Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study

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Background: The accurate diagnosis of gastric small depressive lesions (SDLs), including gastritis and cancerous lesions, is difficult with conventional endoscopy when using white-light imaging (WLI). Narrow-band imaging (NBI) is expected to make a more accurate diagnosis of gastric SDLs than WLI because it provides better visualization of the mucosal surface and microvascular architecture when combined with magnifying endoscopy.

Objective: To compare the real-time diagnostic accuracy of magnifying WLI and magnifying NBI for gastric SDLs.

Design: Prospective study.

Setting: National Cancer Center Hospital East, Kashiwa, Japan.

Patients: Fifty-seven lesions in 53 consecutive patients were analyzed: 30 cancers and 27 benign lesions.

Interventions: If previously undiagnosed gastric SDLs smaller than 10 mm were identified during an endoscopic examination, magnifying observation with both WLI and NBI was performed for each SDL. Endoscopic diagnosis of SDLs was made by each method on site.

Main Outcome Measurements: The diagnostic accuracy and the time required for diagnosis.

Results: The diagnostic accuracy was significantly higher for NBI than for WLI (79% vs 44%; $P = .0001$), as was its sensitivity (70% vs 33%; $P = .0005$). The diagnostic specificity of NBI (89%) was higher than that of WLI (67%), but the difference was not statistically significant. The time required for the diagnosis was equivalent with both methods.

Limitations: Single-center study, small sample size.

Conclusions: Adding NBI to the WLI examination is essential for making an accurate diagnosis of gastric SDLs compared with magnifying WLI alone. (UMIN Clinical Trials Registry identification number C000000421) (Gastrointest Endosc 2010;71:477-84.)

Gastric cancer is the fourth most common cancer and the second most common cause of cancer death worldwide.[1] Although the early detection of gastric cancer is necessary to improve patient survival, the identification of small gastric cancers is difficult.

The high-resolution endoscopic system has increased the probability of finding small, depressed lesions (SDLs) (≤10 mm) in the stomach. Because gastric SDLs include gastritis and cancer, their differential diagnoses are clinically important. However, the accurate diagnosis of SDLs

Abbreviations: DL, demarcation line; IMVP, irregular microvascular pattern; magnifying WLI, magnifying endoscopic observations combined with white-light imaging; NBI, narrow-band imaging; SDL, small depressive lesion; WLI, white-light imaging.

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by conventional endoscopy is difficult, and the diagnosis of SDLs is usually confirmed by the histopathological examination of biopsy specimens, which increases the number of unnecessary biopsies. Real-time accurate endoscopic diagnosis should reduce the number of unnecessary biopsies. The most important clinical purpose is to detect a gastric cancer accurately at the SDL stage because such lesions are good candidates for minimally invasive endoscopic treatment, which can improve the patient's chance of survival markedly.

Magnifying endoscopy can visualize the microstructures and microvessels of the lesions. Endoscopic differential diagnosis based on the changes in these structures is useful for accurate diagnosis in the GI tract.[2-12] Yao et al[13] reported the following characteristic magnifying endoscopic findings of early gastric cancer: (1) there is a definite demarcation line (DL) between the cancerous lesion and normal areas and (2) an irregular microvascular pattern (IMVP) is present in the cancerous lesions. They also reported the usefulness of magnifying endoscopic observations combined with white-light imaging (WLI; magnifying WLI) and the diagnostic reliability of DL and IMVP findings in a prospective study.[14] However, it is not easy to accurately visualize and evaluate the magnifying endoscopic findings such as DL and IMVP because of the low contrast of WLI images. A novel technique and an excellent diagnostic capacity for magnifying endoscopy are required for an accurate diagnosis when using magnifying WLI.

In contrast, magnifying endoscopic observations combined with narrow-band imaging (magnifying NBI) provide a higher contrast image than does magnifying WLI.[15,16] Magnifying NBI is expected to improve the diagnostic accuracy for gastric SDLs. However, there has been no report of the diagnostic accuracy of magnifying NBI.

This prospective study was conducted to demonstrate the effectiveness of magnifying NBI in the differential diagnosis of gastric SDLs. For this purpose, the real-time diagnostic accuracy of magnifying NBI and conventional magnifying WLI was compared.

METHODS

This trial was conducted in accordance with the Standards for Reporting of Diagnostic Accuracy initiative. The protocol was approved by the Institutional Review Board of the Japanese National Cancer Center. Written informed consent was obtained from all participants who underwent a routine endoscopic examination with the NBI system. The UMIN Clinical Trials Registry identification number for this study is C000000421.

Eligibility criteria

The criteria for eligibility were gastric SDLs (≤10 mm) without ulceration that were detected during a routine endoscopic examination, age older than 20 years, no other serious complications, and the use of no medications that might interfere with obtaining a biopsy specimen.

Capsule Summary

What is already known on this topic

- Diagnosis of gastric small depressive lesions (SDLs), including gastritis and cancerous lesions, is difficult with conventional endoscopy when using white-light imaging (WLI).

What this study adds to our knowledge

- In a prospective study of 57 gastric SDLs, diagnostic accuracy and sensitivity were significantly higher for narrow-band imaging than for WLI.

Study design and examination

The primary endpoint was diagnostic accuracy, calculated from diagnostic sensitivity and specificity, and the secondary endpoint was the time required to establish a diagnosis. When we detected gastric SDLs during routine endoscopic examinations in patients from whom written informed consent was obtained, we registered those lesions.

In this study, we used high-resolution magnifying endoscopy systems: (1) a magnifying endoscope (GIF-Q240Z, GIF-H260Z; Olympus Medical Systems, Tokyo, Japan), (2) a video system center (EVIS LUCELA CV-260SL; Olympus Medical Systems), (3) a high-intensity luminous source (EVIS LUCELA CLV-260NBI; Olympus Medical Systems), and (4) a high-resolution liquid crystal monitor (OEV191H; Olympus Medical Systems).

SDLs were first examined by magnifying WLI, and their endoscopic diagnoses were determined according to the predetermined criteria and recorded immediately. After the first examination, we changed the light from the white light to the narrow-band light with just a single push of a button on the endoscope without changing the endoscope. An examination with magnifying NBI followed thereafter, and the diagnoses and records were processed similarly. Based on the diagnostic criteria, the assistant doctor recorded the presence or absence of DL or IMVP during the procedure in real-time and on-site to ensure the objectivity of the examination. We then applied these findings to the diagnostic criteria and provided endoscopic diagnoses. In each modality, the time from the start of the observation to the time when an endoscopic diagnosis was made was timed with a stopwatch. After all the records were complete, proper biopsies were performed on the SDLs (Fig. 1).

In this design, each imaging method (WLI and NBI) was examined by the same endoscope (GIF-Q240Z or GIF-H260Z; Olympus Medical Systems). This design allowed

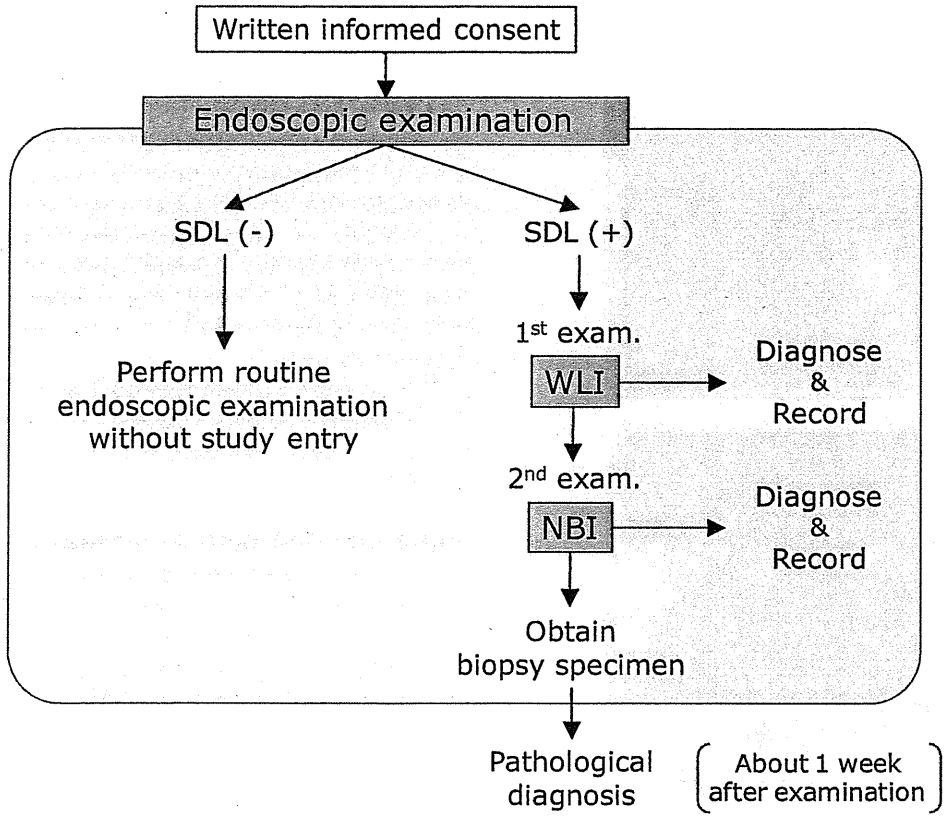

Figure 1. Protocol of the examinations in this study.

us to counteract any bias arising from differences in image quality obtained by using different types of endoscopes.

Five endoscopists participated in this study, and each endoscopist interpreted each lesion individually without consultation with the others. The endoscopists who participated in this study were required to have a level of knowledge and skills commensurate with those of a specialist accredited by the Japan Gastroenterological Endoscopy Society to ensure the quality of the examinations. They were shown magnified endoscopic images and videos for reference and considered the diagnostic criteria together to minimize variation between the endoscopists.

The criterion standard for the diagnosis was the results of the histopathological examination of the biopsy specimens, which were revealed about 1 week after the examination.

Diagnostic criteria for endoscopic findings

The endoscopic diagnostic criteria followed the classification established by Yao et al[13]: (1) a DL between the depressed lesion and the surrounding normal area and (2) an IMVP inside the lesion (Fig. 2). Nakayoshi et al[17] classified the microvessels found in gastric cancers into 2 patterns according to their histological type. However, in our preliminary observation, we found that irregular microvessels are a common finding, regardless of the histological type of the lesion. Therefore, we did not distinguish the microvascular patterns and used IMVP simply as one of the endoscopic criteria for gastric cancer in this study. Although DL and IMVP were reported originally as key findings in magnifying WLI,[13] we used these findings in both WLI and NBI in this study. The visibility of the DL and IMVP of the SDLs was classified into 3 categories: visible, illegible, or invisible. In both modalities, the SDLs were diagnosed according to the combination of the visibility of the DL and IMVP, as shown in Table 1 and as follows. (1) If both DL and IMVP were visible, the diagnosis was cancer. (2) If either DL or IMVP was illegible, the diagnosis was inconclusive. (3) If either or both DL and IMVP were invisible, the diagnosis was noncancer.

Criteria of the pathological diagnosis

The pathological diagnostic criteria were based on the revised Vienna classification[18]: C4 (mucosal high-grade neoplasia) or C5 (submucosal invasion by neoplasia) was diagnosed as carcinoma and C1 (negative for neoplasia), C2 (indefinite for neoplasia), and C3 (mucosal low-grade neoplasia) were diagnosed as non-carcinoma. The biopsy specimens were evaluated with hematoxylin–eosin staining.

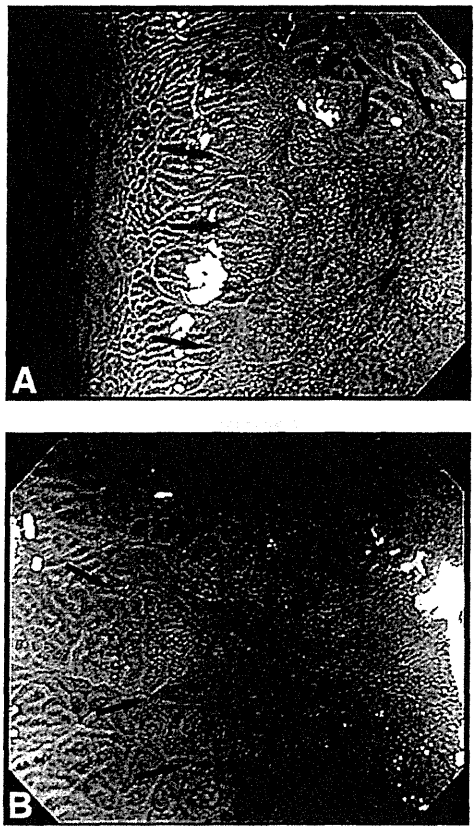

Figure 2. A typical finding of the DL and IMVP **(A, B)**. Magnifying NBI can clearly visualize the DL between the lesion and the surrounding normal mucosa (*arrows*) and IMVP within the lesion.

TABLE 1. Diagnostic criteria for endoscopic findings

Demarcation line	Irregular microvascular pattern		
	Visible	Invisible	Illegible
Visible	Cancer	Noncancer	Inconclusive
Invisible	Noncancer	Noncancer	Inconclusive
Illegible	Inconclusive	Inconclusive	Inconclusive

Statistical analysis

The estimated sample sizes required to achieve a power of the test of 80% and a 2-sided level of significance of 5% were 28 cancerous lesions and 69 noncancerous lesions.

The McNemar test was used for comparison of categorical variables, and the Wilcoxon signed-rank test was used for continuous variables.

All *P* values calculated in this analysis were 2 sided and were not adjusted for multiple testing. *P* values <.05 were considered significant. All statistical analyses were performed by using the Dr. SPSS II statistical software package (SPSS Japan Inc, Tokyo, Japan).

RESULTS

Characteristics of patients and lesions

A total of 60 lesions in 56 patients were examined in this study between March 2006 and February 2008. At the end of enrollment, 3 patients were excluded for the following reasons: no biopsy specimen was obtained for 1 lesion, pre-examination bleeding occurred in 1 lesion, and 1 lesion was larger than 10 mm. Ultimately, 53 patients and 57 lesions were analyzed: 30 cancerous lesions in 30 patients and 27 noncancerous lesions in 24 patients (Fig. 3).

The number of noncancerous lesions did not reach the statistically required number of 69, but enrollment was discontinued because the 2-year enrollment period had ended.

Endoscopic findings of all lesions

The results of endoscopic evaluation of the visibility of the DL and IMVP of all SDLs are shown in Table 2. In cancerous lesions, the numbers of lesions with visible DL or visible IMVP were significantly higher in magnifying NBI than in magnifying WLI ($P = .005$ and $P = .002$, respectively). In contrast, there is no statistical difference in visibility of DL and IMVP between magnifying WLI and magnifying NBI in the noncancerous lesions ($P = .25$ and $P = .07$, respectively).

In the magnifying NBI, the numbers of lesions with visible DL or visible IMVP were significantly higher in cancerous lesions than in noncancerous lesions (83% [25/30] vs 44% [12/27], $P = .003$ and 73% [22/30] vs 7% [2/27], $P < .0001$, respectively). DL could be seen in about half of the noncancerous lesions in both magnifying WLI and magnifying NBI (41% [11/27] and 44% [12/27], respectively).

Diagnostic accuracy (primary endpoint), sensitivity, and specificity

The diagnostic accuracy of magnifying WLI was 44%; a correct diagnosis was obtained for 25 (44%) of 57 lesions, an incorrect diagnosis for 14 (25%) of 57 lesions, and an inconclusive diagnosis for 18 (31%) of 57 lesions. In contrast, the diagnostic accuracy of magnifying NBI was 79%, and the corresponding diagnoses were 45 (79%) of 57 lesions, 8 (14%) of 57 lesions, and 4 (7%) of 57 lesions, respectively. The diagnostic accuracy was significantly better for magnifying NBI than for magnifying WLI ($P = .0001$; Fig. 4). Significantly more cases were diagnosed as inconclusive by magnifying WLI than by magnifying NBI (31% [18/57] vs 7% [4/57], respectively; $P = .001$).

The diagnostic sensitivity of magnifying WLI for small gastric cancer was significantly higher than that of magnifying WLI (23% vs 70%, respectively; $P = .0005$; Fig. 5). In contrast, although the diagnostic specificity of magnifying NBI was higher than that of magnifying WLI

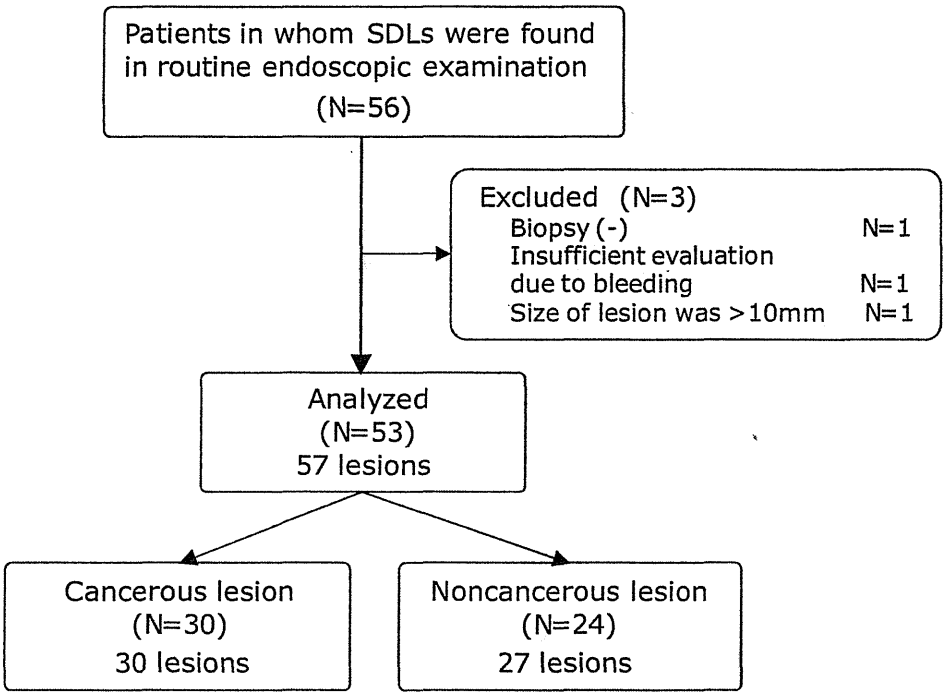

Figure 3. Study flow chart. N = number of patients.

TABLE 2. Endoscopic findings of all lesions

Cancerous lesions (n = 30)				Noncancerous lesions (n = 27)			
	WLI	NBI	*P* value		WLI	NBI	*P* value
DL				DL			
Visible	11 (37)	25 (83)	.005*	Visible	11 (41)	12 (44)	.25†
Illegible	6 (20)	1 (4)		Illegible	4 (15)	0 (0)	
Invisible	13 (43)	4 (13)		Invisible	12 (44)	15 (56)	
IMVP				IMVP			
Visible	10 (33)	22 (73)	.002*	Visible	1 (4)	2 (7)	.07†
Illegible	8 (27)	3 (10)		Illegible	6 (22)	1 (4)	
Invisible	12 (40)	5 (17)		Invisible	20 (74)	24 (89)	

WLI, White-light imaging; *NBI*, narrow-band imaging; *DL*, demarcation line; *IMVP*, irregular microvascular pattern.
The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.
*A *P* value was calculated as a comparison of visible and illegible + invisible.
†A *P* value was calculated as a comparison of invisible and illegible + visible.

(67% vs 89%, respectively), the difference was not significant (P = .08; Fig. 6).

Time required for diagnosis (secondary endpoint)

The median time required for diagnosis did not differ significantly between WLI and NBI (P = .29. The median time required for diagnosis, the secondary endpoint, was 95 seconds (range 10–265 seconds) for magnifying WLI and 99 seconds (range 15–285 seconds) for magnifying NBI (Fig. 7).

Adverse events

We did not observe any adverse events in this study during the endoscopic examinations or biopsy procedures. The endoscopic examinations were not discontinued in any patients.

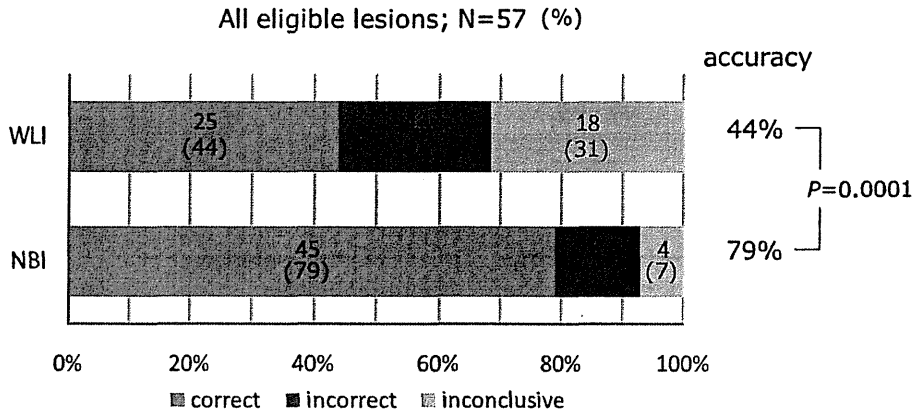

Figure 4. Diagnostic accuracy of magnifying WLI and magnifying NBI (primary endpoint). The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

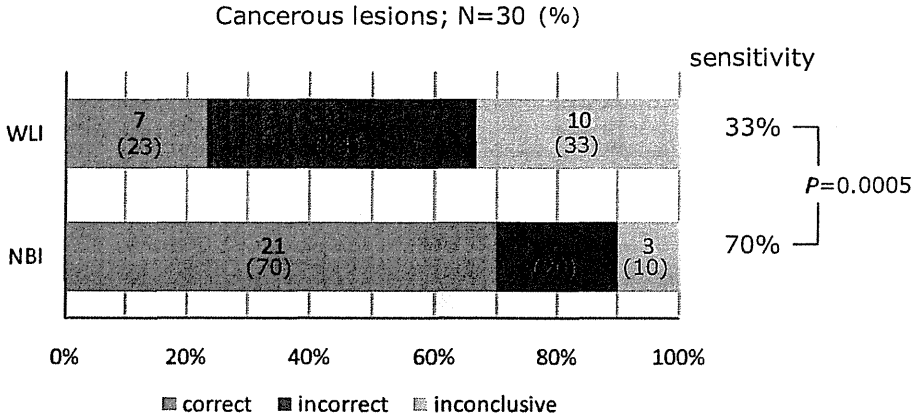

Figure 5. Diagnostic sensitivity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

DISCUSSION

The real-time diagnostic accuracy of magnifying NBI in the diagnosis of gastric cancer has not been reported. Most reports of endoscopic findings when using magnifying examination were made by reviewing only the best images selected by the investigators. Here, we performed the first prospective clinical investigation to compare the diagnostic accuracy of magnifying NBI and magnifying WLI used for the differential diagnosis of gastric SDLs. In this study, we demonstrated clearly that the visibility of DL and IMVP was superior in magnifying NBI compared with magnifying WLI in the differential diagnosis of gastric SDLs and that the DL and IMVP are valuable findings in the differential diagnosis of gastric SDLs. The feasibility of the NBI combination was verified because the observation time required to make a diagnosis was equivalent to that of magnifying WLI, and there was no interruption of the examination procedure in any patient. Taken together, our data from this study led us to conclude that NBI, rather than WLI, should be combined with magnifying endoscopy for the observation of gastric SDLs.

One of the most characteristic features of magnifying NBI is its ability to visualize the mucosal microarchitecture and microvessels in clear contrast to the background mucosa,[15,16] and this may result in a better visualization capacity than that of magnifying WLI. Supporting this possibility, in this study, magnifying NBI showed DL and IMVP in 83% and 73% of the cancerous lesion, respectively, whereas magnifying WLI showed only 37% and 33% of these findings ($P = .005$ and $P = .002$, respectively). These results also indicate that DL and IMVP are important endoscopic findings for the diagnosis of cancerous lesions in gastric SDLs.

In this study, although magnifying NBI showed significant superiority of diagnostic accuracy and sensitivity compared with magnifying WLI, we could not find a significant difference in the specificity. The main reason for the lack of a significant difference in diagnostic specificity may be the association with an insufficient number of

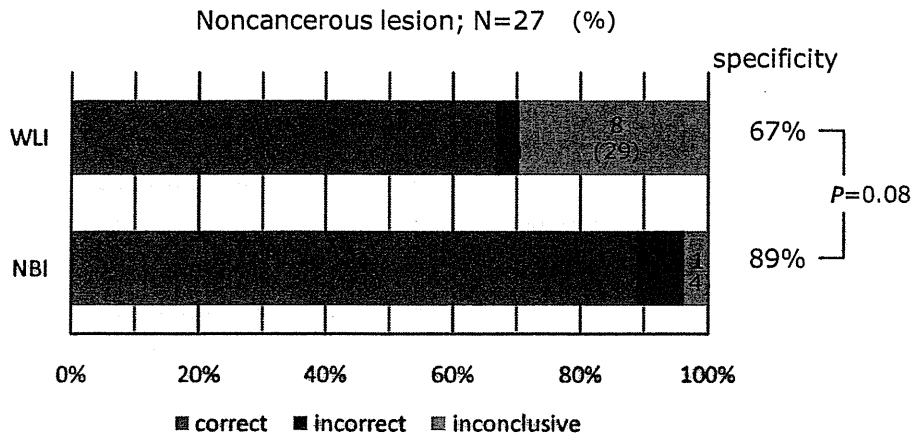

Figure 6. Diagnostic specificity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

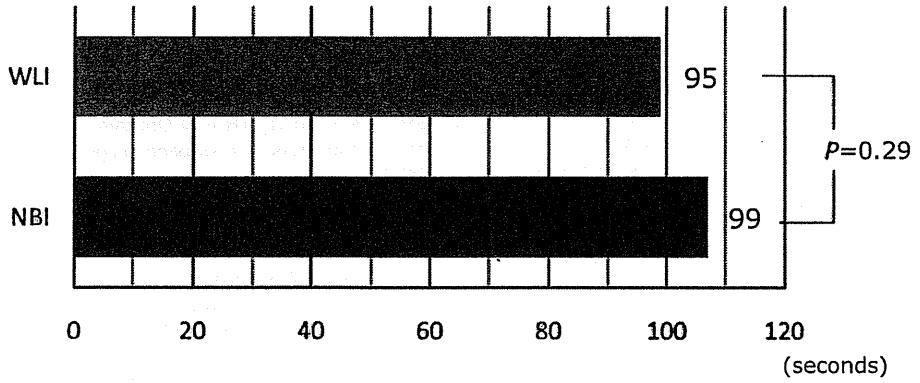

Figure 7. Time required for a diagnosis by magnifying WLI and magnifying NBI (secondary endpoint).

noncancerous lesions. Although the number of noncancerous lesions did not reach the statistically required number, we did not extend the enrollment period in this study because, judging from the rate of case collection, we considered that it would be difficult to achieve the required number of noncancerous lesions. The main reason was that we empirically excluded apparent benign lesions such as erosions and shallow ulcers from this study because this study targeted only SDLs that were suspected of being cancerous.

In this study, although the rate of misdiagnosis was lower with magnifying NBI than with magnifying WLI (14% [8/57] vs 25% [14/57]; $P = .15$), a considerable number of cases were misdiagnosed despite the clear visualization of magnifying NBI. Yao et al[14] reported that 25.3% of gastritis lesions were DL positive even by magnifying WLI. In this study, 41% and 42% of the noncancerous lesions were DL positive by magnifying WLI and magnifying NBI, respectively. Furthermore, in the stomach, the microvascular pattern shows many variations attributed to inflammatory changes. Therefore, it is sometimes difficult to judge the pattern of microvessels inside SDLs as cancerous IMVP or as an irregularity because of inflammatory changes. In this study, 17% of the cancerous lesions were negative for IMVP and 7% of the noncancerous lesions were positive for IMVP. This seems to be the main reason for misdiagnosis and thus may result in a limitation of DL- and IMVP-based diagnoses for gastric SDLs.

In this study, we performed magnifying WLI first and then magnifying NBI to compare their diagnostic accuracy. We chose this procedural order because we considered it unlikely that magnifying NBI would be conducted first followed by magnifying WLI in actual clinical practice. The possibility cannot be excluded that the results of the first examination influence those of the second examination when the comparative examinations are made in a fixed order. Therefore, the operators should be changed at each examination or each case should be randomized to either magnifying WLI or magnifying NBI. However, neither of these designs was adopted here because the former design seemed ethically equivocal for a real examination, and using the latter would make it technically difficult to identify and observe the target lesion by magnifying NBI alone. At least, this study was not a randomized comparison of

magnifying WLI and magnifying NBI for gastric SDLs. All lesions were examined with WLI followed by NBI sequentially, and then this study provided a comparison of the diagnostic yield of WLI and WLI followed by NBI. From this perspective, we could conclude that adding NBI to the WLI examination markedly improved the diagnostic accuracy of gastric SDLs compared with magnifying WLI alone.

This study may have other limitations in that the two modalities were compared by using magnifying endoscopy. The current global standard is to use nonmagnifying WLI. Therefore, as the next step, we should investigate whether magnifying NBI is superior to the conventional nonmagnifying WLI. We are now conducting a multicenter, randomized, controlled trial to compare magnifying NBI with nonmagnifying WLI (UMIN Clinical Trials Registry ID C000001072).

In summary, we demonstrated that adding NBI to the WLI examination is essential for making an accurate diagnosis of gastric SDLs compared with magnifying WLI alone and demonstrated the high reliability of DL and IMVP as diagnostic criteria for gastric SDLs. The excellent diagnostic capacity of magnifying NBI should allow the diagnosis of most SDLs without the need for a biopsy, which should decrease the number of unnecessary biopsy specimens. In addition, magnifying NBI should enhance the early detection of gastric cancer, which should facilitate endoscopic treatments such as EMR and endoscopic submucosal dissection. Magnifying NBI will also benefit the patient because its examination time is no longer than that of magnifying WLI despite its excellent performance.

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Narrow band imaging for detecting superficial squamous cell carcinoma of the head and neck in patients with esophageal squamous cell carcinoma

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Background and study aims: Narrow band imaging combined with magnifying endoscopy (NBI-ME) is useful for the detection of superficial squamous cell carcinoma (SCC) within the oropharynx, hypopharynx, and oral cavity. The risk of a second primary SCC of the head and neck is very high in patients with esophageal SCC. This prospective study evaluated the detection rate of superficial SCC within the head and neck region (superficial SCCHN) with NBI-ME in patients with esophageal SCC.

Patients and methods: Between March 2006 and February 2008, 112 patients with a current or previous diagnosis of esophageal SCC were enrolled. All patients underwent endoscopic screening of the head and neck by NBI-ME. The primary end point was the detection rate for superficial SCCHN. Secondary end points were to compare demographic characteristics between patients with and without superficial SCCHN and to assess the clinical course of patients with superficial SCCHN.

Results: The detection rate for superficial SCCHN was 13% (15/112). The prevalence of multiple Lugol-voiding lesions, observed endoscopically throughout the esophageal mucosa after application of Lugol dye solution, was significantly higher in patients with superficial SCCHN than in those without (100% vs. 24%, $P < 0.0001$). Minimally invasive curative treatment with organ preservation was feasible without severe complications in patients with superficial SCCHN after curative treatment of esophageal SCC.

Conclusions: In patients with esophageal SCC, NBI-ME is useful for detecting superficial SCCHN, thereby facilitating minimally invasive treatment.

Introduction

Gastrointestinal endoscopy is an essential technique for the diagnosis of esophageal and gastrointestinal lesions. Narrow band imaging (NBI) is a novel optical technique that enhances the diagnostic capability of gastrointestinal endoscopy by highlighting the intraepithelial papillary capillary loops of the squamous cell mucosa by means of light passed through filters that narrow the spectral bandwidths, incorporated into a red–green–blue sequential illumination system [1]. It has previously been reported that NBI combined with magnifying endoscopy (NBI-ME) could detect superficial squamous cell carcinoma (superficial SCC) within the oropharynx, hypopharynx, and oral cavity [2–5]. Muto et al. reported that NBI-ME had higher rates for both detection and diagnostic accuracy for superficial SCC within the head and neck region (superficial SCCHN) than did conventional white light observation with magnifying endoscopy on back-to-back endoscopic examination [6].

Since in patients with esophageal cancer the most common site for synchronous and metachronous second primary malignancies is the head and neck [7–9], we prospectively studied the ability of NBI-ME to detect superficial SCCHN in patients with a current or previous diagnosis of esophageal SCC.

Patients and methods

Between March 2006 and February 2008, 112 patients were enrolled who met the following criteria: (i) a current or previous diagnosis of esophageal SCC; (ii) age of at least 20 years; (iii) no history of head and neck cancer; (iv) no symptoms of the head and neck; (v) no previous surgical treatment or radiotherapy of the head and neck; and (vi) no previous endoscopic screening of the head and neck by NBI-ME. The study protocol and informed consent form were approved by our institutional review board in February 2006.

Written informed consent was obtained from all patients.

The patients underwent endoscopic screening of the head and neck by NBI-ME. In this study, we performed NBI using a high definition video endoscopy system (CV-260SL, processor, CLV-260SL light source; Olympus Optical Co., Tokyo, Japan) and an optical magnifying endoscope with a system that could magnify objects up to 80 times (GIF Q240Z video endoscope; Olympus). The diameter of the GIF Q240Z video endoscope was 10.2 mm, and the flexibility was similar to that of a conventional gastrointestinal endoscope. Screening was done in the following order: (i) observation with shifting of the tongue to create sufficient space for screening the oral cavity without mouth gear, and (ii) observation with vocal exercise to create sufficient space for screening the oropharyngeal, hypopharyngeal, and laryngeal regions with mouth gear.

The primary end point was the detection rate of superficial SCCHN by endoscopic screening using NBI-ME in patients with a current or previous diagnosis of esophageal SCC. Secondary end points were: (i) to compare demographic characteristics between patients with and those without superficial SCCHN, and (ii) to assess the clinical course of patients with superficial SCCHN.

Because prospective studies assessing the ability of NBI to detect early, superficial SCCHN have not been reported previously, it was difficult to estimate the required sample size. We therefore set the study period at 2 years, during which we estimated that at least 100 patients could be enrolled.

Only superficial cancers, that is, microinvasive SCC and high grade intraepithelial neoplasia as defined by the World Health Organization classification of tumors, were studied [10]. An NBI diagnosis of superficial SCC required the presence of both (i) a well-demarcated brownish area, and (ii) an irregular microvascular pattern [2–4]. Examples of superficial SCC in the left piriform sinus, the left superior wall of the oropharynx, and the left side of the tongue are shown in **Figs. 1–3**. Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (**Figs. 1a**, **2a**, and **3a**). NBI showed a well-demarcated brownish area (**Figs. 1b**, **2b**, and **3b**). NBI combined with maximum magnification (×80) showed an irregular microvascular pattern (**Figs. 1c**, **2c**, and **3c**).

Biopsy specimens were taken after the completion of screening for all superficial cancers in the head and neck region. Before biopsy in the laryngeal region, 4% lidocaine solution was sprayed through the endoscope to attenuate the gag reflex. Resected specimens, biopsy specimens, or both, were evaluated histopathologically. The histological characteristics of neoplasms were classified according to the World Health Organization criteria for esophageal tumors [10]. We used the histological diagnosis as the gold standard diagnosis. Although the results of endoscopy were not blinded, the histological diagnosis was confirmed by two gastrointestinal pathologists.

Lugol chromoendoscopy of the esophageal mucosa was carried out in all patients, using the Lugol dye staining method [11]. A 1.5% solution of Lugol dye was used in this study. Multiple Lugol-voiding lesions (LVLs) were defined to be numerous, well-defined, irregularly shaped lesions that appeared throughout the entire esophageal mucosa after the application of Lugol dye solution [12, 13].

Because the oral cavity and superior wall of the oropharynx could easily be accessed by a surgical device, transoral surgical mucosectomy (TSM) of lesions in such regions was done by a head and neck surgeon, with the patient under general anesthesia. Lesions were removed using an electric surgical knife or carbon dioxide laser, without injecting saline beneath the epithelium to lift the lesion above the surrounding mucosa [4]. If a transoral direct surgical approach was difficult, endoscopic mucosal resection (EMR) was performed by a gastrointestinal endoscopist with the patient under general anesthesia; lesions were removed using a transparent, soft plastic cap [2, 14]. We used an orotracheal route for intubation at the time of EMR. However, in patients who underwent TSM because a transoral direct surgical approach was possible, a nasotracheal route was used for intubation to secure a good operative field.

In patients with superficial SCCHN treated with curative intent, follow-up examinations by NBI-ME and computed tomography (CT) examination were repeated at least every 6 months after treatment. The duration of follow-up was longer than 1 year in this study.

All statistical analyses were carried out using the StatView software package for Macintosh (Version 5; Abacus Concepts, Inc., Berkeley, California, USA). The significance of differences was assessed with Fisher's exact test. *P* values of < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Patient characteristics are shown in **Table 1**. The study group comprised 100 men (89%) and 12 women (11%), with a mean age (± SD) of 67 ± 7.5 years. The clinical stage of esophageal cancer was stage I in 42 patients (38%), stage II in 26 (23%), stage III in 32 (29%), and stage IV in 12 (11%).

Of the patients, 80 (71%) had a current diagnosis of esophageal SCC and it had been previously diagnosed in 32 (29%). There was a history of cancer in other organs in 12 patients (11%): gastric cancer in 7 (6%), lung cancer in 2 (2%), liver cancer in 1 (1%), bladder cancer in 1 (1%), and leukemia in 1 (1%). The remaining 100 patients (89%) had no history of cancer in other organs.

Habitual alcohol use was reported by 101 patients (90%), and 98 (88%) were smokers. Multiple LVLs of esophageal mucosa were found in 38 patients (34%).

Detection of superficial SCCHN

The detection rate for superficial SCCHN was 13% (15/112), with 16 lesions detected in 15 patients. One patient had two lesions, 1 each in oropharyngeal and hypopharyngeal mucosal sites. No advanced cancer was detected. The 16 lesions comprised 3 (19%) detected in the oral cavity, 4 (25%) in the oropharynx, and 9 (56%) in the hypopharynx (**Table 2**); no laryngeal cancer was detected. For 8 of the 16 lesions, biopsy specimen and resection specimens were available for histological evaluation; for the remaining 8 lesions, only biopsy specimens were available since these patients were treated with techniques other than surgical or endoscopic resection. All 16 superficial SCCHNs were diagnosed endoscopically and confirmed histopathologically.

The characteristics of patients with and without superficial SCCHN are compared in **Table 3**. The prevalence of multiple LVLs of the background esophageal mucosa was significantly higher in patients with superficial SCCHN (100% vs. 24%, $P < 0.0001$). Other characteristics did not differ significantly between the groups.

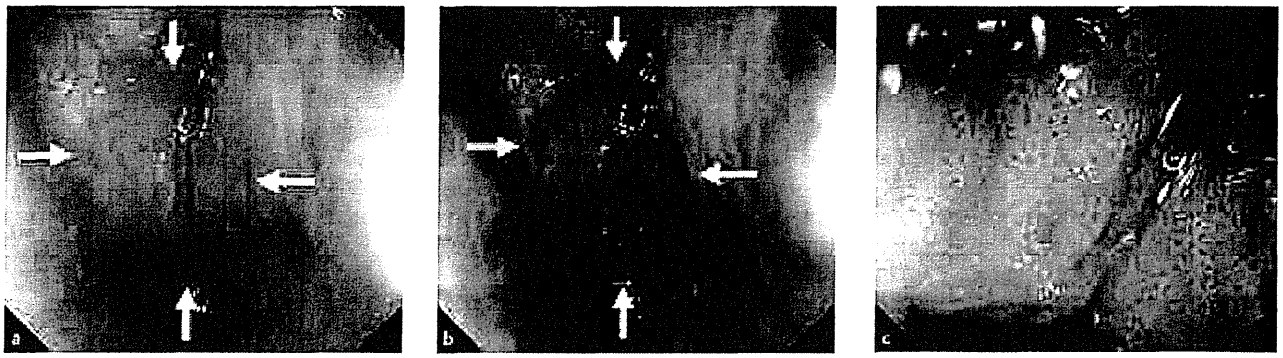

Fig. 1 Superficial squamous cell carcinoma in the left piriform sinus of the hypopharynx. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (arrows). **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (×80) showed an irregular microvascular pattern.

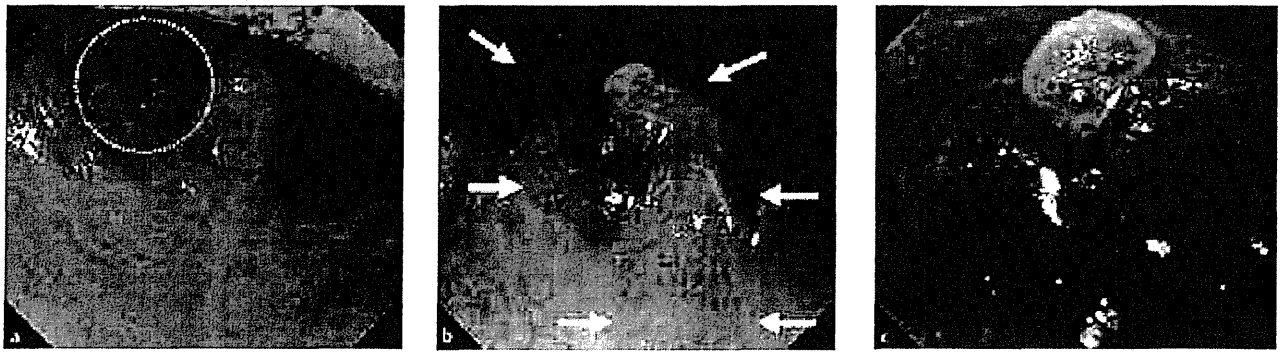

Fig. 2 Superficial squamous cell carcinoma in the left superior wall of the oropharynx. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (dotted line). **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (×80) showed an irregular microvascular pattern.

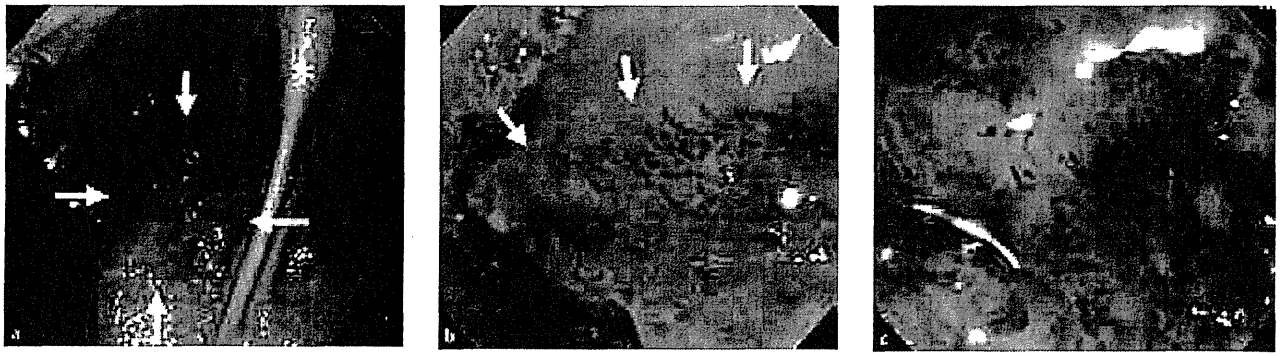

Fig. 3 Superficial squamous cell carcinoma in the left side of the tongue. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (arrows). Frenulum labii inferior. **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (× 80) showed an irregular microvascular pattern.

Treatment and course

In the 15 patients with superficial SCCHN, their esophageal cancer had been previously diagnosed in 3 and had been currently (at the time of the present study) diagnosed in 12. Because 10 patients were transiently disease-free after treatment for esophageal cancer, their superficial SCCHNs were treated with curative intent.

© **Fig. 4** summarizes the clinical courses of the ten patients in whom 11 superficial SCCHNs were treated with curative intent. Of the 11 lesions, 8 were resected (TSM 4, EMR 4; see below for further details); 2 lesions arising in the piriform sinus were treated by chemoradiotherapy [15]; and another 1 lesion in the piriform sinus by radiotherapy. The patient receiving radiotherapy for this hypopharyngeal SCCHN had two lesions and underwent TSM for an oropharyngeal lesion.

All of these patients were followed up every 6 months for at least 1 year. The average follow-up period (± SD) was 25 ± 6.3 months (range 14–33), and the average number of examinations per patient (± SD) was 4.8 ± 1 (range 3–6). No recurrent or newly diagnosed superficial SCCHN was detected during follow up.

One patient had synchronous advanced esophageal cancer and superficial SCC of the oral cavity, which were treated by chemoradiotherapy and TSM, respectively. However, this patient died because of recurrence of the esophageal cancer. The superficial SCC of the oral cavity was unrelated to the cause of death. With a median follow-up period of 29 months (range 14–33), all of

Table 1 Characteristics of patients (n = 112) and lesions.

Men, n (%)	100 (89 %)
Age, mean ± SD, years	67 ± 7.5
Clinical stage of esophageal cancer, n (%)	
I	42 (38 %)
II	26 (23 %)
III	32 (29 %)
IV	12 (11 %)
Esophageal cancer	
Current	80 (71 %)
Previous	32 (29 %)
History of cancer in other organs, n (%)	
None	100 (89 %)
Stomach	7 (6 %)
Lung	2 (2 %)
Liver	1 (1 %)
Bladder	1 (1 %)
Leukemia	1 (1 %)
Habitual alcohol use, n (%)	
Yes	101 (90 %)
No	11 (10 %)
Smoking, n (%)	
Yes	98 (88 %)
No	14 (13 %)
Multiple Lugol-voiding lesions, n (%)	
Yes	38 (34 %)
No	74 (66 %)

the other patients have remained disease-free without severe complications.

Resections. Regarding the 8 resected superficial SCCHNs, 2 lesions arose in the oral cavity, and 2 in the oropharynx, and these were removed by TSM; the remaining 4, in the hypopharynx, were all removed by EMR.

The average resected tumor size (± SD) was 18 ± 5 mm (range 10–25). No lesion was < 10 mm in diameter, 3 were ≥ 10 to < 20 mm in diameter, and 5 were ≥ 20 to < 30 mm in diameter.

Histologically, 4 of these lesions were high grade intraepithelial neoplasia, and 4 were microinvasive SCC. Two of the microinvasive SCCs were treated by EMR, and the deep resection margins in both patients were free of tumor. Lymphatic or vessel invasion was not found in any resected specimen.

In two patients with hypopharyngeal lesions, laryngeal edema developed during the EMR procedure. This complication was treated by temporary tracheotomy. No patient had bleeding, stenosis, or perforation as a complication of resection. The median follow-up period was 27 months (range, 14–33 months), and, as noted above, 1 of the 8 patients died of recurrent esophageal cancer.

Table 2 Detection rate and location of superficial squamous cell carcinomas in the head and neck region (superficial SCCHN) in 112 patients with a previous or current diagnosis of esophageal cancer.

Detection rate per-patient, % (n/n)	13 % (15/112)
Detected lesions, n	16
Tumor location	
Oral cavity	3 (19 %)
Tongue	2 (13 %)
Hard palate	1 (6 %)
Oropharynx	4 (25 %)
Superior wall	3 (19 %)
Posterior wall	1 (6 %)
Hypopharynx	9 (56 %)
Piriform sinus	5 (31 %)
Postcricoid area	4 (25 %)
Larynx	0 (0 %)

Discussion

Annually, about 50000 cases of SCCHN are newly diagnosed worldwide annually. Tumors of the hypopharynx are particularly problematic because they are usually are diagnosed at an advanced stage and carry a poor prognosis [16–19]. Recent studies have reported that NBI-ME is useful for the detection of superficial SCCHN [2–5]. In patients with esophageal cancer, synchronous and metachronous second primary malignancies most commonly arise in the upper aerodigestive organs, including the head and neck, stomach, and lung [7–9,20–22]. An exceptionally strong association of esophageal cancer with head and neck cancer has been reported [7–9,23,24]. Matsubara et al. reported that the risk of head and neck cancer markedly increases after esophagectomy (relative risk 34.9; 95 %CI 24.3–48.6). The 5-year cumulative risk of developing head and neck cancer was estimated to be 7 % [9]. Consistent with these results, the detection rate of a second head and neck cancer in patients who had previously had esophageal cancer was 9 % (3/32) in our study. These findings suggest that endoscopic screening of the head and neck region by NBI-ME may substantially contribute to the early detection of head and neck cancer in patients with esophageal SCC. In the future, large prospective follow-up studies are needed to establish the optimal interval for surveillance by NBI-ME after treatment for esophageal SCC.

In the esophagus and head and neck region, the development of multiple primary SCCs and widespread epithelial oncogenic alterations, including carcinoma in situ, dysplasia, and hyperkeratosis, have long been a recognized phenomenon [25]. Clinically, Lugol chromoendoscopy can be used to visualize epithelial changes such as multiple LVLs, since dysplastic or hyperkeratotic epithelium does not stain with Lugol iodine solution and appears white or pink, whereas normal epithelium is stained brown

	With superficial SCCHN n = 15	Without superficial SCCHN n = 97	*P* value
Males	15 (100 %)	85 (88 %)	0.36
Older (≥70 years)	3 (20 %)	35 (36 %)	0.26
Current esophageal cancer	12 (80 %)	68 (70 %)	0.55
History of cancer in other organs	3 (20 %)	9 (9 %)	0.2
Habitual alcohol use	15 (100 %)	86 (89 %)	0.35
Smoking	15 (100 %)	83 (86 %)	0.21
Habitual alcohol use with smoking	15 (100 %)	83 (86 %)	0.21
Multiple Lugol-voiding lesions (LVLs)	15 (100 %)	23 (24 %)	< 0.0001

* *P* values were calculated using Fisher's exact test.

Table 3 Comparison of demographic characteristics between those with and those without superficial squamous cell carcinomas in the head and neck region (superficial SCCHN), in 112 patients with a previous or current diagnosis of esophageal cancer.

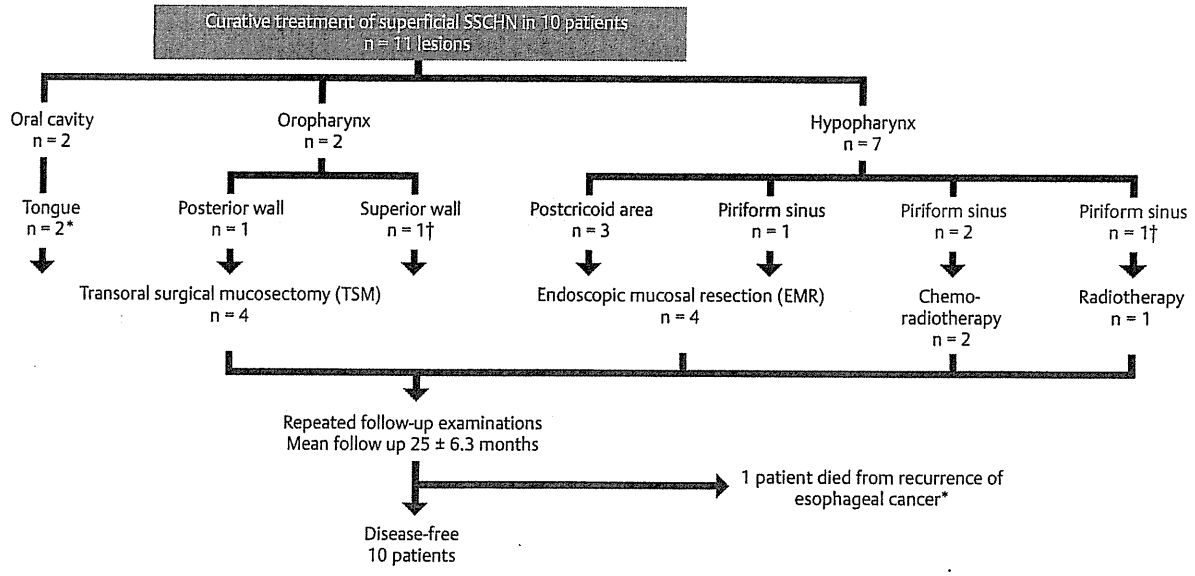

Fig. 4 Clinical course of curative treatment of 11 lesions in 10 patients with superficial squamous cell carcinoma within the head and neck region (superficial SCCHN). * One patient died of recurrent esophageal cancer; † one patient had 2 lesions, 1 each in oropharyngeal and hypopharyngeal mucosal sites.

[11,12]. Multiple LVLs of esophageal mucosa are considered precursors for a second primary esophageal cancer in patients with head and neck cancer [12], and have also been associated with a very high risk of multiple cancers in the esophagus, as well as the head and neck [13,26,27]. In our study, the prevalence of multiple LVLs of esophageal mucosa was significantly increased in patients with superficial SCCHN. The presence of multiple LVLs of esophageal mucosa may therefore be a powerful biomarker for detecting a second primary superficial SCCHN. The Lugol dye staining method cannot be used in the head and neck region because it causes severe mucosal irritation, leading to pain and discomfort; the dye solution may even be aspirated into the airway. Therefore, patients with esophageal cancer who have multiple LVLs of the esophageal mucosa should undergo careful endoscopic screening of the head and neck by NBI-ME.

Effective treatment of superficial SCCHN is considered essential for cure in patients with esophageal SCC, but definitive studies are lacking. The safety and efficacy of follow-up treatment for superficial SCC thus remains unclear. In our series, curative treatment of superficial SCCHN was possible without severe complications in all patients in whom the esophageal SCC was successfully treated. Although 2 of 4 patients (50%) had laryngeal edema during the EMR procedure, which was treated by temporary tracheotomy, the incidence of laryngeal edema can be lowered by minimizing mechanical stimulation caused by contact with surgical devices and chemical stimulation caused by Lugol dye solution on the laryngeal and hypopharyngeal regions at the time of treatment. All patients who underwent curative treatment remained disease-free and retained their larynx. Our results suggest that minimally invasive curative treatment with organ preservation is possible in patients with superficial SCCHN. Since EMR or TSM of head and neck region is less invasive than chemoradiotherapy or radiotherapy, expected benefits should be weighed against potential risks when selecting the treatment strategy. If superficial SCCHN is detected in patients with esophageal SCC, our results may suggest important clues for disease management. In the future, more definitive studies are needed to clarify the safety and efficacy of follow-up treatment for superficial SCCHN.

In conclusion, our results suggest that endoscopic screening by NBI-ME is useful for the detection of superficial SCCHN in patients with esophageal SCC. In particular, patients with multiple LVLs of the esophageal mucosa should be closely monitored to facilitate early detection of superficial SCCHN and permit minimally invasive curative treatment with organ preservation.

Competing interests: None

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Usefulness of Narrow-band Imaging for Detecting the Primary Tumor Site in Patients with Primary Unknown Cervical Lymph Node Metastasis

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Objective: We sometimes experienced patients with primary unknown cervical lymph node metastasis. In such cases, if computed tomography, magnetic resonance imaging, laryngoscopy and gastrointestinal endoscopy cannot detect a primary site, there is no other effective method to identify a possible primary tumor. We investigated whether narrow-band imaging can detect a possible primary tumor in such.

Methods: Forty-six patients with primary unknown cervical lymph node metastasis were surveyed about primary tumors, from January 2003 to December 2006. All cervical lymph nodes were histologically proved to be squamous cell carcinoma by fine-needle aspiration cytology. Narrow-band imaging combined with magnifying endoscopy was used to identify the primary site in the head and neck region and cervical esophagus. Histological analysis was performed for all suspicious lesions by a biopsy specimen.

Results: Twenty-six lesions were suspected to be cancerous lesions by narrow-band imaging in the head and neck region. Sixteen lesions in 16 (35%, 16/46) patients were squamous cell carcinoma. Ten lesions were located in the hypopharynx and the remaining six lesions were located in the oropharynx. White light endoscopy could not point out any lesion.

Conclusions: Narrow-band imaging endoscopy can detect possible primary cancer in patients with primary unknown cervical lymph node metastasis.

Key words: NBI – pharynx – primary unknown cancer – neck lymph node metastasis

INTRODUCTION

In the head and neck region, we sometimes treat patients with cervical lymph node metastasis where a primary tumor cannot be identified by laryngoscopy, computed tomography (CT) and magnetic resonance imaging (MRI). Primary unknown cervical lymph node metastasis (PUCLNM) is reported in 2–9% of metastases in the head and neck region. Additional work-up including upper gastrointestinal endoscopy can detect possible primary lesions in about 10% of the patients, but the possible primary site is not identified in 90% of the patients with PUCLNM.

The inability to find the primary tumor makes it difficult to decide on the most appropriate treatment for the patient, and the clinician must consider different options for the initial treatment. In some cases, the primary tumor is detected during treatment for the lymph node metastasis, but the primary site remains unidentified in some. In cases where the primary tumor is detected after the start of

treatment, it is impossible to switch the treatment. Thus, to stage and evaluate the treatment strategy, the clinician should be able to detect the primary site before starting treatment.

To find a primary lesion, blind biopsy (1–3) or tonsillectomy (4) is sometimes used in patients with PUCLNM. However, these surveillance methods do not always detect the primary lesion. In the case of PUCLNM, whole-neck irradiation will be indicated after cervical lymph node excision because we cannot pinpoint the primary cancer-based treatment strategy (5–7). Whole-neck irradiation causes adverse events such as salivary gland disorder, severe mucositis and taste disorder. In addition, if primary cancer could be detected after irradiation, re-irradiation would not be needed; this is important because surgery after irradiation increases the risk of leakage of the anastomosis.

Muto et al. (8,9) reported that narrow-band imaging (NBI) can detect superficial cancer in the oropharynx and hypopharynx. Although NBI is expected to help identify the primary lesion in patients with PUCLNM, there are no reports on this issue. We surveyed primary lesions in such patients using NBI endoscopy of the gastrointestinal tract.

PATIENTS AND METHODS

From January 2003 to December 2006, 46 consecutive patients with PUCLNM were surveyed about the primary site using a gastrointestinal NBI endoscope in National Cancer Center Hospital East, Chiba, Japan. Written informed consent for the examination was obtained from all patients.

The definition of PUCLNM was in accordance with the report by Greenberg (10) as follows.

- It is proven to have malignant cells histologically.
- We cannot identify a primary tumor using ocular inspection or pharyngolarynx fiberoscopy.
- We cannot identify a primary tumor by CT or MRI.
- Other organs except the head and neck do not show a carcinoma.

In all patients, the possible primary tumor could not be detected by examination using CT, MRI, pharyngolaryngoscopy and standard white-light gastrointestinal endoscopy.

We used a magnifying videoendoscope (Q240Z, Olympus Medical Systems, Tokyo, Japan) and sequential RGB light source with NBI function (CLV-Q260SL, Olympus Medical Systems). The magnifying endoscope had a capability of $\times 80$ optical magnification. The NBI system has been described in detail in previous studies (8,9). In this system, the central wavelengths of NBI were 415 and 540 nm, and each had a bandwidth of 30 nm.

During the survey of the primary site in the head and neck region including the cervical esophagus, if the lesions showed both a well-demarcated brownish area and an irregular microvascular pattern (11), we diagnosed cancer. After this examination, we took a biopsy specimen to confirm the histological diagnosis.

RESULTS

The patients' characteristics are shown in Table 1. Thirty-eight patients were men and eight were women. Their median age was 66 years (range, 38–81 years). Twenty-eight cases were N2 and 18 cases were N3. Thirty-one patients had metastatic lymph nodes in the upper jugular area (Level II), 13 had middle jugular lymph node metastasis (Level III) and 2 had lower jugular lymph node metastasis (Level IV).

Twenty-six lesions were suspected to be the cancerous site in 25 patients. Sixteen lesions in 16 patients were confirmed histologically as squamous cell carcinoma. Histological assessment of all of the possible primary lesions showed the similar feature of squamous cell carcinoma. Thus, primary cancer in the head and neck region was detected in 16 patients (35%) by NBI endoscopy. The patients' characteristics are shown in Table 2. Ten patients had metastatic lymph nodes in the upper jugular area, five had middle jugular lymph node metastasis and one had lower jugular lymph node metastasis. Nine cases were N3 and seven cases were N2. All of the lesions detected were superficial neoplasia. Ten lesions were located in the hypopharynx and the remaining six lesions were located in the oropharynx (three were tonsil). All lesions were T1 stage or Tis, and all lesions were <2 cm in size. Biopsy specimens revealed that one lesion was intraepithelial cancer and the other had invaded to the subepithelial layer.

Table 1. Patient characteristics

	Patients
Age (years)	66 (38–81)
Gender	
Male	38
Female	8
N stage	
N2a	4
N2b	20
N2c	4
N3	18
Levels of cervical metastasis	
Upper jugular (II)	31
Middle jugular (III)	13
Lower jugular (IV)	2

Thirty-eight patients were males and eight were females. Median age was 65 years (range, 38–81 years). Twenty-eight cases were N2 and 18 cases were N3. Thirty-one patients had metastatic lymph node in the upper jugular area (Level II), 15 had middle jugular lymph node metastasis (Level III) and 2 cases had lower jugular lymph node metastasis (Level IV).

Table 2. Characteristics of possible primary lesions detected by NBI

	Primary	Endoscopic findings	*n* (levels)	Treatment
1	Oropharynx	Superficial	3 (II)	CRT
2	Oropharynx	T1	3 (II)	CRT
3	Hypopharynx	Superficial	3 (II)	RT
4	Oropharynx	Superficial	3 (III)	CRT
5	Hypopharynx	Superficial	3 (II)	CRT
6	Hypopharynx	Superficial	3 (II)	EMR + ND
7	Hypopharynx	Superficial	3 (II)	CRT
8	Hypopharynx	Superficial	3 (II)	Surgery + ND
9	Oropharynx	Superficial	2b (III)	Surgery + ND
10	Oropharynx	T1	2a (II)	Surgery + ND
11	Hypopharynx	Superficial	2b (IV)	Surgery + ND
12	Hypopharynx	T1	2a (II)	Surgery + ND
13	Hypopharynx	Superficial	2b (II)	EMR + ND
14	Hypopharynx	Superficial	3 (III)	RT
15	Oropharynx	Superficial	2c (II)	Surgery + ND
16	Hypopharynx	Superficial	2b (III)	EMR + ND

Nine cases were N3 and seven cases were N2. Five cases were treated by concurrent chemoradiation therapy and in nine cases, primary site was removed by surgery or endoscopic resection and they underwent neck dissection for lymph node metastasis. NBI, narrow-band imaging; CRT, chemoradiation therapy; EMR, endoscopic mucosal resection; ND, neck dissection.

Five patients were treated by concurrent chemoradiation therapy (CRT). Two patients were treated with a chemotherapy regimen comprising 5-fluorouracil (800 mg/m^2, days 1–5) and cisplatin (80 mg/m^2, day 1). Two patients were treated with tegafur-gimeracil-oteracil potassium (60 mg/m^2, days 1–14) and cisplatin (20 mg/m^2, day 1). One patient was treated with cisplatin (80 mg/m^2, day 1). The irradiation field covered the whole neck, and the total radiation dose was 70 Gy (2 Gy/fr). Two patients were treated by radiation therapy (total 70 Gy) alone. For the other nine patients, the primary site was removed by surgery or endoscopic resection, followed by neck dissection of the lymph node metastasis. No patient received whole-neck irradiation after neck dissection.

Treatment of the 20 patients who cannot detect cancer lesion were CRT (for N3 or N2b), and neck dissection and close follow-up with NBI endoscopy (for N2a or N2b).

Figure 1 shows a representative case where the primary cancer was detected by NBI. This patient had a swollen lymph node (2.5 cm in size) on the left side of the upper jugular area (Level II) (Fig. 1). The specimen taken using a fine-needle aspiration method from the swollen lymph node revealed squamous cell carcinoma, which was confirmed later as metastatic. CT scan, MRI, laryngoscopy and standard gastrointestinal endoscopy could not detect any primary site. NBI detected easily a well-demarcated brownish area in the uvula to the right anterior palatine arch (Fig. 2B). In contrast, the conventional white-light image made it difficult to visualize the cancerous lesion (Fig. 2A). Magnifying the observation with NBI revealed easily an irregular microvascular pattern inside the lesion (Fig. 2D), but magnifying the observation with white light made it difficult to see this irregular microvascular pattern (Fig. 2C). We diagnosed cancer for this lesion. The biopsy specimen revealed squamous cell carcinoma, which was similar histologically to that of the metastatic lymph node. Treatment of this patient involved neck dissection and resection for primary disease, and we were able to avoid irradiation of the whole neck.

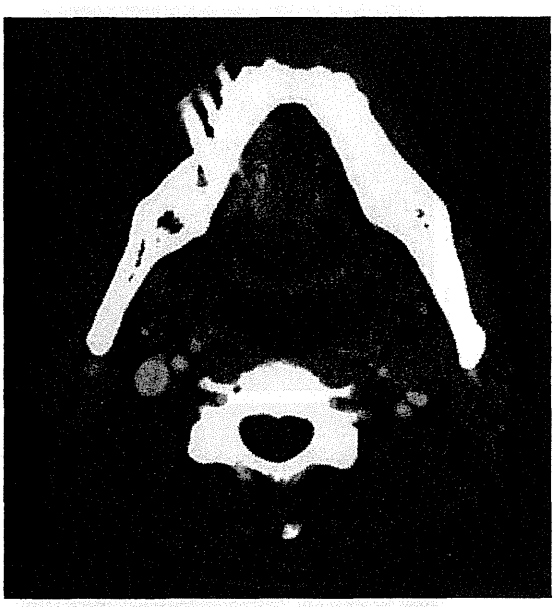

Figure 1. Computed tomographic scan shows lymph node metastasis at left upper jugular area.

DISCUSSION

We report for the first time that NBI endoscopy can detect possible primary cancer in patients with PUCLNM. Information about the primary site is very important for deciding on the appropriate treatment because the treatment strategy may differ for each primary site. Our data indicate that NBI can be helpful to the clinician when deciding on the treatment.

According to Greenberg (10), primary unknown carcinoma is defined when primary tumor cannot be detected by an autopsy. However, this definition cannot be applied in clinical decision-making. We defined a PUCLNM as one for which we could not detect any primary site by CT, MRI, laryngoscopy and gastrointestinal endoscopy (11). Although recent advance in technologies of CT, MRI and PET makes it possible to detect a small lesion precisely, the primary cancer is detected in only 2–9% of the patients with PUCLNM (1,2,12,13). Positron emission tomography (PET) or CT is also useful to detect occult cancer, but this primary site is too small to point out with PET. Random biopsy in the head and

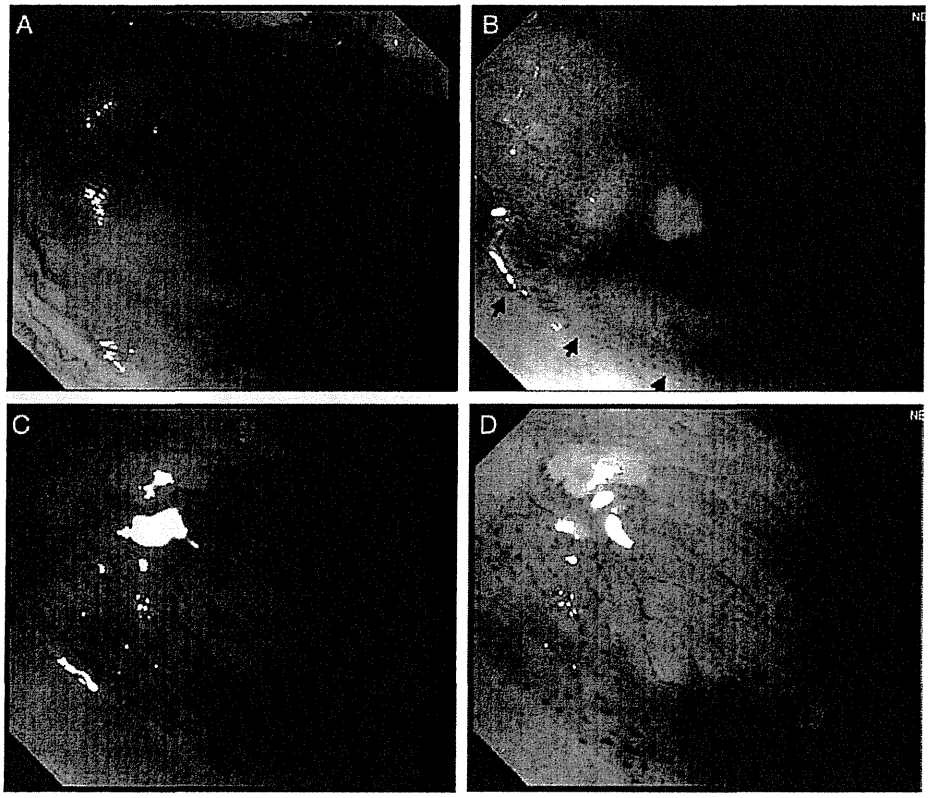

Figure 2. (A–D) Endoscopic findings. Conventional white-light image (A), narrow-band imaging (NBI) image (B), magnifying conventional white-light image (C) and magnifying the NBI images (D). NBI detected a well-demarcated brownish area in the uvula to right anterior palatine arch (B). In contrast, conventional white-light image was difficult to visualize the cancerous lesion (A). Magnifying the observation with NBI revealed an irregular microvascular pattern inside the lesion (D).

neck region may be useful for detecting possible primary cancer in patients with PUCLNM, but the detection rate is only around 10% (1,2). However, tonsillectomy is very useful to detect the primary cancer but tonsillectomy can detect only tonsil cancer. Because only 3 of 16 cases have a cancerous lesion on tonsil in this study, NBI endoscopy was better than tonsillectomy to detect occult tumor.

In the esophagus, Lugol chromoendoscopy is useful for detecting superficial squamous cell carcinoma. However, Lugol's solution cannot be applied in the head and neck region because of the risk of aspiration into the airway. NBI is now recognized as a useful and safe method for detecting superficial squamous cell carcinoma in the head and neck region because it uses no solution and improves the visibility. Muto et al. (8,9,16) reported that both a well-demarcated brownish area and an irregular microvascular pattern are typical characteristics of the superficial squamous cell carcinoma in the head and neck region. In this study, we evaluated the lesion according to these two endoscopic characteristics, and we were able to confirm 64% (16/25) of the lesions in the suspicious cancerous area as squamous cell carcinoma. This positive rate is better than that from a random biopsy (~10%). Finally, possible primary cancer could be detected in 35% (16/46) of the patients. These results indicate that NBI should be applied when surveying the primary site in patients with PUCLNM. Moreover, it is not impossible to detect cancerous lesion only using white-light endoscopy by trained endoscopist but NBI endoscopy is very easy for beginners to detect lesion.

Nine of 16 patients underwent surgery or endoscopic resection of the primary site and subsequent lymph node dissection. In such cases, post-operative whole-neck radiation is one treatment option (13–15). However, the indications for post-operative radiation therapy for PUCLNM are still controversial because these patients are at high risk for developing metachronous multiple cancers in the head and neck region (16). If they received radiation therapy as a post-operative radiation therapy, there is no radiotherapy treatment option for the later appearance of a metachronously developed second primary cancer in the head and neck region (14–16). The clinician must thus plan the post-operative radiation therapy carefully.

We cannot conclude with certainty whether the lesions detected by NBI were the true primary sites unless we identify their clonality. As a next step, we will compare the clonality of both primary sites and metastatic lymph nodes. In this study, at least, histological assessment showed the same histological features of the primary site and metastatic lymph

node. Clinically, histological accordance would be enough to consider whether the lesion is primary.

Although we could not evaluate the depth of invasion in all patients, we know that micro-invasive cancer can metastasize to the lymph node. The risk of lymph node metastasis of superficial squamous cell carcinoma is unknown, but collection of data from a large number of cases should help clarify this.

In conclusion, our data indicate that NBI has the potential to identify primary cancer in patients with PUCLNM. Identification of the primary site provides helpful information for deciding on the treatment strategy.

Conflict of interest statement

None declared.

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