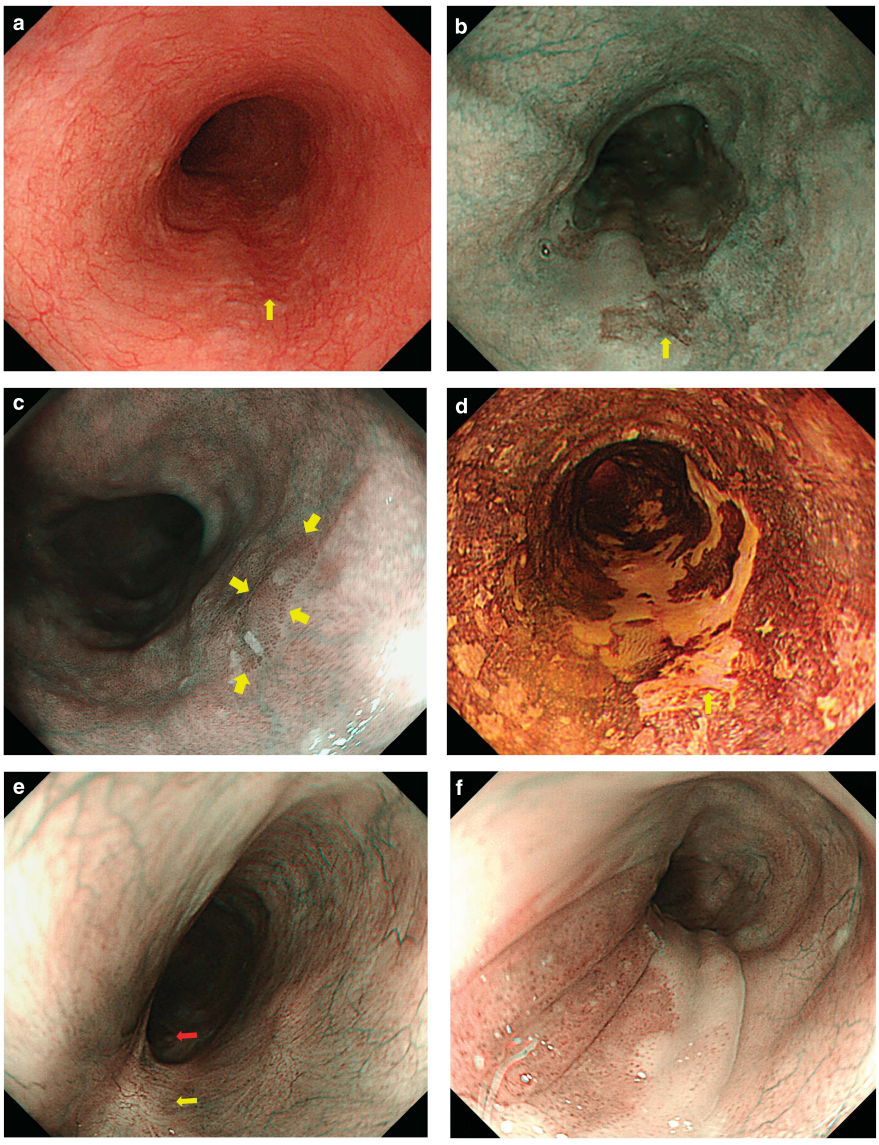

Figure 2. (**a**) White-light endoscopy shows a reddish color change with disappearance of the normal vascular network at the posterior wall (yellow arrow). (**b**) Non-magnifying endoscopy with narrow-band imaging (NBI) shows a well-demarcated brownish area (BA) as a superficial esophageal squamous cell carcinoma (SCC; yellow arrow). (**c**) Scattered brown dots were observed in a well-demarcated BA on NBI (yellow arrows). (**d**) Chromoendoscopy with iodine staining shows a well-demarcated unstained area (yellow arrow). (**e**) NBI shows the endoscopic resection (ER) scar as a longitudinal whitish area with contraction at the posterior wall (yellow arrow). BA was observed at the anal side (red arrow). (**f**) A well-demarcated BA with scattered brown dots was observed at the anal side in panel **e**.

a greedy matching technique. After matching, crude comparisons of the matched cohorts were made using the McNemar's test and paired *t* tests. A two-tailed *P* value of <0.05 was considered statistically significant. Generalized estimating equations were used with various proper distributions. The analysis accounted for the intra-class correlation between repeated observations of the same subject. However, the per-lesion analysis lacked independence between the observations, which may result in underestimation of the variance in the sensitivity and specificity estimates. Therefore, we calculated the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy using generalized estimating equations (33).

Classification performance was assessed by computing the area under the curve (AUC). AUC values, a measure of the overall predictive validity of the test, were evaluated as follows: AUC = 0.50, random prediction; AUC = 0.60–0.70, poor validity; AUC = 0.70–0.80, fair validity; AUC = 0.80–0.90, good validity; and AUC >0.90, excellent validity (34). A κ-value of 0.21–0.40 was regarded as representing poor inter-observer agreement, a κ-value of 0.41–0.60 was regarded as representing fair agreement, a κ-value of 0.61–0.80 was regarded as representing good agreement, and a κ-value of more than 0.80 was regarded as representing excellent agreement (35). Statistical analyses were performed using the SPSS version software 21.0 for Windows (SPSS, Tokyo, Japan).

RESULTS

Background of patients enrolled in this study

Between May 2008 and January 2011, 202 patients (males/females = 180/22; median age, 67 years; 254 lesions in total) were enrolled. Three patients were excluded because of a history of prior chemoradiotherapy ($n = 2$) and complete obstruction caused by hypopharyngeal cancer ($n = 1$). Patients with a history of head and neck carcinoma ($n = 120$), a history of previous ER for esophageal cancer ($n = 78$), or a history of head and neck carcinoma and previous ER ($n = 4$) were enrolled in this study. Of 124 patients with head and neck carcinoma, 112 patients underwent pretreatment endoscopic examination at a mean duration of 13.8±10.2 days after diagnosis. Twelve patients underwent endoscopy after treatment, and the mean duration between endoscopy and treatment was 869.3±678.3 days. **Table 1** shows the locations of head and neck carcinomas in the study participants. For patients who underwent ER for esophageal cancer before this study, the mean time since the operation was 858±361 days. The clinical characteristics of the patients are summarized in **Table 1**.

Table 1. Characteristics of the enrolled patients

	N=202 (%)
Age (years)	
Median	67
Range	46–84
Sex	
Male	180 (89.1)
Female	22 (10.9)
(i) *Head and neck carcinoma*	124 (61.4)
Pharyngeal cancer	62 (30.7)
Laryngeal cancer	36 (17.8)
Oral cavity cancer	12 (5.9)
Lingual cancer	14 (6.9)
(ii) Previous ER for esophageal cancer	82 (40.6)
(iii) Both (i) and (ii)	4 (2.0)
Drinking habits	160 (79.2)
Duration (years)	
Median	40
Range	20–65
Smoking habits	177 (87.6)
Duration (years)	
Median	40
Range	10–60
No. of patients with HGIN/SCC	22 (10.9)
Synchronous cancers	6 (27.2)
Frequency of ESCC	
With HNC	18 (14.5)
Post ER for ESCC	6 (7.3)

ER, endoscopic resection; ESCC, esophageal squamous cell carcinoma; HGIN, high-grade intraepithelial neoplasia; HNC, head and neck carcinoma; SCC, squamous cell carcinoma.

Detection rate for superficial esophageal SCC by NBI according to the respective typical endoscopic features (BA)

To confirm the concordance rate for the detection of superficial esophageal cancer, we evaluated the inter- and intra-observer agreements between two endoscopists (YN and HM) for the endoscopic finding of BA on NM-NBI. We confirmed good inter-observer agreement (κ-value = 0.73, 95% confidence interval: 0.59–0.87) and excellent intra-observer agreement (κ-value = 0.84, 95% confidence interval: 0.74–0.95) for BA detected by NM-NBI. The typical features indicating superficial esophageal SCC, such as BA, were detected by NM-NBI (**Figure 2b,c**). In the per-lesion-based analysis of 84 lesions with BA detected by NM-NBI, 29 lesions were diagnosed as SCC ($n = 19$) or HGIN ($n = 10$; sensitivity, 90.6%; specificity, 75.2%; **Figure 3**). Fifty-five BA lesions were diagnosed as LGIN ($n = 13$), esophagitis ($n = 12$), or no tumor ($n = 30$). However, 170 lesions without BA were diagnosed as no tumor and 3 lesions without BA were diagnosed as SCC ($n = 2$) or HGIN ($n = 1$; **Figure 3**). In addition, no abnormalities were found in 42 biopsy specimens obtained from areas that appeared normal in 13 patients. Previous reports show that the prevalence of HGIN derived from an iodine-stained area is quite low (< 1%) (36), and therefore only a few biopsy specimens were obtained from normal areas in the present study. In the per-patient-based analysis, all of the 22 patients diagnosed as SCC or HGIN exhibited a BA on NM-NBI (**Figure 4**).

Propensity score matching analysis

We can create a quasi-randomized experiment by propensity score matching—i.e., two subjects were randomly assigned to each group in the sense that they were equally likely to be BA positive or BA negative (**Table 2**). The propensity score model was well calibrated (Hosmer Lemeshow test, $P = 0.42$) and discriminated well between patients who were BA positive and BA negative (c-statistic = 0.78).

Comparison of the accuracy, sensitivity, and specificity of NBI with those of CE-Iodine for diagnosing esophageal SCC

Using generalized estimating equations, the accuracy, sensitivity, and specificity of NM-NBI were 77.0, 88.3, and 75.2%, respectively, and the values for the unstained areas by using CE-Iodine were 68.0, 94.2, and 64.0%, respectively. Before matching, the accuracy and specificity of NM-NBI were superior to those of CE-Iodine ($P = 0.03$ and $P = 0.01$). However, there were no significant differences in the sensitivity between NM-NBI and CE-Iodine before matching ($P = 0.67$; **Table 3**). The accuracy and specificity of NM-NBI before matching were superior to those of CE-Iodine after matching ($P = 0.04$ and $P = 0.03$). However, there were no significant differences in the sensitivity of NM-NBI and CE-Iodine after matching ($P = 1.00$). Moreover, there were no changes in the accuracy, sensitivity, and specificity when comparing NM-NBI

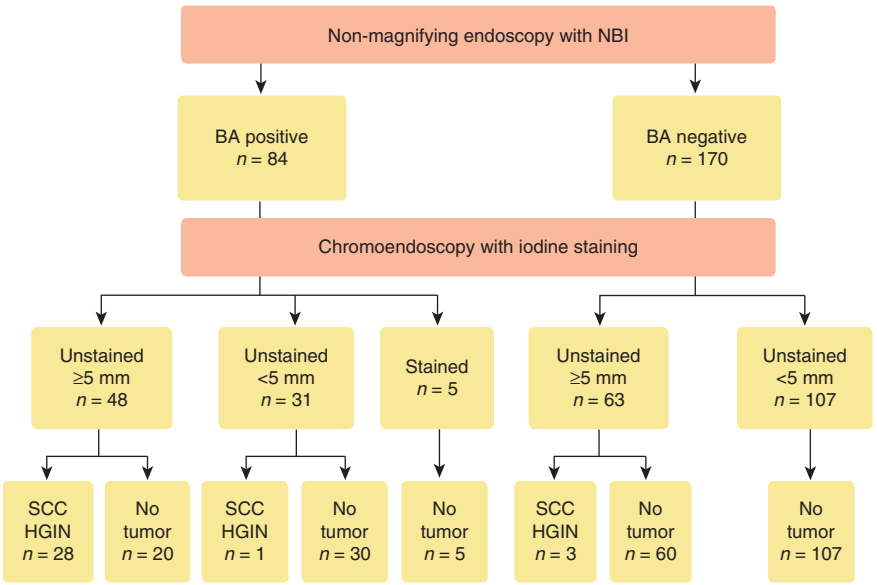

Figure 3. Flowchart of lesion-based analysis. BA detected by non-magnifying endoscopy with narrow-band imaging, following chromoendoscopy with iodine staining. BA, brownish area; HGIN, high-grade intraepithelial neoplasia; NBI, narrow-band imaging; SCC, squamous cell carcinoma.

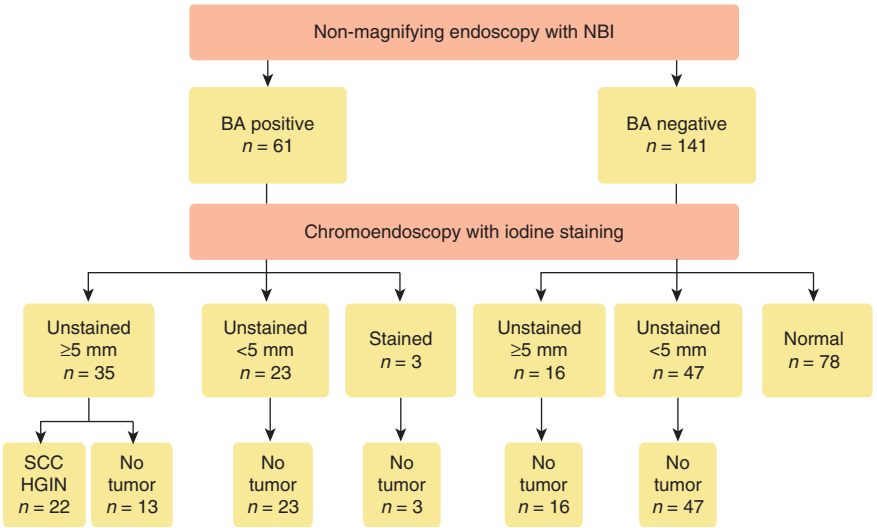

Figure 4. Flowchart of patient-based analysis. BA detected on non-magnifying endoscopy with narrow-band imaging, following chromoendoscopy with iodine staining. BA, brownish area; CRT, chemoradiotherapy; HGIN, high-grade intraepithelial neoplasia; NBI, narrow-band imaging; SCC, squamous cell carcinoma.

with CE-Iodine before and after propensity matching (**Table 3**). The AUC of NBI and CE-Iodine before matching was 0.83 and 0.80, and the AUC of CE-Iodine after matching was 0.81.

Incidence rate of histologically diagnosed esophageal cancer (SCC or HGIN)

From biopsy or ER specimens, 21.7% ($n = 32$) of the suspicious lesions ($n = 147$) were eventually diagnosed as superficial esophageal SCC (SCC or HGIN). The incidence rate of superficial esophageal SCC (SCC or HGIN) was 10.9% (22/202) of the enrolled patients (**Table 1**). The frequency of esophageal SCC in patients with previous head and neck SCC or previous history of ER for esophageal SCC (metachronous type of esophageal SCC) was 14.5% (18/124) or 7.3% (6/82), respectively. No correlation was found between the location of head and neck carcinoma and the frequency of esophageal SCC. Synchronous multiple esophageal SCC was detected in 27.2% of the patients (6/22).

DISCUSSION

We used propensity score matching analysis to indicate that the accuracy, sensitivity, and specificity of BA detected by NM-NBI

Table 2. Baseline characteristics before and after propensity score matching

	Before matching (*n*=254)			After matching (*n*=80)		
	BA-positive (*n*=84)	BA-negative (*n*=170)	*P* value	BA-positive (*n*=40)	BA-negative (*n*=40)	*P* value
Endoscopist						
No 1	14	33	0.08	8	11	0.18
No 2	14	12		8	3	
No 3	56	125		24	26	
Size of the lesion (mm)	9.4±11.5	4.6±2.8	<0.01	4.75±3.6	4.78±3.6	0.97
FIT (mm)	31.2±5.9	31.2±5.1	0.99	31.6±4.6	30.8±5.8	0.19
Endoscope						
GIF-Q260	32	82	0.12	18	17	0.82
GIF-H260Z	52	88		22	23	
Macroscopic appearance						
Elevated	1	3	1.00	0	0	1.00
Flat or depressed	83	167		40	40	
White light diagnosis						
SCC-negative	38	165	<0.01	35	35	1.00
SCC-positive	46	5		5	5	
Circumferential location						
Anterior wall	23	47	0.26	11	13	0.37
Right side wall	13	41		6	11	
Posterior wall	31	60		19	13	
Left side wall	17	22		4	3	

BA, brownish area; FIT, distance from the incisor teeth to the upper-end of the lesion. Data are presented as mean±s.d. and numbers.

Table 3. Diagnostic performance before and after propensity score matching

	Before matching (*n*=254)			After matching (*n*=80)	
	NBI	CE	*P* value	CE	*P* value
Sensitivity (%) (95% CI)	88.3 (72.6–96.7)	94.2 (80.4–99.3)	0.67	83.3 (35.9–99.6)	1.00
Specificity (%) (95% CI)	75.2 (69.0–80.8)	64.0 (57.3–70.3)	0.01	61.8 (50.0–72.8)	0.03
PPV (%) (95% CI)	34.3 (25.2–46.4)	28.6 (20.4–37.9)	0.32	14.7 (5.0–31.1)	0.03
NPV (%) (95% CI)	97.7 (94.1–99.4)	98.6 (95.1–99.8)	0.69	100 (93.9–100)	1.00
Accuracy (%) (95% CI)	77.0 (71.3–82.0)	68.0 (61.9–73.6)	0.03	63.4 (52.0–73.8)	0.04
Positive LR (95% CI)	3.66 (2.84–4.72)	2.69 (2.23–3.24)		2.62 (1.97–3.49)	
AUC	0.83 (0.76–0.90)	0.80 (0.74–0.87)		0.81 (0.70–0.94)	

AUC, area under the curve; CE, chromoendoscopy with iodine staining; CI, confidence interval; LR, likelihood ratio; NBI, narrow-band imaging; NPV, negative predictive value; PPV, positive predictive value.
CE before matching was compared with NBI before matching. CE after matching was compared with NBI before matching.

are acceptable. We suggest that NM-NBI is suitable for screening high-risk patients for esophageal SCC.

The incidence of esophageal SCC in patients with primary head and neck SCC has been reported as 10–15% and that of metachronous esophageal SCC after ER has been reported as 14.6% (4–9). Therefore, an accurate noninvasive surveillance technique is critical, especially for high-risk patients, because early diagnosis and treatment with surgical resection and ER improves survival

(2,10–12). The detection of early esophageal SCC using WLI endoscopy has a very low sensitivity of 55.2–62.9% (8,13–19). Therefore, WLI endoscopy is inadequate for the surveillance of high-risk patients. Magnifying endoscopy with NBI can be used to obtain a definite endoscopic diagnosis of esophageal SCC, with a sensitivity ranging from 88.9 to 100% (14,15). However, many general hospitals usually do not have the resources to use magnifying endoscopy, and therefore non-magnifying endoscopy is frequently used for routine general screening. Furthermore, only a few studies have reported the use of NM-NBI for esophageal SCC screening (16–18). CE-Iodine can be used to detect esophageal SCC and has sensitivity ranging from 88.9 to 100% (4–8,15–19). However, its specificity is low (4.4–84.7%) because of a high number of false-positive lesions, which results in unnecessary biopsies (4–8). Our results show a comparable sensitivity (94.2%) for unstained lesions when using CE-Iodine. Therefore, most unstained lesions were easily detected and did not need any treatment, because they were caused by histological inflammation or LGIN. In addition, iodine solution irritates the mucosa and may cause retrosternal chest pain and discomfort; it is also limited by the occurrence of hypersensitivity and the risk of chemical esophagitis, laryngitis, and bronchopneumonia (17). Several reports have shown that necrosis and injury to the esophageal and gastric mucosa can be caused by hypersensitivity to iodine solution (6,20–22). Therefore, the detection of BA by NM-NBI is more useful for the diagnosis of esophageal SCC or HGIN because it does not cause mucosal irritation.

As stated previous, NBI and iodine staining can be performed sequentially during the same endoscopy procedure (15–19), but it is not possible to perform these procedures in the reverse order, thus making a random cross-over trial difficult. Therefore, we used propensity score matching to compare the accuracy of the diagnosis of esophageal SCC between NM-NBI and CE-Iodine. In this analysis, we found that NM-NBI was superior to CE-Iodine in the accurate diagnosis of esophageal SCC both before and after matching. However, the above finding alone may suggest a possibility that the WLI diagnosis might influence the NM-NBI diagnosis. Therefore, we performed propensity score matching analysis to reduce selection bias. We compared the NM-NBI findings before and after matching to determine the influence of WLI diagnosis on the subsequent NM-NBI diagnosis and created a propensity score-matched cohort by matching a patient diagnosed as cancer positive and negative on WLI. As a result, no difference was found in the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of NM-NBI before and after matching. Accordingly, we conclude that NM-NBI is superior to CE-Iodine in the accuracy of the diagnosis of esophageal SCC, independent of the WLI diagnosis.

A BA was not detected in two SCC cases and one HGIN case using NM-NBI. These three lesions were small superficial cancers (6–10 mm in diameter) and had a flat macroscopic appearance in the upper part of the esophagus. In addition, two lesions were diagnosed as multiple synchronous esophageal SCC, but were retrospectively diagnosed as having a BA near the synchronous esophageal SCC by NBI during the same endoscopy procedure. The field of view when using NBI is dark, and therefore careful observation is required to detect synchronous lesions. However, in the per-patient-based analysis, all patients ($n = 22$) diagnosed with SCC or HGIN were diagnosed as having a BA on NM-NBI. Among the 141 patients in whom a BA was not detected on NM-NBI, 78 patients had no abnormality, as determined by CE-Iodine, and 63 patients had unstained lesions on CE-Iodine and required no treatment (**Figure 4**). These results suggest that the patients in whom BA was not detected by NM-NBI did not need to undergo the CE-Iodine procedure.

We should also consider the influence of the previous ER procedure on the detection rate by each modality. However, ER scars manifested as longitudinal whitish areas with contraction (**Figure 2e**), and neoplasia was primarily detected as metachronous lesions at sites other than the ER scar. In this study, neoplasia was detected close to a previous ER scar in two cases, but NBI detected them without any difficulty (**Figure 2e,f**). Therefore, we conclude that patients who have had previous ER are suitable for inclusion in this or similar studies, and this result has been supported by other studies (14,16–17,24). Of the 124 patients with head and neck carcinoma, 18 patients had esophageal carcinoma, 6 died of head and neck carcinoma, and 12 patients with controlled head and neck carcinoma were treated for esophageal carcinoma. The median survival time was 1516 (range, 767–1,841) days. Morimoto *et al.* (37) also reported similar findings. Therefore, early detection of esophageal cancer is believed to contribute to the prognosis in patients with head and neck carcinoma.

Our study has several limitations. First, the propensity score analysis is a statistical technique for adjusting selection bias in observational studies and approximates randomized trial approaches (32,38). Logistic regression was used to generate a model to calculate propensity scores. Each patient with positive findings was matched with a patient with negative findings using the closest propensity score. Matching patients produce well-balanced groups comparable to a randomized, controlled trial. In addition, even in cases of a small study sample or low prevalence of treatment, propensity score matching can yield unbiased estimations of treatment effect, unless the true confounders and the variables related only to the outcome are not included in the propensity model (39). However, propensity score matching has inherent limitations, such as the choice of finite covariates, which implies that the relevant covariates may be omitted. In this study, we aimed to distinguish between BA-positive and BA-negative specimens using the per-lesion-based analysis. Therefore, we used a previously reported method (14–15) and our clinical experience to choose the possible confounders for their potential association with the outcome. **Table 2** lists the seven factors that may have influenced our findings. The propensity score model discriminated well between patients who were BA positive and BA negative (c-statistic = 0.78). Therefore, we suggest that the most likely confounders were identified in our study. However, we recognized that it is difficult to adjust for potential confounders using propensity-matching analysis. We believe that this point is a major limitation of the present study. Second, the sample size decreased after propensity score matching. The matched samples represented a subset of the entire study population, and the smaller sample size was associated with a

reduced power. Pirracchio *et al.* (39) reported that even in the case of small study samples or low prevalence of treatment propensity score matching can yield unbiased estimates of treatment effect. However, the reliability of the sensitivity and specificity measurements may have decreased because of the small sample size after matching. Third, LGIN can be pathologically diagnosed at one site in a lesion by examination of biopsy specimens, and a focal region of LGIN can be present adjacent to an HGIN or cancer lesion. Furthermore, LGIN often directly transforms into HGIN or cancer. Therefore, sampling errors might occur.

In conclusion, we found that NM-NBI is efficient and reliable for the surveillance of esophageal SCC in high-risk patients without causing patient discomfort. The initial use of NM-NBI for detecting BA lesions and subsequent iodine staining for these lesions is a promising screening strategy for general populations, as well as for the surveillance of high-risk patients.

CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The usefulness of non-magnifying endoscopy with narrow-band imaging (NBI) (NM-NBI) for diagnosing esophageal squamous cell carcinoma (SCC) remains unclear.
- ✓ Chromoendoscopy with iodine staining (CE-Iodine) is useful but often causes chest pain and discomfort.
- ✓ There are few comparative studies of NM-NBI and CE-Iodine in patients at high risk for esophageal SCC.

WHAT IS NEW HERE

- ✓ The accuracy and specificity of the brownish area detected by NM-NBI were superior to those of CE-Iodine in the high-risk patients using propensity score matching analysis.
- ✓ There was no significant difference between the sensitivities of NM-NBI and CE-Iodine.
- ✓ NM-NBI is useful for surveillance for the diagnosis of esophageal SCC without discomfort.

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