definitive diagnosis, as the neurological symptoms are reversible after discontinuance of the causative drug.

Conflict of interest statement

None declared.

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DISEASES OF THE ESOPHAGUS

Original article

Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

C.-H. Tu,[1] M. Muto,[2] T. Horimatsu,[2] K. Taku,[3] T. Yano,[4] K. Minashi,[4] M. Onozawa,[5] K. Nihei,[5] S. Ishikura,[5] A. Ohtsu,[4] S. Yoshida[4]

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan; and* [2]*Department of Gastroenterology and Hepatology, Kyoto University, Kyoto, Japan, and* [3]*Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan,* [4]*Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, and* [5]*Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

SUMMARY. **Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore, a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis. From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT, and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination. Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Of biopsy-proven recurrences, 81% were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77 patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer. Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.**

KEY WORDS: **chemoradiotherapy, esophageal cancer, recurrence, surveillance.**

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy,

Address correspondence to: Dr Manabu Muto, MD PhD, Department of Gastroenterology and Hepatology, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Email: mmuto@kuhp.kyoto-u.ac.jp
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have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However, the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered 'optional' in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were added for those patients who showed a good initial response to treatment.[9]

Table 1 Clinical data of 133 patients achieving complete remission with definitive chemoradiotherapy

Characteristic		Number of patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5
Macroscopic classification			
Type 0		30	22.6
Type 1		19	14.3
Type 2		60	45.1
Type 3		24	18.0

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (i) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (ii) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (iii) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (5) these criteria were met for at least 4 weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6

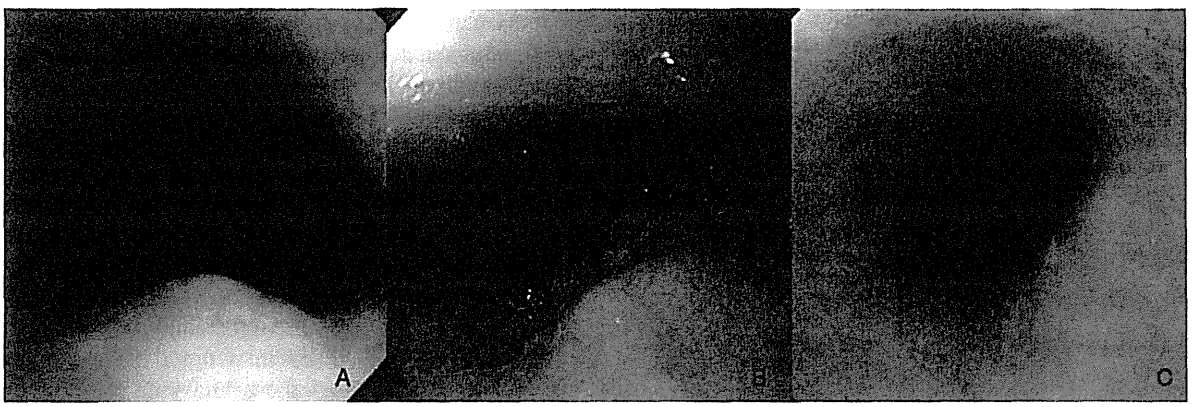

Fig. 1 Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

months for 2 years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling submucosal tumors (SMT), typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B and 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients) SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	Number of patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	Number of patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy results of the latest surveillance endoscopy for patients who achieved complete remission and remained free of metastasis

Evolving lesion found at preceding endoscopies	Numer of patients (%)	Biopsy result of the latest endoscopy	Number of patients (%)
SMT	7 (9)	Recurrence	6 (86)
		Negative	1 (14)
Erosion	8 (10)	Recurrence	5 (63)
		Negative	3 (37)
Mild stricture	6 (8)	Recurrence	2 (33)
		Negative	4 (67)
No evolving lesion	56 (73)	Recurrence	3 (5)
		Negative	53 (95)
Total	77 (100)		

SMT, submucosal tumor.

endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation, and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of

SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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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.

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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.

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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.

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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.

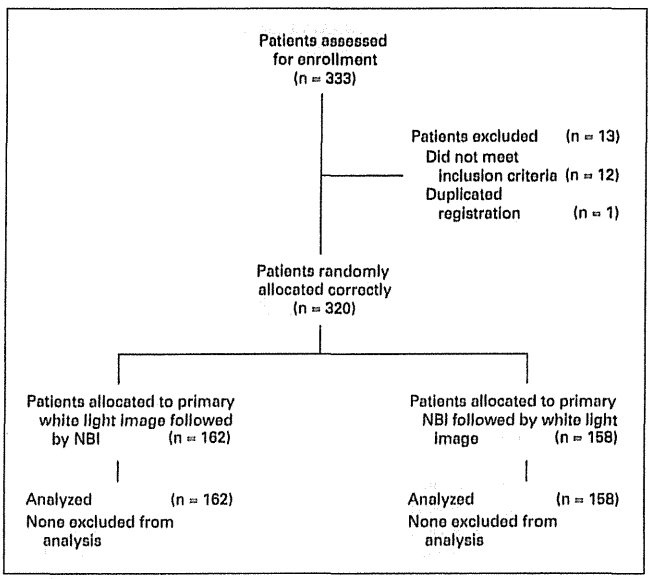

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

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.

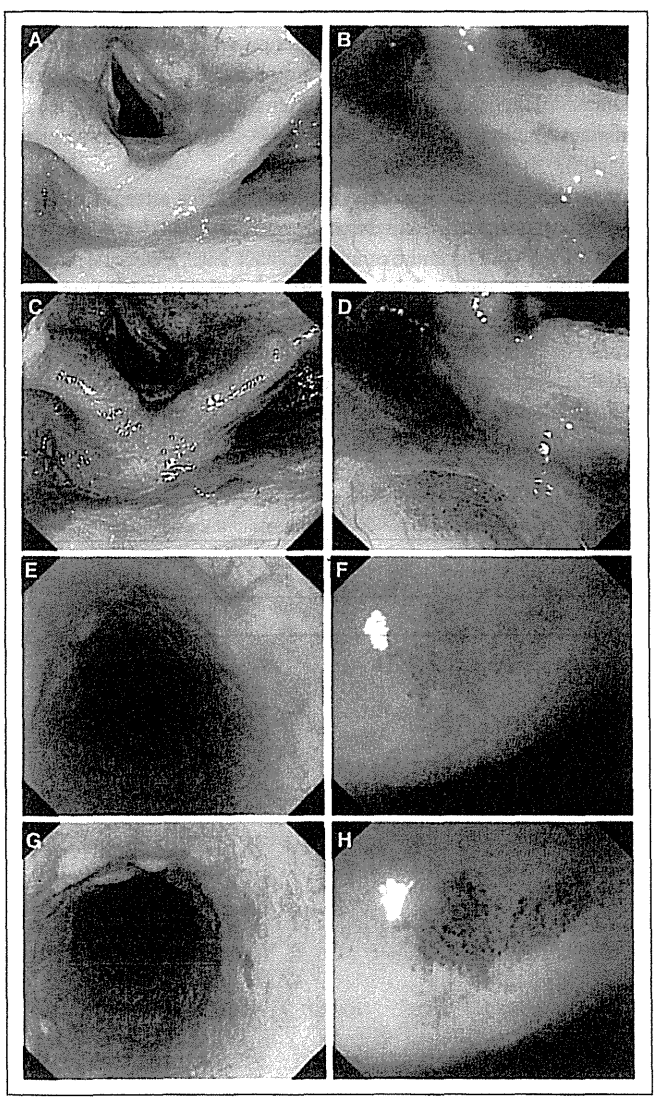

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated 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) No.	%	95% CI	Primary NBI (n = 158) No.	%	95% CI	*P*
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

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ORIGINAL ARTICLE: Clinical Endoscopy

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.

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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.

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.

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.

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

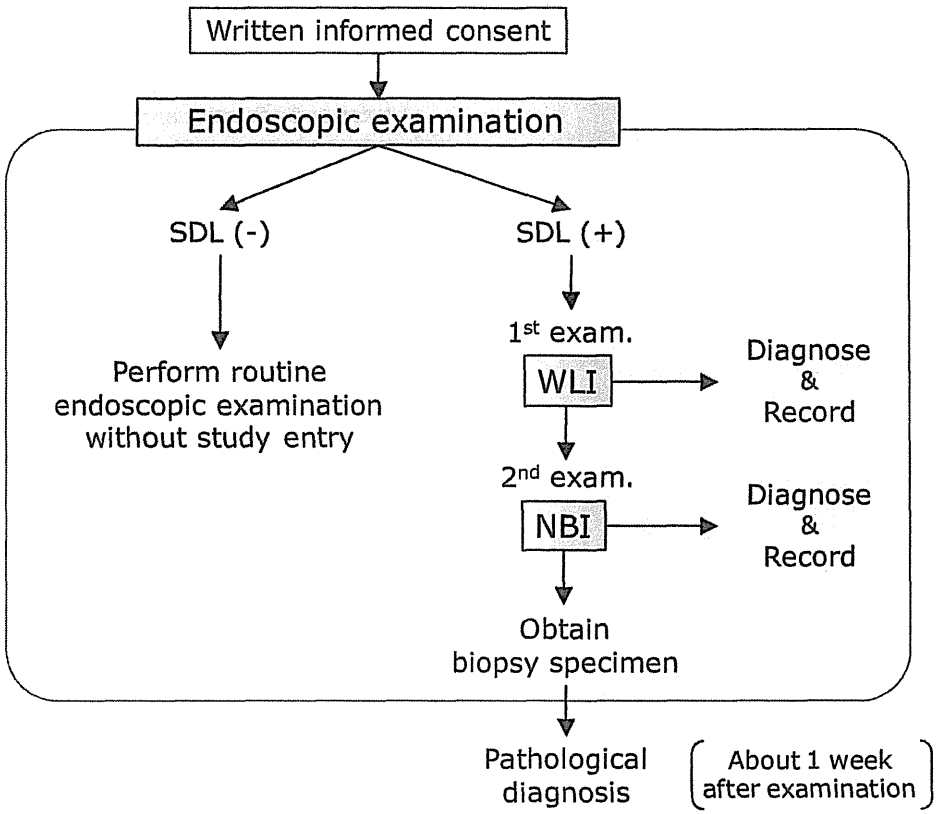

Figure 1. Protocol of the examinations in this study.

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.

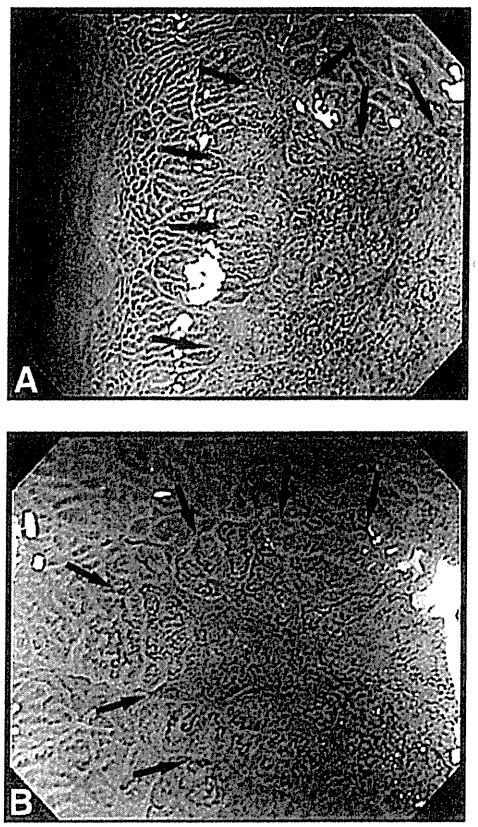

Figure 2. A typical finding of the DL and IMVP **(A, B)**. Magnifying NBI can clearly visualize the DL between the lesion and the surrounding normal mucosa (*arrows*) and IMVP within the lesion.

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

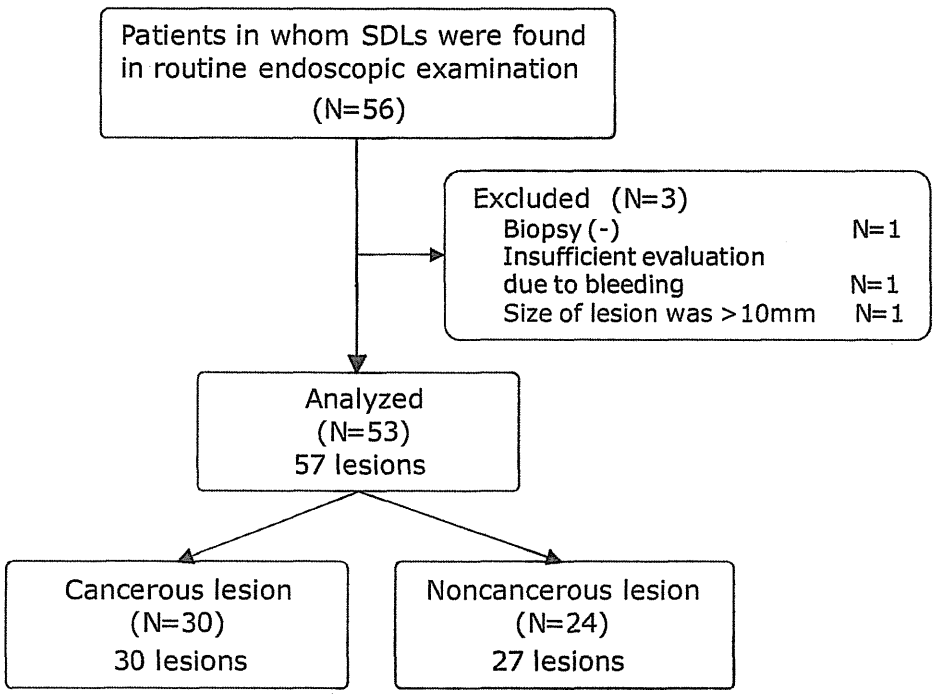

Figure 3. Study flow chart. N = number of patients.

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.

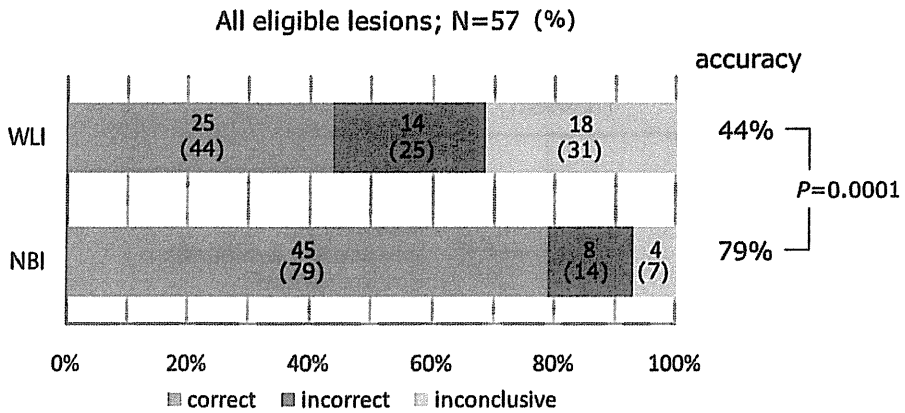

Figure 4. Diagnostic accuracy of magnifying WLI and magnifying NBI (primary endpoint). The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

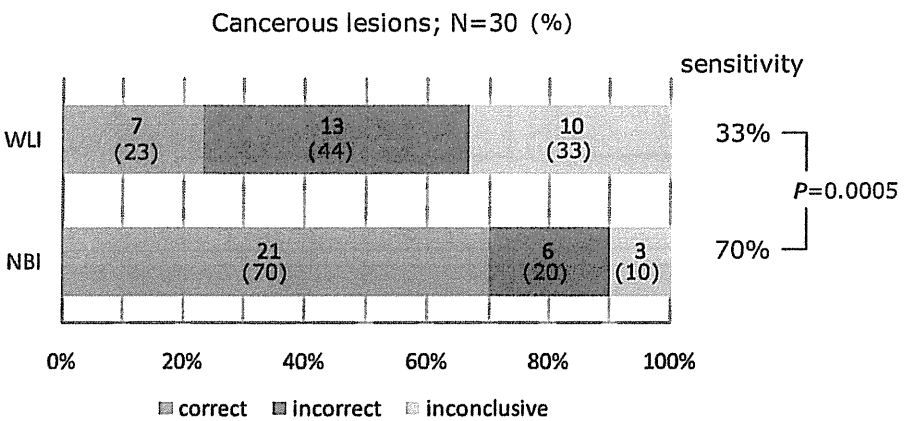

Figure 5. Diagnostic sensitivity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

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

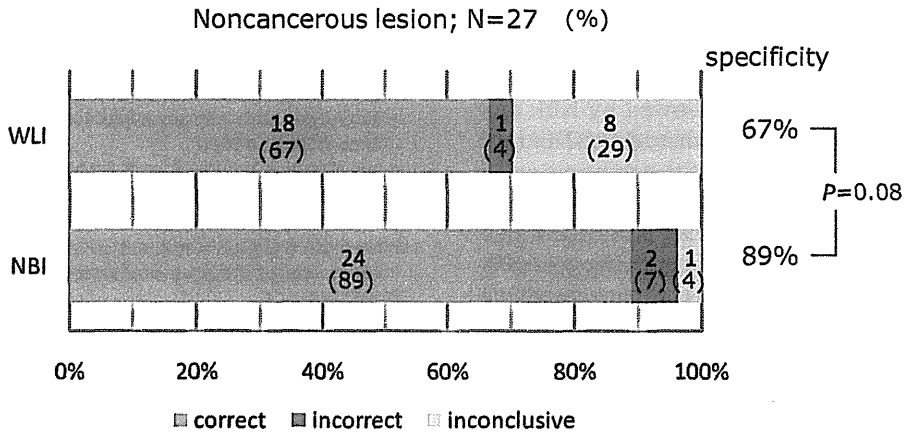

Figure 6. Diagnostic specificity of magnifying WLI and magnifying NBI. The numbers of lesions are shown. Values in parentheses are percentages of all the lesions.

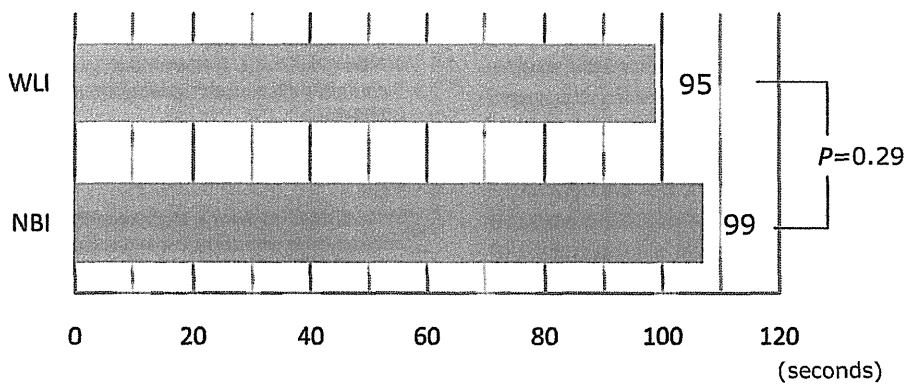

Figure 7. Time required for a diagnosis by magnifying WLI and magnifying NBI (secondary endpoint).

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