10 *Hamilton SR, Aaltonen LA.* World Health Organization classification of tumors. Pathology and genetics of tumors of the digestive system. Lyon: IARC Press, 2000: 9–30
11 *Inoue H, Rey JF, Lightdale C.* Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 2001; 33: 75–79
12 *Muto M, Hironaka S, Nakane M et al.* Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002; 56: 517–521
13 *Muto M, Takahashi M, Ohtsu A et al.* Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 2005; 26: 1008–1012
14 *Inoue H, Endo M, Takeshita K et al.* A new simplified technique of endoscopic mucosal resection using a capfitted panendoscope (EMRC). Surg Endosc 1992; 6: 264–265
15 *Ohtsu A, Yoshida S, Boku N et al.* Concurrent chemotherapy and radiation therapy for locally advanced carcinoma of the esophagus. Jpn J Clin Oncol 1995; 25: 261–266
16 *Kraus DH, Zelefsky MJ, Brock HA et al.* Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. Otolaryngol Head Neck Surg 1997; 116: 637–641
17 *Wahlberg PC, Andersson KE, Biorklund AT et al.* Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck 1998; 20: 714–719
18 *Johansen LV, Grau C, Overgaard J.* Hypopharyngeal squamous cell carcinoma – treatment results in 138 consecutively admitted patients. Acta Oncol 2000; 39: 529–536
19 *Eckel HE, Staar S, Volling P et al.* Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. Otolaryngol Head Neck Surg 2001; 124: 561–569
20 *Poon RTP, Law SYK, Chu KM et al.* Multiple primary cancers in esophageal squamous cell carcinoma: Incidence and implications. Ann Thorac Surg 1998; 65: 1529–1534
21 *Hoar SK, Wilson J, Blot WJ et al.* Second cancer following cancer of the digestive system in Connecticut, 1935–82. Natl Cancer Inst Monogr 1985; 68: 49–82
22 *Fogel TD, Harrison LB, Son YH.* Subsequent upper aerodigestive malignancies following treatment of esophageal cancer. Cancer 1985; 55: 1882–1885
23 *Petit T, Georges C, Jung GM et al.* Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. Ann Oncol 2001; 12: 643–646
24 *Dubuc J, Legoux JL, Winnock M et al.* Endoscopic screening for esophageal squamous-cell carcinoma in high risk patients: a prospective study conducted in 62 French endoscopy centers. Endoscopy 2006; 38: 690–695
25 *Slaughter DP, Southwick HW, Smejkal W.* Field cancerization in oral stratified squamous epithelium: clinical implications of multicentric origin. Cancer 1953; 6: 963–968
26 *Shimizu Y, Tsukagoshi H, Fujita M et al.* Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy 2003; 35: 322–626
27 *Urabe Y, Hiyama T, Tanaka S et al.* Metachronous multiple esophageal squamous cell carcinomas and Lugol-voiding lesions after endoscopic mucosal resection. Endoscopy 2009; 41: 304–309

Published Ahead of Print on February 22, 2010 as 10.1200/JCO.2009.25.4680
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.25.4680

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial

Manabu Muto, Keiko Minashi, Tomonori Yano, Yutaka Saito, Ichiro Oda, Satoru Nonaka, Tai Omori, Hitoshi Sugiura, Kenichi Goda, Mitsuru Kaise, Haruhiro Inoue, Hideki Ishikawa, Atsushi Ochiai, Tadakazu Shimoda, Hidenobu Watanabe, Hisao Tajiri, and Daizo Saito

From the Department of Gastroenterology and Hepatology, Kyoto University, Kyoto; Divisions of Gastrointestinal Oncology/Endoscopy and Pathology, National Cancer Center Hospital East, Kashiwa; Divisions of Endoscopy and Pathology, National Cancer Center Hospital; Department of Gastroenterology and Hepatology, Tokyo Jikei University, Tokyo; Department of Surgery, Kawasaki City Municipal Hospital, Kawasaki; Department of Surgery, Showa University Yokohama Northern Hospital, Yokohama; Department of Hygiene and Public Health, Kyoto Prefectural Medical University, Kyoto; and Department of Pathology, Niigata University, Niigata, Japan.

Submitted August 5, 2009; accepted December 3, 2009; published online ahead of print at www.jco.org on February 22, 2010.

Supported in part by Grant No. H15-008 from the Ministry of Health, Labor, and Welfare of Japan.

Presented in part at Digestive Disease Week, May 20-23, 2007, Washington, DC.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Manabu Muto, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507 Japan; e-mail: mmuto@kuhp.kyoto-u.ac.jp

0732-183X/10/2899-1/$20.00

DOI: 10.1200/JCO.2009.25.4680

ABSTRACT

Purpose
Most of the esophageal squamous cell carcinomas (ESCCs) and cancers of the head and neck (H&N) region are diagnosed at later stages. To achieve better survival, early detection is necessary. We compared the real-time diagnostic yield of superficial cancer in these regions between conventional white light imaging (WLI) and narrow band imaging (NBI) in high-risk patients.

Patients and Methods
In a multicenter, prospective, randomized controlled trial, 320 patients with ESCC were randomly assigned to primary WLI followed by NBI (n = 162) or primary NBI followed by WLI (n = 158) in a back-to-back fashion. The primary aim was to compare the real-time detection rates of superficial cancer in the H&N region and the esophagus between WLI and NBI. The secondary aim was to evaluate the diagnostic accuracy of these techniques.

Results
NBI detected superficial cancer more frequently than did WLI in both the H&N region and the esophagus (100% *v* 8%, $P < .001$; 97% *v* 55%, $P < .001$, respectively). The sensitivity of NBI for diagnosis of superficial cancer was 100% and 97.2% in the H&N region and the esophagus, respectively. The accuracy of NBI for diagnosis of superficial cancer was 86.7% and 88.9% in these regions, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both regions ($P < .001$ and $P = .02$ for the H&N region; $P < .001$ for both measures for the esophagus, respectively).

Conclusion
NBI could be the standard examination for the early detection of superficial cancer in the H&N region and the esophagus.

J Clin Oncol 28. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, accounting for 462,000 new cases in 2002, and is the sixth most common cause of cancer-related death (386,000 deaths).[1] Squamous cell carcinoma (SCC) is the most common histologic type worldwide.[1] Head and neck (H&N) cancer accounted for 607,000 new cases and 261,000 deaths in 2002.[1] The most common histologic type of H&N cancer is also SCC.

The early detection of cancer offers the best prognosis. Currently, however, esophageal SCC (ESCC) and H&N SCC (HNSCC) are detected at a late stage and then have poor prognoses.[1] Early detection of these cancers is difficult by conventional endoscopic white light imaging (WLI). Lugol chromoendoscopy can be used to detect superficial ESCC, but it causes unpleasant adverse effects such as severe chest pain and chest discomfort,[2-4] and it cannot be used for HNSCC screening because of the risk of aspiration.

The narrow band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow bandwidth NBI filters.[5,6] The central wavelengths of the NBI filters are 415 and 540 nm and each has a bandwidth of 30 nm. This system is easily activated by pushing a button on the endoscope. NBI combined with magnifying endoscopy can clearly visualize the microvascular structure of the organ surface,[6,7] because the 415-nm light is well absorbed by hemoglobin. Surface microvascular irregularities provide useful landmarks for identifying an early neoplasm in the H&N region, bronchus,

and the GI tract.[7-15] We previously reported that NBI was useful for identifying HNSCC at an early stage.[8] Watanabe et al[16,17] also reported the usefulness of NBI rhinolaryngovideoscopy for the diagnosis of HNSCC. Yoshida et al[18] reported that NBI improves the accuracy of magnifying WLI in the assessment of ESCC.

However, the diagnostic yield of NBI in the early detection of superficial SCC has not been investigated. We conducted a prospective randomized study to directly compare WLI and NBI in the early diagnosis of SCC in the H&N region and the esophagus among high-risk patients.

PATIENTS AND METHODS

Study Rationale

Because ESCC patients frequently develop multiple intraesophageal SCC and second primary HNSCC synchronously and metachronously,[4,19-22] they provide a good cancer screening model. Whereas massively invasive SCC is easy to detect by endoscope, superficial cancer has been difficult. Furthermore, detection of high-grade intraepithelial neoplasia (HGIN) is clinically important because HGINs have the potential to become malignant invasive cancers.[23,24] Therefore, in this study, we targeted only macroscopic superficial cancer including HGIN that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression. Lesions with an apparent elevation greater than 5 mm or those with apparent deeper ulceration were not evaluated.

The primary analysis of this study was a comparison of the detection rates of superficial cancer (HGIN, carcinoma in situ, and microinvasive SCC) using WLI and NBI. The secondary analysis was a comparison of the diagnostic accuracy (sensitivity and specificity) of the two imaging methods, size of the lesion detected, and the examination time. To evaluate diagnostic accuracy, we used the histologic diagnosis from a biopsy specimen as the gold standard diagnosis.

Study Populations

The protocol and consent form for this study were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients. The inclusion criteria were histologically confirmed present or previous ESCC and an age of 20 years or older. Although this study included patients with advanced ESCC, we evaluated only concomitant superficial cancer but not primary advanced cancer. Patients who had been previously treated for ESCC by endoscopic mucosal resection were included, because their esophagus was preserved with minimal damage. Patients with prior chemotherapy, radiotherapy, chemoradiotherapy, or surgical resection for ESCC or HNSCC were excluded, because their esophagus or pharynx was removed or too damaged to evaluate. Patients referred from another hospital with newly diagnosed ESCC were also included because they required more detailed examination (Fig 1). The endoscopists were blinded to the endoscopic information. Patients with esophageal stricture, esophageal varices, or allergy to lugol dye solution were excluded.

Study Design

Patients were randomly assigned to receive primary WLI or primary NBI. To investigate whether a lesion detected by primary imaging could be identified subsequently by the other type of imaging, or whether a lesion missed by primary imaging could be identified subsequently by the other type of imaging, we performed both imaging methods in a back-to-back fashion so that primary WLI was followed by NBI and primary NBI was followed by WLI. To avoid affecting the first imaging results, the report of the first examination was completed before the second imaging was started.

To improve the quality of the reporting in the diagnostic accuracy study, we complied with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[25] We set WLI as reference standard and NBI as index test.

Random assignment was performed in each case by an investigator using a computer-aided system on Medical Research Support Web site (Kyoto, Japan). This Web site was available only to the study participants. Using a minimization algorithm, the selection of the primary examination was balanced with respect to five stratification variables: institution, age (< 60 and ≥ 60 years), sex, alcohol consumption, and smoking habit.

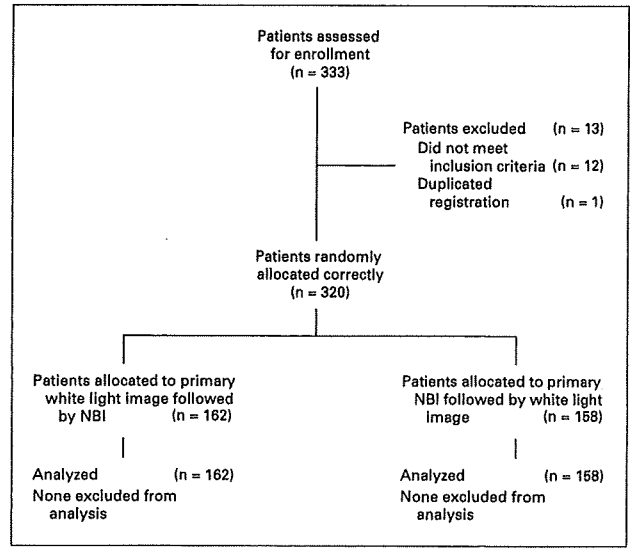

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

Calculation of the Sample Size

For the purposes of this study, we set the probability for error (α) to .05 with a power of 0.80 (reflecting a β error of .2). Because there are no published comparative studies of NBI in ESCC patients, we estimated that the NBI system would increase the detection yield for superficial cancer by at least threefold compared with conventional WLI. This resulted in a calculated sample size of 250 patients (125 per group). Finally, we recruited an additional 50 patients in anticipation of instances of ineligibility or withdrawal during the examination because of discomfort (25 per group).

Endoscopic Examination

We used the same magnifying endoscope, with the capability for 80 times optical magnification (GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) for both WLI and NBI. The two imaging methods can be performed in a same video-endoscopy system (EVIS LUCERA system, Olympus Medical Systems, Tokyo, Japan). The details of the NBI system have been published elsewhere.[1,2,26,27] To maintain the quality of the endoscopic images, we used the same liquid-crystal color display for both imaging methods. Before the study started, all the participating endoscopists were trained using a central review of demonstrable NBI images of superficial squamous lesions (13 neoplasias and seven non-neoplastic lesions).

All endoscopic observations were made according to the protocol. During the first imaging, all parts of the oropharynx and hypopharynx were evaluated. The nasopharynx was not included the examination. After the first imaging was completed, an assistant physician immediately recorded the results on the case record form (CRF). After completion of the first imaging CRF, the second imaging of the oropharynx and hypopharynx was performed and the results were recorded on the CRF.

Next, all parts of the esophagus were evaluated using the same imaging as used for the H&N region. The endoscope was inserted to gain a view from the cervical esophagus to the esophagogastric junction, and the results were recorded on the CRF. The second imaging was performed on withdrawal of the endoscope, and the results were recorded on the CRF. During the procedure, we measured the examination time from start to finish of each imaging at each site. These procedure times included the evaluation of the lesion but not the biopsy procedure. The findings obtained by lugol chromoendoscopy are not included in this study.

Endoscopic Evaluation of Superficial Cancers

In this study, the real-time on-site diagnosis was evaluated because making an accurate diagnosis during an examination is clinically more important than a retrospective evaluation using a stored database. On WLI, if the lesion showed both a reddish color with uneven surface and disappearance of the vascular network pattern (Fig 2A), we diagnosed it as endoscopically suspected "superficial cancer." On NBI, if the lesion exhibited a well-demarcated brownish area as well as irregular microvascular patterns (Fig 2B), we diagnosed it as endoscopically suspected "superficial cancer." Details of these findings have been described previously.[7,8] If the lesion did not show these characteristics, the lesion was diagnosed as "non-cancer." Mucosal abnormalities were recorded with regard to endoscopic diagnosis, location, and size of the lesion.

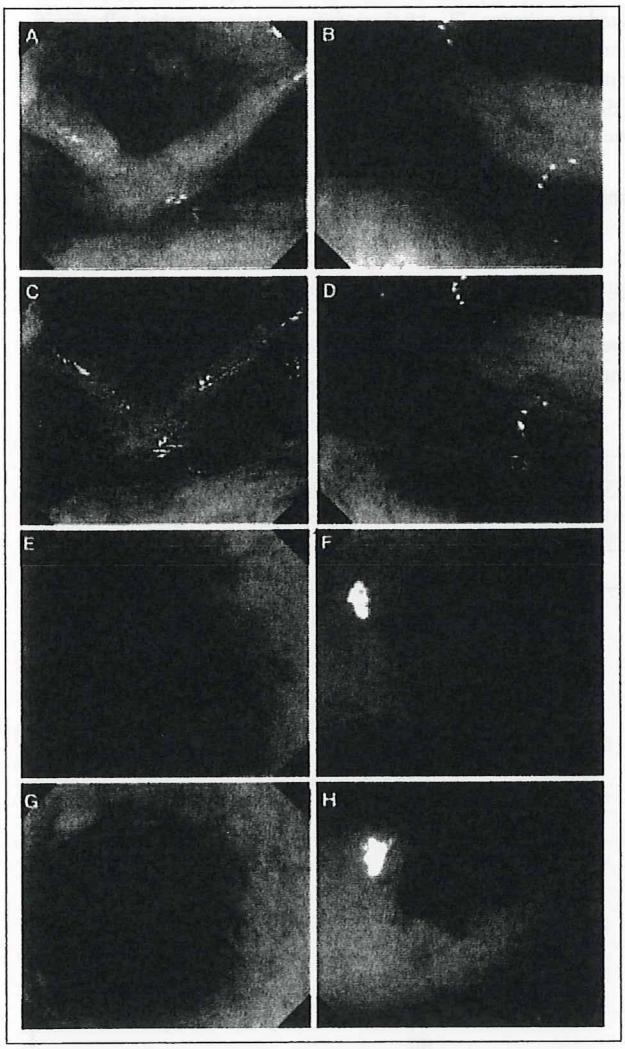

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated brownish area (arrows) in the posterior wall of the hypopharynx. (D) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as squamous cell carcinoma in situ. (E) WLI shows a slightly reddish and depressed lesion (arrows) in the esophagus, although it is difficult to detect by WLI alone. (F) Magnifying WLI shows a slightly reddish area with an irregular microvascular pattern. (G) NBI shows a well-demarcated brownish area (arrows). (H) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as high-grade intraepithelial cancer.

Pathologic Evaluation

Biopsy specimens were taken from each lesion after the completion of both types of imaging. Histologic evaluation was performed by central review by four experienced pathologists (H.S., A.O., T.S., and H.W.) who were blinded to the recorded endoscopic assessment. Histologic diagnoses were made according to WHO criteria[23] and were classified into two groups. One group included superficial cancers and the other group included non-cancers such as parakeratosis and inflammation. Microinvasion was estimated by the subepithelial invasion. The final pathologic diagnosis was made by the agreement of three of the four pathologists.

Statistical Analysis

The absolute and relative frequencies for qualitative variables were calculated for each group. Statistical analysis was performed using SPSS version

Table 1. Characteristics of Patients

Characteristic	Primary WLI (n = 162) No.	%	Primary NBI (n = 158) No.	%	P
Age, years					
Median	64		64		
Range	39-84		46-84		.99
Male sex	143	88	141	89	.86
Alcohol habit					
Drinking duration, years	157	97	148	94	.19
Median	41		40		.17
Range	10-63		5-60		
Favorite beverage					
Beer	61	38	59	37	1.00
Shochu	66	41	55	35	.30
Sake	43	27	48	30	.71
Whisky	22	14	24	15	.75
Wine	8	5	7	4	1.00
Others	1	0.6	0	0	1.00
Hot flashes					
Formerly had hot flashes	117	72	109	69	.62
Currently has hot flashes	75	46	70	44	.91
Smoking habit					
No. of smokers	145	90	142	90	1.00
Smoking duration, years					
Median	37		40		
Range	1-61		5-61		.41
No. of packs per day					
Median	1		1		
Range	0.05-4		0.125-4		.64
No. of packs per year					
Median	41		42		
Range	0.5-180		1.3-160		.89
Esophageal cancer					
No. of patients newly diagnosed	110	68	115	73	.39
Previously treated EMR	52	32	43	27	.39
Duration from previous EMR, years					
> 1	17	10	20	13	.60
1	45	28	33	21	.16
Depth of invasion					
Tis-T1a	74	46	67	42	.57
T1b	25	15	20	13	.27
T2	12	7	22	14	.07
T3	49	30	46	29	.90
T4	2	1	3	2	.68

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

17 software (SPSS, Chicago, IL). The continuous variables are expressed as medians and ranges. Continuous data were compared using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to analyze categoric data to compare proportions. All P values were two-tailed, and a P value of $< .05$ was considered significant.

RESULTS

Between March 2005 and December 2005, 333 patients were enrolled onto this study (Fig 1). Twelve patients did not meet the inclusion criteria, and one was registered twice, so the remaining 320 patients were randomly assigned correctly into two groups: (1) 162 patients who underwent primary WLI followed by NBI, and (2) 158 patients who were examined by primary NBI followed by WLI.

The characteristics of the two groups are listed in Table 1. The two groups did not differ significantly in age, sex, alcohol consumption, smoking habits, or history of esophageal cancer treatment. In both groups, approximately 70% of the patients had newly diagnosed ESCC. Sixty-three (39%) patients in the primary WLI group and 71 (45%) patients in the primary NBI group had advanced ESCC deeper than the submucosal layer.

Table 2 provides the distribution of histologically confirmed superficial cancers. The total numbers of superficial cancer in the H&N region and the esophagus were 28 and 212, respectively. Total numbers of histologically confirmed non-cancer were 36 and 38 in each region. In all patients, superficial cancers were detected in 8% (26 of 320) in the H&N region and in 38% (121 of 320) in the esophagus. Multiple cancers were found in 0.6% of the patients in the H&N region and in 12% in the esophagus. The number of patients with superficial cancer, total number of superficial cancers, and their sizes and distribution did not differ between the two groups.

The diagnostic yields for superficial cancer using primary WLI and primary NBI detection are summarized in Table 3. The total numbers of superficial cancers detected by primary imaging differed between the two groups. In the H&N region, primary NBI detected all (100%; 15 of 15) of the superficial cancers, but primary WLI detected only one lesion (8%; 1 of 13). In the esophagus, only 58 (55%) lesions were detected by primary WLI, whereas 104 (97%) lesions were detected by primary NBI. All these differences were statistically significant ($P < .001$). The detection rate was significantly higher with primary NBI than with primary WLI, even for small lesions (< 10 mm in diameter) in both the H&N region ($P < .001$) and the esophagus ($P = .03$).

In the back-to-back analysis, secondary NBI after primary WLI significantly increased the detection rate in both the H&N region (8% v 77%; $P < .001$) and esophagus (55% v 95%; $P < .001$; Appendix Table A1, online only). In contrast, secondary WLI after NBI significantly decreased the detection rate (Appendix Table A1). Moreover, 16 (57%) superficial cancers in the H&N region and 48 (23%) superficial cancers in the esophagus were detected only by NBI (Appendix Table A2, online only). In contrast, no lesion was detected only

Table 2. Distribution of Histologically Confirmed Superficial Cancer According to Lesion in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of patients	12	7	3.3 to 11.4	14	9	4.4 to 13.3	.66
No. of lesions per patient							
1	12	7	3.3 to 11.4	14	9	4.4 to 13.3	> .999
≥ 2	1	0.6	−0.6 to 1.8	1	0.6	−0.5 to 1.9	
Total No. of superficial neoplasias	13			15			
Size threshold, mm							
< 10	7			10			.50
11-20	5			5			
≥ 21	1			0			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	10			15			.09
Microinvasive cancer	3			0			
Esophagus							
No. of patients	58	36	28.4 to 43.2	63	40	32.2 to 47.6	.49
No. of lesions per patient							
1	39	24	17.4 to 30.7	43	27	20.3 to 34.2	> .999
≥ 2	19	12	6.7 to 16.7	20	13	7.4 to 17.9	
Total No. of superficial cancers	105			107			
Size threshold, mm							
< 10	18			18			.91
11-20	21			19			
≥ 21	66			70			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	73			84			.16
Microinvasive cancer	32			23			

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table 3. Diagnostic Yield of Primary WLI and Primary NBI for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of superficial cancers	1/13	8	0.2 to 36.0	15/15	100	78.2 to 100	< .001
Size of superficial cancer, mm							
< 10	0/7	0	0 to 41.0	10/10	100	69.2 to 100	< .001
11-20	1/5	20	0.5 to 71.6	5/5	100	48.7 to 100	.12
≥ 21	0/1	0	0.0 to 0.0	to			—
Esophagus							
No. of superficial cancers	58/105	55	45.2 to 65.0	104/107	97	92.0 to 99.4	< .001
Size of superficial cancer, mm							
< 10	7/18	39	17.3 to 64.3	17/18	94	72.7 to 99.9	.03
11-20	7/21	33	14.6 to 57.0	18/19	95	74.0 to 99.9	.02
≥ 21	44/66	67	54.0 to 77.8	69/70	99	92.3 to 100	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

by WLI, except one lesion of > 20 mm in the esophagus. No lesions were undetected by both WLI and NBI in either region.

Table 4 summarizes the diagnostic performance of primary WLI and primary NBI for detecting superficial cancer. The sensitivity of primary NBI was significantly higher than that of primary WLI in both the H&N region (100% *v* 7.7%; $P < .001$) and the esophagus (97.2% *v* 55.2%; $P < .001$). Accuracy was also significantly higher for primary NBI than for primary WLI in both regions (85.7% *v* 62.9%, $P = .02$ and 88.9% *v* 56.5%, $P < .001$, respectively). Specificity was not significantly different in the two regions ($P = .28$ and $P = .33$, respectively). The positive predictive value did not differ between the two imaging techniques, but the negative predictive value was significantly higher for primary NBI than for primary WLI in both the H&N region ($P = .02$) and the esophagus ($P < .002$).

The median procedure times of primary WLI and primary NBI for the H&N region were 120 seconds (range, 34 to 275 seconds) and 162 seconds (range, 30 to 525 seconds), respectively. Those for the esophagus were 95 seconds (range, 30 to 360 seconds) and 135 seconds (range, 30 to 616 seconds), respectively. These differences were statistically significant ($P < .001$). The procedure times in the secondary imaging in the back-to-back experiments also differed significantly between WLI and NBI in both regions (Appendix Table A3, online only). There were no serious adverse events related to examination with either procedure. All patients tolerated both procedures well.

DISCUSSION

This study clearly demonstrates that NBI is a more sensitive method for detecting and diagnosing superficial SCC in the H&N region and the esophagus. According to the concept of "field cancerization,"[28] patients with ESCC or HNSCC are at high risk for the development of multiple SCCs. In the clinical context, the early detection strategy for superficial SCC is the same between patients at high risk and those at risk because of heavy drinking, smoking, or aldehyde dehydrogenase 2 deficiency.[20-35] In addition, detection technique should not only be sensitive but should also be easily applicable. From this perspective, NBI is easily applied with a modicum of experience and will have a rapid learning curve compared with WLI. Thus, NBI is the ideal method for effectively detecting superficial SCC.

Table 4. Diagnostic Performance of Primary WLI and Primary NBI Observation for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI			Primary NBI			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck							
Sensitivity	1/13	7.7	0.2 to 36.0	15/15	100	100	< .001
Specificity	21/22	95.5	77.2 to 99.9	11/14	78.6	54.6 to 98.1	.28
Accuracy	22/35	62.9	47.6 to 76.4	26/29	86.7	72.6 to 97.8	.02
PPV	1/2	50	1.3 to 98.7	15/18	83.3	58.6 to 96.4	.37
NPV	21/33	63.6	54.1 to 79.6	11/11	100	100	.02
Esophagus							
Sensitivity	58/105	55.2	45.2 to 65.0	104/107	97.2	92.0 to 99.4	< .001
Specificity	12/19	63.2	38.4 to 83.7	8/19	42.1	20.3 to 66.5	.33
Accuracy	70/124	56.5	47.3 to 65.3	112/126	88.9	82.1 to 93.8	< .001
PPV	58/65	89.2	79.1 to 95.6	104/115	90.4	85.3 to 95.1	.80
NPV	12/59	20.3	11.0 to 32.8	8/11	72.8	39 to 94	< .002

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; PPV, positive predictive value; NPV, negative predictive value.

Detecting cancer at an early stage is an optimal strategy for preventing the development of advanced cancer and improving survival. Furthermore, early detection uses a minimally invasive treatment (eg, endoscopic resection) with curative intent.[8,36-38] In fact, in our study, 75% (21 of 28) of the superficial HNSCCs were completely removed by endoscopic resection or biopsy alone, while early detection of HNSCC had been quite difficult. These results provide us with new diagnostic and treatment strategies for ESCC patients, because the risk of development of HNSCC after esophagectomy is quite high.[21]

As the criteria for diagnosing superficial SCC by NBI, we used two endoscopic findings: a well-demarcated brownish area and an irregular microvascular pattern.[7-9] Using only these two findings, the sensitivity of primary NBI for the diagnosis of superficial SCC was 100% in the H&N region and 97.2% in the esophagus. The diagnostic accuracy was nearly 90%. These results indicate that these NBI findings are quite useful for the accurate diagnosis of superficial SCC.

Lugol chromoendoscopy is useful for the detection of superficial ESCC.[2-3] However, the administration of lugol solution is time-consuming, and accurate diagnosis by lugol chromoendoscopy is difficult[4] because the staining pattern shows wide variations.[2] This increases the incidence of false-positive lesions and leads to unnecessary biopsies. In contrast, NBI is easily manipulated and shows high sensitivity. Thus, NBI could reduce the number of unnecessary biopsies and shorten examination time. Furthermore, lugol chromoendoscopy is more invasive than both WLI and NBI, and WLI is still the gold standard for cancer screening. Therefore, we did not compare the diagnostic yield of NBI and lugol chromoendoscopy, and we used WLI as the standard reference to compared the diagnostic yield of WLI and NBI.

NBI required a significantly longer examination time than WLI. This might be related to the high detection rate and more frequent time spent in magnification during NBI, because if the lesions were not seen by WLI, no magnification was performed. The actual time difference between NBI and WLI was only 20 to 42 seconds. This is clinically acceptable, because the important time issue is not that NBI takes slightly longer than WLI, but rather that endoscopists spend more time in the careful observation of high-risk patients.

In this study, ESCC patients referred from another hospital were included. Even if the biopsies were previously done, the earlier biopsy sites were healed by the time of this study and were not generally detectable by either imaging method. Therefore, we thought that it was not a confounding factor.

The same endoscopists performed both imaging procedures in this study, whereas the endoscopists ideally should be separated and blinded to each imaging procedure. However, it was clinically impossible to change and blind the endoscopists during this series of examinations. Furthermore, the result produced with NBI first followed by WLI might underestimate the benefit of NBI because NBI is more sensitive than WLI. However, the detection and diagnosis of superficial SCC by NBI was significantly better than that using WLI in both the H&N region and the esophagus, regardless of whether NBI was primary or secondary. These results indicate that NBI should be the standard examination.

Significant detection results seen in this study were all achieved without the newest generation high-definition endoscope. If we use the newest high-definition endoscope with NBI, the rates of detection might increase compared with those found in this study. Furthermore, the endoscopy system used in this study and in most Asian countries was different from those used in North America and Europe.[26,27] However, we previously reported that even the nonmagnifying laryngoscope based on same system as that used in North America and Europe could dramatically improve the visualization of both the brownish area and irregular microvascular patterns.[39] Therefore, we believe that differences in the system are no longer as important as careful observation by NBI.

In conclusion, NBI combined with magnifying endoscopy significantly improved the detection rates for SCC with quite high sensitivity, and this new image-enhanced technology can be applied easily in clinical practice. Furthermore, early detection facilitates the potential of minimally invasive treatment, such as endoscopic resection or partial surgical resection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Manabu Muto, Hideki Ishikawa
Financial support: Daizo Saito
Administrative support: Manabu Muto, Hisao Tajiri, Daizo Saito
Provision of study materials or patients: Manabu Muto, Keiko Minashi, Tomonori Yano, Yutaka Saito, Ichiro Oda, Satoru Nonaka, Tai Omori, Hitoshi Sugiura, Kenichi Goda, Mitsuru Kaise, Haruhiro Inoue, Atsushi Ochiai, Tadakazu Shimoda, Hidenobu Watanabe
Collection and assembly of data: Manabu Muto, Hitoshi Sugiura, Hideki Ishikawa, Atsushi Ochiai, Tadakazu Shimoda, Hidenobu Watanabe
Data analysis and interpretation: Manabu Muto, Hideki Ishikawa
Manuscript writing: Manabu Muto
Final approval of manuscript: Manabu Muto, Keiko Minashi, Tomonori Yano, Yutaka Saito, Ichiro Oda, Satoru Nonaka, Tai Omori, Hitoshi Sugiura, Kenichi Goda, Mitsuru Kaise, Haruhiro Inoue, Atsushi Ochiai, Tadakazu Shimoda, Hidenobu Watanabe, Hisao Tajiri, Daizo Saito

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al: Global cancer statistics, 2002. CA Cancer J Clin 55:74-108, 2005

2. Mori M, Adachi Y, Matsushima T, et al: Lugol staining pattern and histology of esophageal lesions. Am J Gastroenterol 88:701-705, 1993

3. Inoue H, Rey JF, Lightdale C: Lugol chromoendoscopy for esophageal squamous cell cancer. Endoscopy 33:75-79, 2001

4. Muto M, Hironaka S, Nakane M, et al: Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 56:517-521, 2002

5. Gono K, Yamazaki K, Doguchi N, et al: Endoscopic observation of tissue by narrow band illumination. Opt Rev 10:211-215, 2003

6. Gono K, Obi T, Yamaguchi M, et al: Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt 9:568-577, 2004

7. Muto M, Katada C, Sano Y, et al: Narrow band imaging: A new diagnostic approach to visualize angiogenesis in the superficial neoplasia. Clin Gastroenterol Hepatol 3:S16-S20, 2005 (suppl 1)

8. Muto M, Nakane M, Katada C, et al: Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 101:1375-1381, 2004

9. Muto M, Ugumori T, Sano Y, et al: Narrow-band imaging combined with magnified endoscopy for the cancer at the head and neck region. Dig Endoscopy 17:S23-S24, 2005

10. Shibuya K, Hoshino H, Chiyo M, et al: High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer. Thorax 58:989-995, 2003

11. Hamamoto Y, Endo T, Nosho K, et al: Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. J Gastroenterol 39:14-20, 2004

12. Sharma P, Bansal A, Mathur S, et al: The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. Gastrointest Endosc 64:167-175, 2006

13. Nakayoshi T, Tajiri H, Matsuda K, et al: Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: Correlation of vascular pattern with histopathology. Endoscopy 36:1080-1084, 2004

14. Sumiyama K, Kaise M, Nakayoshi T, et al: Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. Gastrointest Endosc 60:79-84, 2004

15. Machida H, Sano Y, Hamamoto Y, et al: Narrow-band imaging in the diagnosis of colorectal lesions: A pilot study. Endoscopy 36:1094-1098, 2004

16. Watanabe A, Tsujie H, Taniguchi M, et al: Laryngoscopic detection of pharyngeal carcinoma in situ with narrowband imaging. Laryngoscope 116: 650-654, 2006

17. Watanabe A, Taniguchi M, Tsujie H, et al: The value of narrow band imaging endoscope for early head and neck cancers. Otolaryngol Head Neck Surg 138:446-451, 2008

18. Yoshida T, Inoue H, Usui S, et al: Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 59:288-295, 2004

19. Shimizu Y, Tukagoshi H, Fujita M, et al: Metachronous squamous cell carcinoma of the esophagus arising after endoscopic mucosal resection. Gastrointest Endosc 54:190-194, 2001

20. Shimizu Y, Tsukagoshi H, Fujita M, et al: Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy 35:322-326, 2003

21. Matsubara T, Yamada K, Kakegawa A: Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:4336-4341, 2003

22. Kumagai Y, Kawano T, Nakajima Y, et al: Multiple primary cancers associated with esophageal carcinoma. Surg Today 31:872-876, 2001

23. Tumors of the esophagus, in Hamilton R, Aaltonen LA, eds. WHO Classification of Tumors of the Digestive System. Lyon, France, IARC Press, 2000, pp 11-19

24. Schlemper RJ, Dawsey SM, Itabashi M, et al: Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. Cancer 88:996-1006, 2000

25. Moher D, Schulz KF, Altman D: The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 285:1987-1991, 2001

26. Muto M, Horimatsu T, Ezoe Y, et al: Narrow-band imaging of the gastrointestinal tract. J Gastroenterol 44:13-25, 2009

27. Muto M, Horimastu T, Ezoe Y, et al: Improving visualization techniques by narrow band imaging and magnification endoscopy. J Gastroenterol Hepatol 24:1333-1346, 2009

28. Slaughter DP, Southwick HW, Smejkal W: Field cancerization in oral stratified squamous epithelium: Clinical implications of multicentric origin. Cancer 6:963-968, 1953

29. Bossuyt PM, Reitsma JB, Bruns DE, et al: Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. Ann Intern Med 138:40-44, 2003

30. Franco EL, Kowalski LP, Kanda JL: Risk factors for second cancers of the upper respiratory and digestive systems: A case-control study. J Clin Epidemiol 44:615-625, 1991

31. Hsairi M, Luce D, Point D, et al: Risk factors for simultaneous carcinoma of the head and neck. Head Neck 11:426-430, 1989

32. Morita M, Kuwano H, Ohno S, et al: Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: Reference to smoking, drinking, and family history. Int J Cancer 58:207-210, 1994

33. Yokoyama A, Kato H, Yokoyama T, et al: Genetic polymorphisms of alcohol and aldehyde dehydrogenases and glutathione S-transferase M1 and drinking, smoking, and diet in Japanese men with esophageal squamous cell carcinoma. Carcinogenesis 23:1851-1859, 2002

34. Yokoyama A, Watanabe H, Fukuda H, et al: Multiple cancers associated with esophageal and oropharyngolaryngeal squamous cell carcinoma and the aldehyde dehydrogenase-2 genotype in male Japanese drinkers. Cancer Epidemiol Biomarkers Prev 11:895-900, 2002

35. Muto M, Takahashi M, Ohtsu A, et al: Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 26:1008-1012, 2005

36. Katada C, Muto M, Momma K, et al: Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae—a multicenter retrospective cohort study. Endoscopy 39:779-783, 2007

37. Katada C, Muto M, Manabe T, et al: Local recurrence of squamous-cell carcinoma of the esophagus after EMR. Gastrointest Endosc 61:219-225, 2005

38. Shimizu Y, Yamamoto J, Kato M, et al: Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. Gastrointest Endosc 64:255-259, 2006

39. Ugumori T, Muto M, Hayashi R, et al: Prospective study of early detection of pharyngeal superficial carcinoma with the narrowband imaging laryngoscope. Head Neck 31:189-194, 2009

Acknowledgment

We are grateful to the following collaborative members of this study: Chikatoshi Katada, MD, Takashi Kojima, MD, Keisei Taku, MD, at National Cancer Center Hospital East, Kashiwa, and Haruhisa Suzuki, MD, Kozu Takahiro, MD, at National Cancer Center Hospital, Tokyo, for technical support, Kenichi Yoshimura, PhD, Translational Research Center, Kyoto University, Kyoto, for statistical analysis support, and Ayako Nasu, Medical Research Support, Osaka, for data collection and management.

Appendix

Results

Among the 28 superficial head and neck squamous cell carcinomas (HNSCCs) detected, 16 lesions were treated with endoscopic resection, five lesions disappeared after only biopsy, and one lesion was treated with radiotherapy. The remaining six lesions were not treated, because the concomitant esophageal cancers had distant metastasis. Among 16 lesions removed by endoscopic resection, seven lesions were carcinoma in situ and the remaining nine lesions were microinvasive SCC. With a median follow-up of 33 months (range, 6 to 59 months), no patients developed lymph node metastasis from HNSCC.

Among the 212 superficial esophageal squamous cell carcinomas, those with accompanying advanced cancers and those with submucosal invasive cancers were treated with surgery or chemotherapy with or without radiotherapy. The remaining superficial cancers within the mucosal layer were removed by endoscopic resection.

Discussion

Most research on the endoscopic detection and diagnosis of GI disease has been performed by retrospectively reviewing static images in a database and selecting only the best of the stored images (Singh R: Endoscopy 40:457-463, 2008; Sharma P: Gastroenterology 133:454-464, 2007; Chiu HM: Gut 56:373-379, 2007). Evaluating selected stored images by retrospective review does not exclude the

possibility of selection bias. From the viewpoint of clinical practice, real-time detection and diagnosis are important. To avoid selection bias and to evaluate the actual diagnostic yield, we recorded the data during the procedure and completely separated the evaluation of white light imaging and narrow band imaging. We also conducted this study according to the Standards for Reporting of Diagnostic Accuracy checklist[29] to obtain high-quality data and to assess the generalizability and applicability of the results. Our data are therefore relevant to daily clinical practice.

Table A1. Rate of Superficial Cancer by Method of Detection in Back-to-Back Fashion

Region	No. of Patients	Primary Examination WLI			Secondary Examination NBI			*P*
		No.	%	95% CI	No.	%	95% CI	
Head and neck	13	1	8	0.2 to 36.0	10	77	46.2 to 95	< .001
Esophagus	105	58	55	45.2 to 65.0	100	95	89.2 to 98.4	< .001
			NBI			WLI		
Head and neck	15	15	100	78.2 to 100	5	33	11.8 to 61.6	< .001
Esophagus	107	104	97	92 to 99.4	85	79	70.5 to 86.6	< .001

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A2. Size of Superficial Cancer by Method of Detection

Tumor Size (mm)	WLI Positive		NBI Positive		NBI and WLI Positive		Both Negative (false negative)	
	No.	%	No.	%	No.	%	No.	%
Head and neck region								
< 10	0	0	12	70	5	30	0	0
11-20	0	0	4	40	6	60	0	0
≥ 21	0	0	0	0	1	100	0	0
Total	0	0	16	57	12	43	0	0
Esophagus								
< 10	0	0	14	39	22	58	0	0
11-20	0	0	12	30	28	70	0	0
≥ 21	1	0.7	22	16	113	83	0	0
Total	1	0.5	48	23	163	77	0	0

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A3. Median Procedure Time

Region	Primary WLI (seconds)		Primary NBI (seconds)		*P*
	Median	Range	Median	Range	
Head and neck	120	34-275	162	30-525	< .001
Esophagus	95	30-360	135	30-616	< .001
	Secondary WLI		Secondary NBI		
Head and neck	90	10-300	135	30-540	< .001
Esophagus	80	19-776	45	18-700	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Japanese Journal of Clinical Oncology Advance Access published February 4, 2010

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010
doi:10.1093/jjco/hyp197

Original Article

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

Tomomasa Hayashi[1,2,3], Manabu Muto[4], Ryuichi Hayashi[3], Keiko Minashi[5], Tomonori Yano[5], Seiji Kishimoto[2] and Satoshi Ebihara[1]

[1]Department of Head and Neck Surgery, Kyoundo Hospital Sasaki Foundation, [2]Department of Head and Neck Surgery, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, [3]Department of Head and Neck Surgery, National Cancer Center Hospital East, Chiba, [4]Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto and [5]Department of Gastroenterology, National Cancer Center Hospital East, Chiba, Japan

For reprints and all correspondence: Tomomasa Hayashi, Department of Head and Neck Surgery, Kyoundo Hospital Sasaki Foundation, Tokyo, Japan. E-mail: hayashi@po.kyoundo.jp

Received October 29, 2009; accepted December 24, 2009

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

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.

lesion was intraepithelial cancer and the other had invaded to the subepithelial layer.

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.

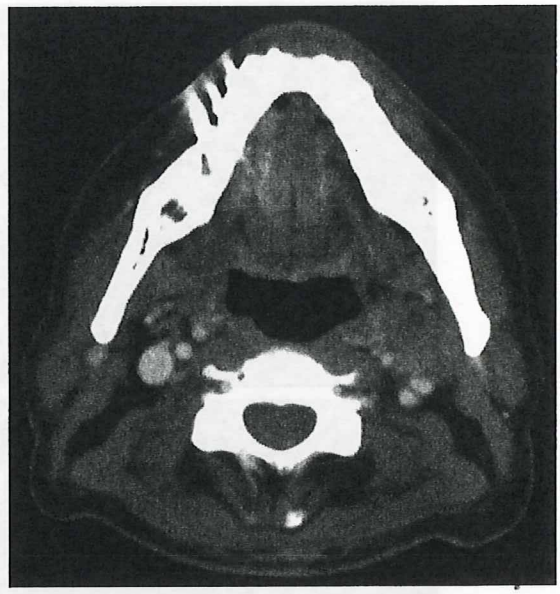

Figure 1. Computed tomographic scan shows lymph node metastasis at left upper jugular area.

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

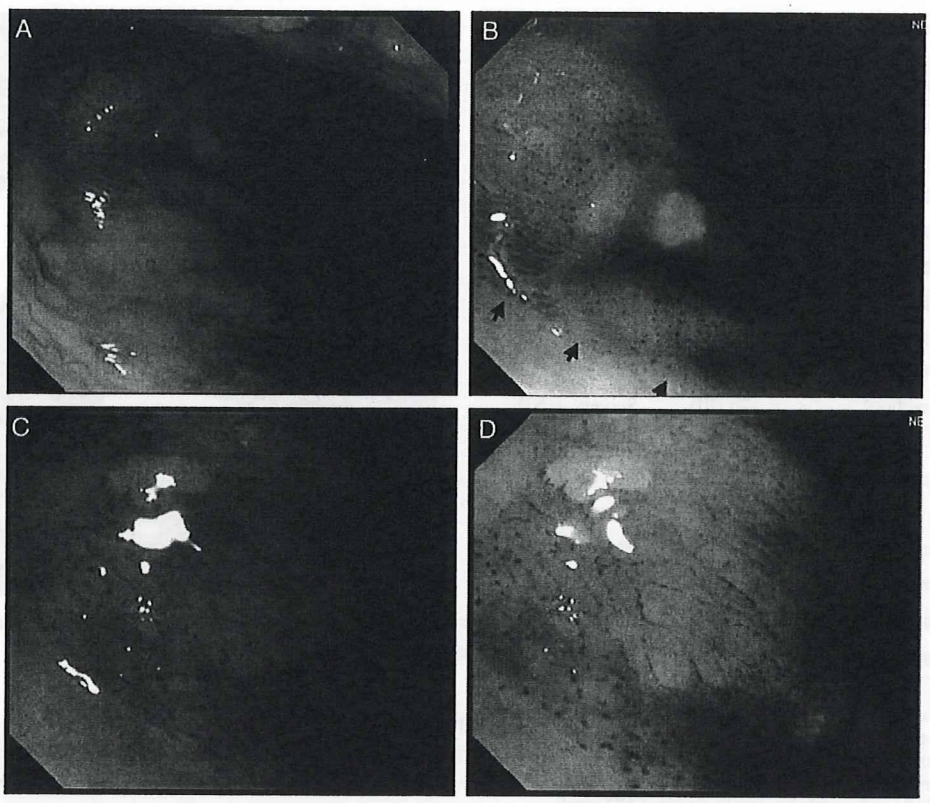

Figure 2. (A–D) Endoscopic findings. Conventional white-light image (A), narrow-band imaging (NBI) image (B), magnifying conventional white-light image (C) and magnifying the NBI images (D). NBI detected a well-demarcated brownish area in the uvula to right anterior palatine arch (B). In contrast, conventional 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).

also useful to detect occult cancer, but this primary site is too small to point out with PET. Random biopsy in the head and 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.

References

1. Coker D, Casterline P, Chambers R, Jaques D. Metastases to lymph nodes of the head and neck from an unknown primary site. *Am J Surg* 1977;134:517–22.
2. Gluckman J, Robbins K, Fried M. Cervical metastatic squamous carcinoma of unknown or occult primary source. *Head Neck* 1990;12:440–3.
3. Jones A, Cook J, Phillips D, Roland N. Squamous carcinoma presenting as an enlarged cervical lymph node. *Cancer* 1993;72:1756–61.
4. Righi P, Sofferman R. Screening unilateral tonsillectomy in the unknown primary. *Laryngoscope* 1995;105:548–50.
5. Medini E, Medini A, Lee C, Gapany M, Levitt S. The management of metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary. *Am J Clin Oncol* 1998;21:121–5.
6. Jesse R, Perez C, Fletcher G. Cervical lymph node metastasis: unknown primary cancer. *Cancer* 1973;31:854–9.
7. McCunniff A, Raben M. Metastatic carcinoma of the neck from an unknown primary. *Int J Radiat Oncol Biol Phys* 1986;12:1849–52.
8. Muto M, Ugumori T, Sano YI, Otsu A, Yoshida S. Narrow-band imaging combined with magnified endoscopy for cancer at the head and neck region. *Dig Endosc* 2005;17:S23–4.
9. Muto M, Nakane M, Katada C, Sano Y, Ohtsu A, Esumi H, et al. Squamous cell carcinoma *in situ* at oropharyngeal and hypopharyngeal mucosal sites. *Cancer* 2004;101:1375–81.
10. Greenberg B. Cervical lymph node metastasis from unknown primary sites. An unresolved problem in management. *Cancer* 1966;19:1091–5.
11. Muto M, Katada C, Sano Y, Yoshida S. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. *Clin Gastroenterol Hepatol* 2005;3(7 Suppl 1):S16–20.
12. Nguyen C, Shenouda G, Black M, Vuong T, Donath D, Yassa M. Metastatic squamous cell carcinoma to cervical lymph nodes from unknown primary mucosal sites. *Head Neck* 16:58–63.
13. Mendenhall W, Million R, Cassisi N. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. *Int J Radiat Oncol Biol Phys* 1986;12:733–40.
14. Freeman D, Mendenhall W, Parsons J, Million R. Unknown primary squamous cell carcinoma of the head and neck: is mucosal irradiation necessary? *Int J Radiat Oncol Biol Phys* 1992;23:889–90.
15. Coster J, Foote R, Olsen K, Jack S, Schaid D, DeSanto L. Cervical nodal metastasis of squamous cell carcinoma of unknown origin: indications for withholding radiation therapy. *Int J Radiat Oncol Biol Phys* 1992;23:743–9.
16. Muto M, Takahashi M, Ohtsu A, Ebihara S, Yoshida S, Esumi H. Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. *Carcinogenesis* 2005;26:1008–12.

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

Yasumasa Ezoe, MD, Manabu Muto, MD, PhD, Takahiro Horimatsu, MD, Keiko Minashi, MD, Tomonori Yano, MD, Yasushi Sano, MD, PhD, Tsutomu Chiba, MD, PhD, Atsushi Ohtsu, MD, PhD

Kyoto, Japan

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.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2009.10.036

Received May 30, 2009. Accepted October 14, 2009.

Current affiliations: Department of Multidisciplinary Cancer Treatment, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Reprint requests: Yasumasa Ezoe, MD, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

If you would like to chat with an author of this article, you may contact Dr. Ezoe at yasuzoe@kuhp.kyoto-u.ac.jp.

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

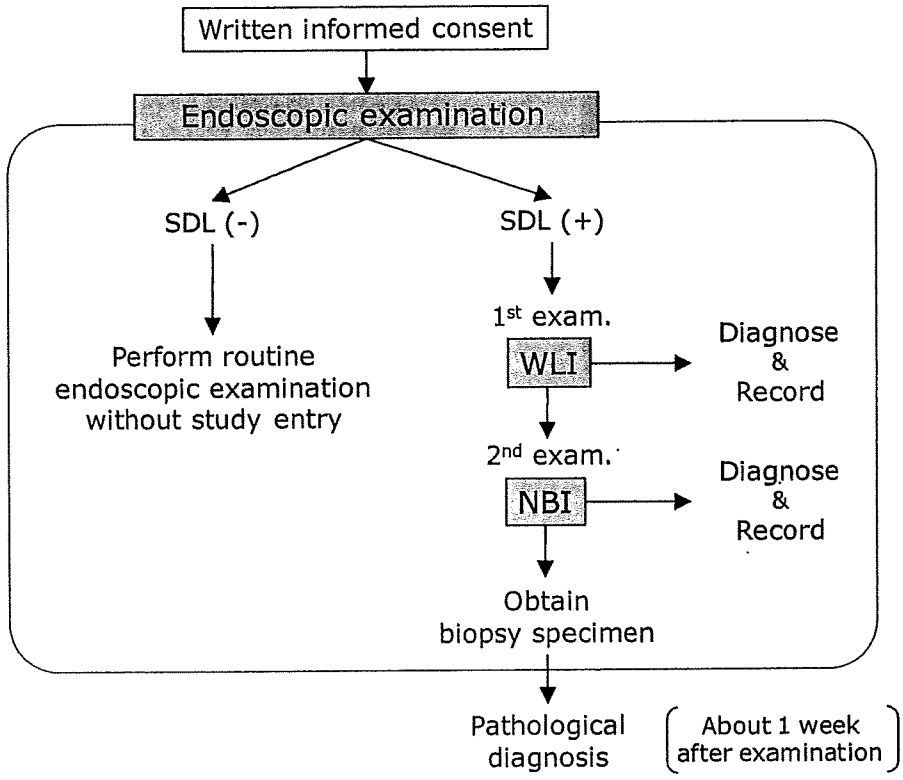

Figure 1. Protocol of the examinations in this study.

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 noncarcinoma. The biopsy specimens were evaluated with hematoxylin–eosin staining.

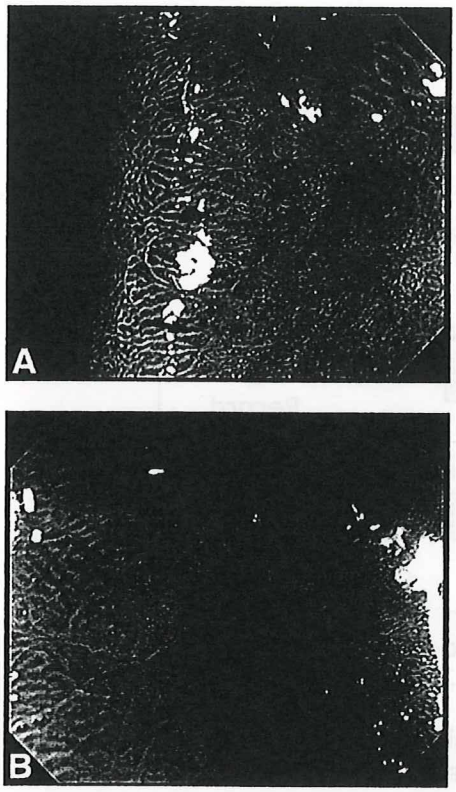

Figure 2. A typical finding of the DL and IMVP **(A, B)**. Magnifying NBI can clearly visualize the DL between the lesion and the surrounding normal mucosa (*arrows*) and IMVP within the lesion.

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

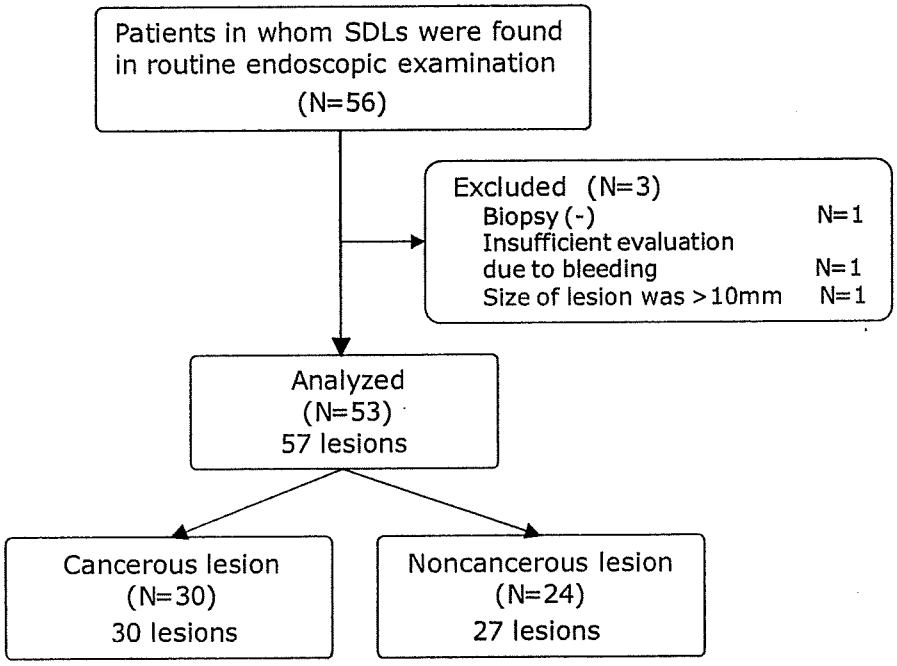

Figure 3. Study flow chart. N = number of patients.

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.

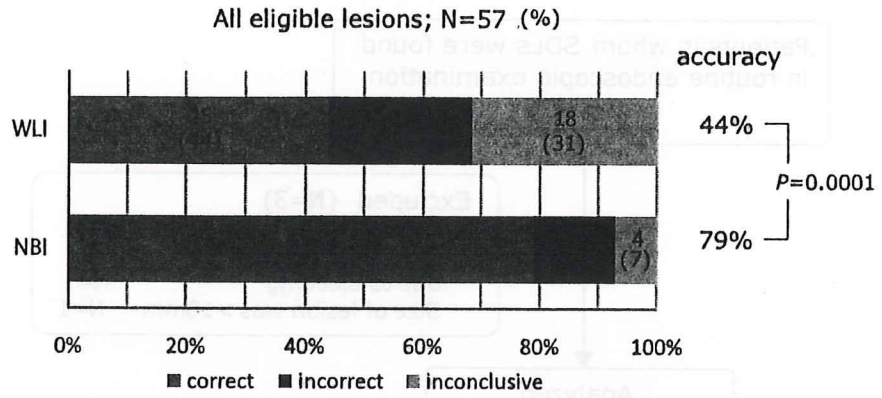

Figure 4. Diagnostic accuracy of magnifying WLI and magnifying NBI (primary endpoint). The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

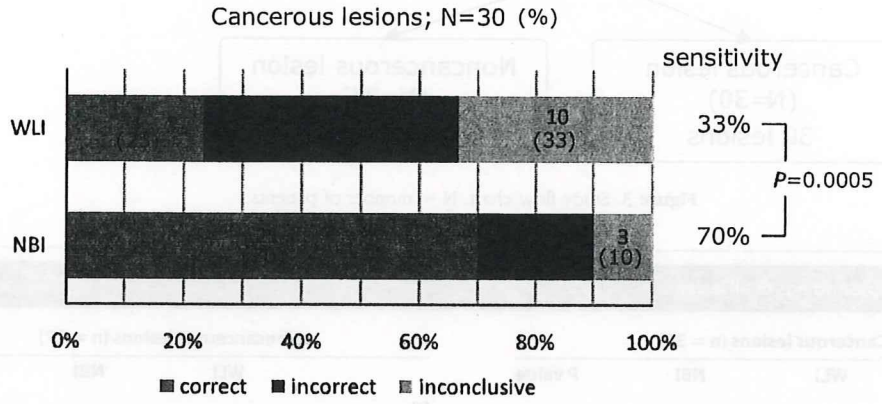

Figure 5. Diagnostic sensitivity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

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