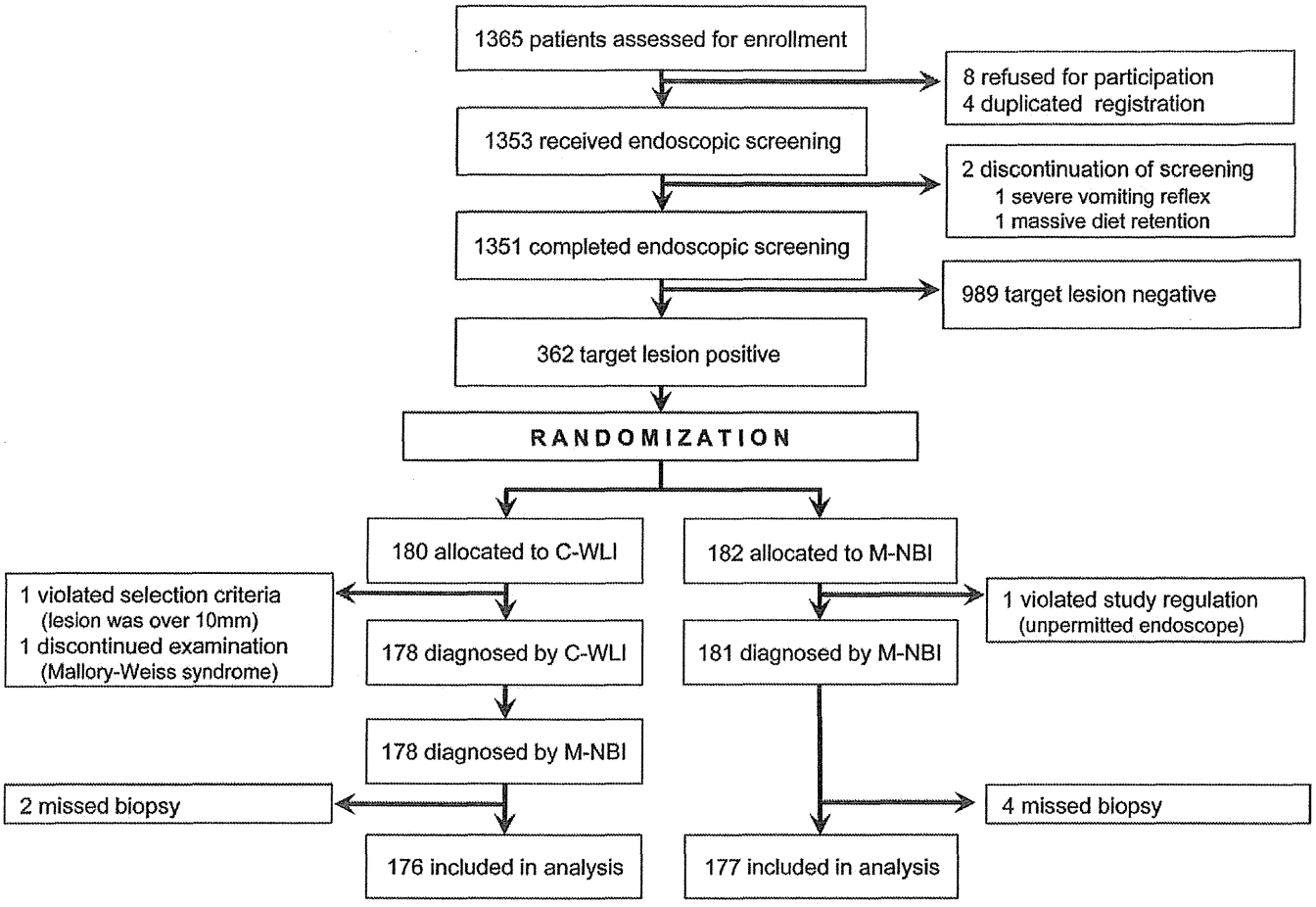

Figure 2. Patient enrollment, randomization, and examination.

C-WLI alone ($P < .001$). All patients tolerated the procedures well (Table 3).

Figure 3 shows the PPV and NPV data for each examination. M-NBI significantly improved the PPV compared with C-WLI alone to 57.1% (95% CI, 36.0%–78.3%) from 13.8% (95% CI, 2.9%–22.7%; $P = .001$). Furthermore, C-WLI followed by M-NBI dramatically improved the PPV from 13.8% (95% CI, 2.9%–22.7%) to 79.2% (95% CI, 62.9%–95.4%; $P < .001$). Similarly, the NPV of C-WLI of 89.8% (95% CI, 84.4%–95.3%) was improved by M-NBI to 94.9% (95% CI, 91.4%–98.3%; $P = .16$) and by C-WLI followed by M-NBI to 99.3% (95% CI, 98.1%–100%; $P < .001$).

Detailed C-WLI examination was discontinued during the procedure in one patient (1/362; 0.3%) because of bleeding associated with Mallory–Weiss syndrome. Although the bleeding stopped spontaneously without any endoscopic hemostatic treatment, a biopsy specimen was not obtained because the suspicious target lesion was missed. Two patients (2/362; 0.6%) were hospitalized on the day after examination because of bleeding from the biopsy site; although one patient needed a blood transfusion, both patients were discharged within a few days. None of the 3 patients experienced prolonged adverse effects. There were no serious adverse events directly related to the endoscopic observations.

Table 4 summarizes the clinical courses and pathologic diagnoses of 40 gastric cancers in 40 patients. Thirty-two patients were treated endoscopically (by endoscopic mucosal resection or endoscopic submucosal dissection). Five patients underwent surgical resection for synchronous advanced gastric cancers. The remaining 3 patients did not receive any treatment; 2 had other concomitant noncurable malignancies, and one refused treatment. Histologically, 39 lesions were of the intestinal type and one lesion was of the diffuse type. Regarding the depth of the 37 lesions that were removed, 35 were mucosal cancers, 2 of which were accompanied by submucosal invasion (0.3 mm and 0.8 mm). The depths of the 3 untreated lesions were estimated endoscopically as 2 mucosal cancers and one submucosal cancer.

Discussion

In this multicenter randomized trial, we compared the diagnostic yield of C-WLI with that of M-NBI for small gastric cancers. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities. One was the worldwide standard method of C-WLI; the other was M-NBI, which is the most advanced imaging method at present. This end point is the most impor-

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group

	C-WLI (n = 176)	M-NBI (n = 177)	*P* value
Age (*y*)			
Median (range)	69 (45–93)	69 (37–87)	.56
Sex			
Male	138	140	.79
Female	38	37	
Endoscope			
GIF-Q240Z	71	65	.83
GIF-H260Z	104	109	
GIF-FQ260Z	1	3	
Size of lesion (*mm*)			
≤5	74	71	.75
>5	102	106	
Mean	5.6	5.6	.97
Location of lesion			
Upper third			
Anterior wall	4	2	.51
Lesser curvature	9	10	
Posterior	22	12	
Greater curvature	4	3	
Middle third			
Anterior wall	7	7	
Lesser curvature	13	25	
Posterior	12	11	
Greater curvature	8	6	
Lower third			
Anterior wall	18	23	
Lesser curvature	25	33	
Posterior	26	18	
Greater curvature	28	27	
Histopathology diagnosis			
Cancer	20	20	1.00
Noncancerous	156	157	

tant aspect of this study, because if C-WLI proves superior to M-NBI, such advanced methods are not needed in practice. However, if M-NBI is indeed better than C-WLI, it should be used more in daily practice. The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI. This end point is also important, because in daily practice M-NBI is usually performed after C-WLI. Therefore, the results might reflect the practical diagnostic potential. To evaluate these aims, we used a strictly controlled randomized study. Furthermore, the endoscopic diagnosis in each method (C-WLI and M-NBI) was made on-site and independently to avoid any bias.

M-NBI, especially when used in conjunction with C-WLI, significantly enhanced real-time sensitivity, specificity, and accuracy of diagnosis; therefore, we concluded that M-NBI is an essential modality for diagnosing small gastric mucosal cancer. Although there are reports on the diagnostic yield of M-NBI for differential diagnosis of gastric lesions, some were performed at only one institute,[9,10,12,13] one was evaluated by several expert endoscopists using stored images and did not involve real-time assessment,[12] and one included gastric lesions with a definite diagnosis.[13] To overcome these limitations, our study targeted newly detected and undiagnosed gastric superficial lesions, which were evaluated on-site. For these reasons, the present results are the most reliable and could be a milestone in the field of endoscopic diagnosis of early gastric cancers.

Regarding accuracy and specificity, M-NBI alone yielded excellent results (90.4% and 94.3%, respectively), which were significantly better than those obtained with C-WLI. However, the sensitivities of M-NBI alone (60.0%) and C-WLI alone (40.0%) were lower than the estimated values: 85% for M-NBI and 60% for C-WLI. The low sensitivity of C-WLI might be acceptable considering the difficulty of diagnosing small gastric cancers in daily clinical practice. Although the reason for the low sensitivity of the M-NBI group is unknown, it might be associated with the examination protocol in this study; M-NBI observation was performed without evaluating a gross finding of lesions using C-WLI. In daily practice, magnifying examinations are usually performed after C-WLI. Actually, when performed after the C-WLI observation, M-NBI yielded excellent diagnostic performance in terms of accuracy, sensitivity, and specificity (all values were >95%). In addition, M-NBI and C-WLI followed by M-NBI significantly improved the PPV and NPV compared with C-WLI alone. This has enormous significance in clinical practice, because the examination with high PPV and high NPV might enable the clinician to make appropriate judgments as to which lesion needs pathology to confirm the diagnosis. When the lesion is suspected to be a neoplasm by C-WLI followed by M-NBI, taking a biopsy specimen is highly recommended to confirm the pathology. On the other hand, when the lesion is not suspected to be a neoplasm by M-NBI alone or by C-WLI followed by M-NBI, we could avoid a negative biopsy. These results have the potential to enable so-called "optic biopsy." Taken together, C-WLI followed by M-NBI might be the best

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

		Cancerous lesion (%)			Noncancerous lesion (%)		
Group	Method	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis
M-NBI	M-NBI	12/20 (60.0)	7/20 (35.0)	1/20 (5.0)	146/157 (93.0)	9/157 (5.7)	2/157 (1.3)
C-WLI	C-WLI	8/20 (40.0)	12/20 (60.0)	0/20 (0)	100/156 (64.1)	50/156 (32.1)	6/156 (3.8)
	C-WLI+M-NBI	19/20 (95.0)	1/20 (5.0)	0/20 (0)	149/156 (95.5)	5/156 (3.2)	2/156 (1.3)

Table 3. Diagnostic Performance of C-WLI and M-NBI for Gastric Small Depressed Lesions

Group	Method	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Examination time (s), median (interquartile range)
M-NBI	M-NBI	90.4[a] (85.1–94.3)	60.0 (36.1–80.9)	94.3[a] (89.4–97.3)	55[a] (23–97)
C-WLI	C-WLI	64.8 (57.2–71.8)	40.0 (19.1–63.9)	67.9 (60.0–75.2)	21 (12–40)
	C-WLI + M-NBI	96.6[b] (93.5–99.1)	95.0[b] (75.1–99.9)	96.8[b] (92.7–99.0)	72[b] (40–144)

[a]$P < .001$ for M-NBI vs C-WLI; [b]$P < .001$ for C-WLI vs C-WLI + M-NBI.

approach for making accurate diagnoses of small gastric cancers.

The durations of the M-NBI and C-WLI followed by M-NBI examinations were 34 seconds and 51 seconds, respectively, significantly longer than that required for C-WLI alone. However, these durations are clinically acceptable, because we managed to make accurate diagnoses without having to insert a spraying catheter or use indigo carmine. The importance of simple methods and accurate diagnoses for clinical practice is indisputable. Thus, Li et al showed that confocal laser endomicroscopy can be used to identify gastric superficial cancers with high validity and reliability.[26] However, confocal laser endomicroscopy requires the intravenous administration of a contrast agent. In contrast, M-NBI can be used by simply pushing a button on the endoscope. In addition, evaluation of demarcation lines and irregular microvascular patterns is sufficient for diagnosis with M-NBI, whereas confocal laser endomicroscopy requires knowledge of histopathology procedures for diagnosis.

Major bleeding caused by an endoscopic biopsy is rarely reported.[27] However, in our study, 2 patients experienced bleeding from the biopsy site. The best way of avoiding such bleeding is to avoid unnecessary biopsies. M-NBI, especially when used in conjunction with C-WLI, could help to reduce the number of unnecessary biopsies.

Our study has some limitations. First, the number of cancerous lesions was small, and it was less than the required sample size. This might be associated with insufficient power to evaluate sensitivity adequately. Then, further large numbers of patients for screening are needed to evaluate the sensitivity for diagnosing small gastric mucosal cancers of each modality. Second, this study was open labeled because the endoscopists knew which imaging modality was in use. Thus, a blinded study was impossible. Third, there is no arm that includes a dye-based imaging method such as indigo carmine or acetic acid. Indigo carmine and acetic acid are useful, but these dyes are only used in a few countries and institutes, and the standard worldwide endoscopic method to diagnose early gastric cancer is still C-WLI without any dye use. In addition, if we added a chromoendoscopy arm in this study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. For these reasons, we did not include the dye-based imaging method.

Early detection of small gastric cancers makes it possible to effect a cure using minimally invasive treatments such as endoscopic mucosal resection and endoscopic

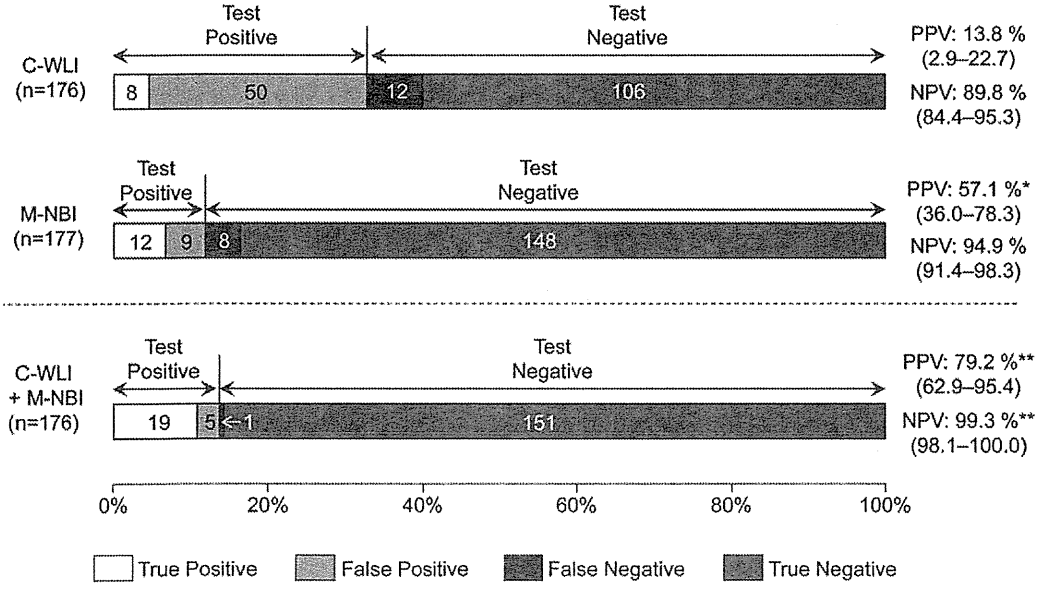

Figure 3. PPV and NPV in each examination. *The PPV for M-NBI was significantly higher than for C-WLI ($P = .001$). The NPV in M-NBI was higher than that of C-WLI; however, the difference was not significant ($P = .16$). **Both PPV and NPV were significantly enhanced by additional examination using M-NBI compared with C-WLI alone ($P < .001$).

Table 4. Clinical Course and Pathologic Diagnosis of Patients With Gastric Cancers

No. of patients	40
Treatment	
Endoscopic mucosal resection/endoscopic submucosal dissection	2/30
Surgery	5
No treatment	3
Histologic type	
Adenocarcinoma	40
Intestinal type	39
Diffuse type	1
Other diagnosis	0
Pathologic depth	
Mucosa	35
Submucosa	2
Muscularis propria	0
Unknown	3

submucosal dissection. In this study, all of the newly diagnosed small gastric cancers were good candidates for these procedures. Among the 37 cancers removed, 35 (95%) were mucosal. Early diagnosis using M-NBI and minimally invasive treatment is ideal for patients with gastric cancers, because it will improve their survival and quality of life. Although eradication of *Helicobacter pylori* is effective in reducing the incidence of gastric cancer,[17,28] endoscopic examination using M-NBI in conjunction with C-WLI should be indicated for high-incidence areas such as East Asia, South America, Eastern European countries, and Russia.[29]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.08.007.

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Conflicts of interest

The authors disclose no conflicts.

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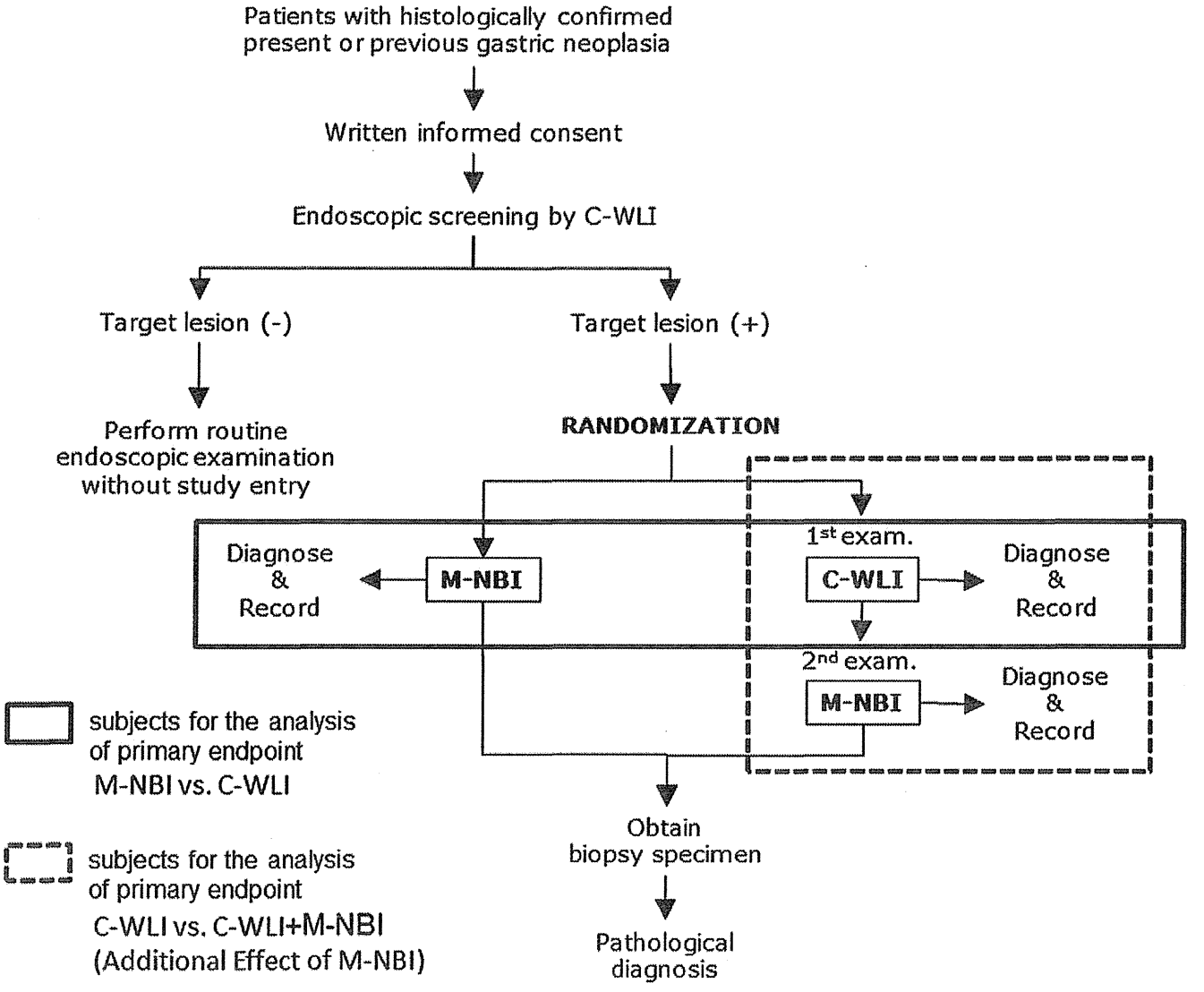
Supplementary Materials and Methods

Study Flow

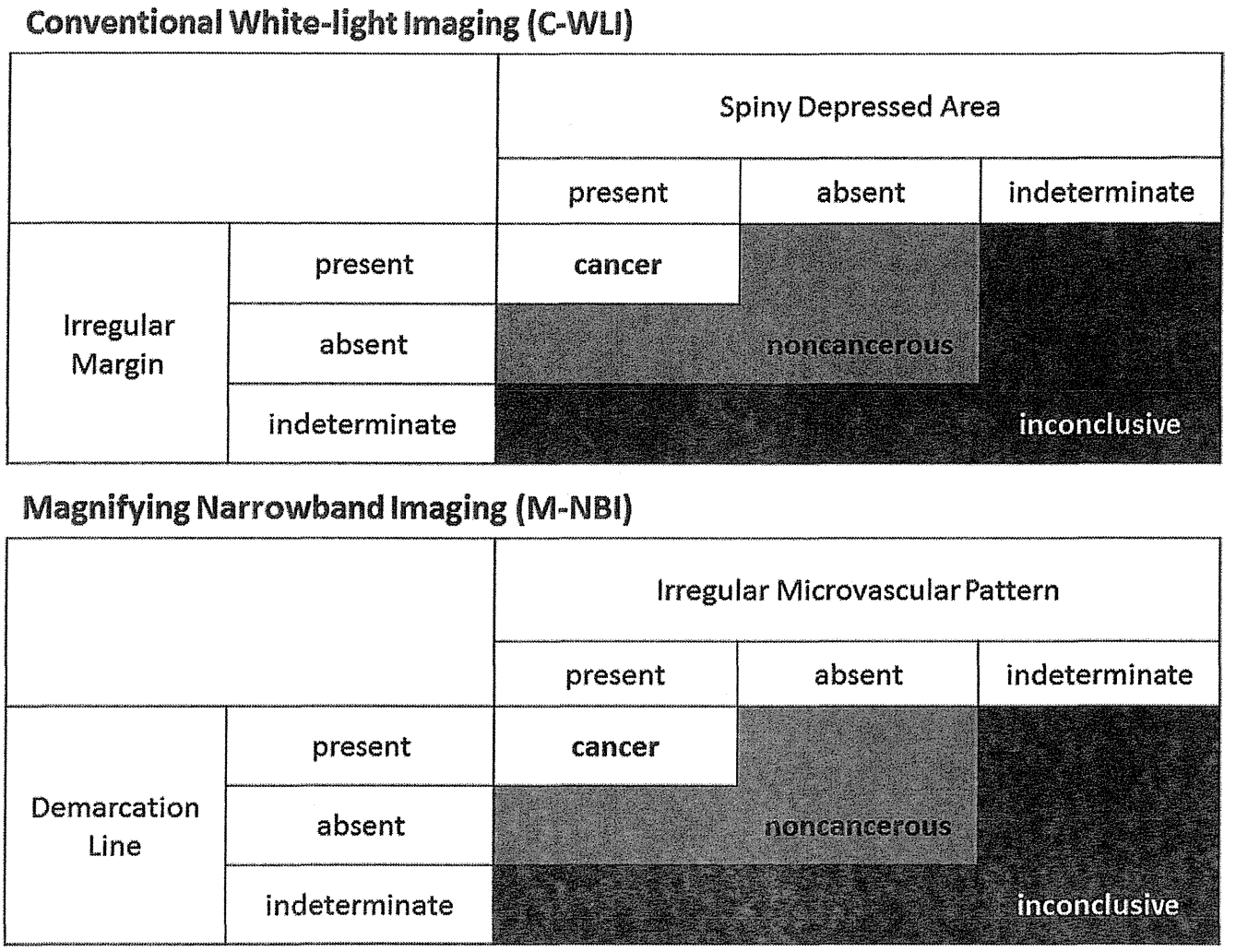
Written informed consent was obtained from all eligible patients. To detect a target lesion, endoscopic screening was performed using C-WLI. If no target lesion was detected, routine endoscopic examination was performed without study entry. When a target lesion was detected, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. After all diagnoses were compiled, at least one biopsy specimen was obtained from the target lesion. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities: C-WLI and M-NBI (*solid line box*). The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI (*dashed line box*).

Diagnostic Method Based on Endoscopic Findings

Endoscopic diagnoses were made according to the combination of the endoscopic findings. In the case of C-WLI, an irregular margin and a spiny depressed area were used for the diagnostic findings. In the case of M-NBI, a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion were used for the diagnosis. If both findings were present in each examination, the diagnosis of "cancer" was made. If either finding was indeterminate, the diagnosis was "inconclusive." If either or both findings were absent, the diagnosis was "noncancerous."



Supplementary Figure 1. Study flow.



Supplementary Figure 2. Diagnostic method based on endoscopic findings.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

The impact of narrow band imaging for colon polyp detection: a multicenter randomized controlled trial by tandem colonoscopy

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Abstract
Background Previous studies have yielded conflicting results on the adenoma detection rate with narrow band imaging (NBI) compared with white light imaging (WLI). To overcome the confounding factors of these studies, we aimed to evaluate the colonic adenoma detection rate with primary NBI versus that with primary WLI by using consistent NBI system, endoscope, and imaging settings, and experienced colonoscopists.
Methods In this multicenter prospective trial, 813 patients were randomized to undergo high-definition, tandem colonoscopy in the right colon with either NBI followed by WLI (NBI–WLI group) or WLI followed by NBI (WLI–NBI group). The NBI settings were fixed at surface structure enhancement level A-5 and adaptive index of hemoglobin color enhancement level 3. All detected polyps were resected or biopsied for histopathological analysis. The primary and secondary outcome measures were the adenoma detection rates and miss rates, respectively, with primary imaging.
Results The NBI–WLI and WLI–NBI groups comprised 389 and 393 patients, respectively, who met the inclusion criteria. The groups did not differ significantly in age, gender, institution, indication for colonoscopy, bowel preparation, or observation time. The adenoma detection rates of primary NBI and WLI were 42.3 and 42.5 %, respectively [difference not significant (NS)]. The adenoma miss rate was significantly less with primary NBI than with primary WLI (21.3 vs. 27.8 %; $p = 0.03$).
Conclusions NBI does not improve the adenoma detection rate during primary colonoscopy; however, it has a lower miss rate for adenoma lesions in the proximal colon than WLI.

Keywords Adenoma detection rate · Colonoscopy · Screening

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Introduction

Early detection and removal of colorectal adenoma lesions by screening colonoscopy are the most effective means of colorectal cancer prevention [1–3]. The adenoma detection rate is an important quality indicator for colonoscopy; moreover, this detection rate is an independent predictor of the risk of colorectal cancer after screening colonoscopy

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[4]. Colonoscopy is considered the gold standard for the detection and treatment of colorectal polyps; however, white light imaging (WLI) has an adenoma miss rate of 10–30 % during colonoscopy [5–7]. Various methods, such as pan-colonic dye-spraying [8, 9], wide-angle colonoscopy [10, 11], Third Eye Retroscope colonoscopy [12, 13], and cap-fitted colonoscopy [14] reportedly reduce the adenoma miss rate. Similarly, some researchers have indicated improvements in the adenoma detection rate by performing colonoscopy with narrow band imaging (NBI) [15–21].

NBI is an innovative imaging technology that uses narrow band width filters [22, 23]. The center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm. NBI enables endoscopic imaging with a one-touch electrical button and without indigo carmine dye-spraying. It also helps in clearly visualizing the microvascular structure of the organ surface, because the 415-nm light is well absorbed by hemoglobin. Given that the microvascular surface of an adenoma lesion is thicker and more irregular than that of normal mucosa, surface microvascular irregularities are useful landmarks for identifying an early neoplasm in the gastrointestinal tract; such lesions appear brownish during NBI. In addition, lesion detection and diagnosis can be performed simultaneously with NBI.

Muto et al. [24] reported the efficiency of NBI for the early detection of superficial cancers in the head and neck region and the esophagus. In the colorectal region, this modality was expected to enable the early detection of adenoma lesions; however, both positive [15–17] and negative [18–21] results have been reported, and some researchers have concluded that there was no improvement in the adenoma detection rate of NBI compared with that of WLI. One reason for these conflicting findings could be a difference between the optical-electronic technologies employed in the video endoscopes in the different NBI systems used [sequential system (LUCERA; Olympus Optical, Tokyo, Japan) vs. non-sequential system (EXERA II; Olympus Optical)]. Further, differences in the endoscope (low-resolution vs. high-resolution) and imaging (surface structure enhancement and index of hemoglobin color enhancement) settings can lead to different findings in the detection of the same lesion [25, 26]. Moreover, the colonoscopist's experience may have a considerable impact on the detection rate: if the colonoscopist does not have sufficient training in the chromoendoscopy of flat and depressed lesions with an NBI system, the usefulness of NBI for adenoma detection may not be evident. Finally, we note that most of the previous studies of NBI used a single-center design.

To overcome the aforementioned confounding factors, we aimed to evaluate the colonic adenoma detection rate achieved with NBI versus that achieved with WLI by using consistent NBI system, endoscope, and imaging settings, and experienced colonoscopists.

Patients and methods

Study population

Consecutive patients who were scheduled to undergo total colonoscopy with NBI at six institutions were considered eligible for inclusion in the study. The study was performed in university settings/academic centers. Patients with a history of surgical colorectal resection or those with inflammatory bowel disease, familial adenomatous polyposis, or hereditary non-polyposis colorectal cancer were excluded.

The institutional medical ethics committees approved the study protocol, which adhered to the tenets of the Declaration of Helsinki, and all patients gave written informed consent for diagnosis and treatment before the procedures. This study was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN 000002934).

This study was supported by the Ministry of Health, Labour and Welfare of Japan, and there are no conflicts of interest between the authors and this or any other organization or company.

Study design

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, the enrolled patients were randomized to undergo tandem colonoscopy with either NBI followed by WLI (NBI–WLI group) or WLI followed by NBI (WLI–NBI group).

After the endoscopists had achieved complete colonoscope insertion into the cecum with WLI, they were informed of the patient's allocation. Patients with poor bowel preparation, those with melanosis coli, those with multiple polyps unresectable in a single endoscopic examination, and those with advanced cancer were withdrawn.

We examined only the right colon, including the cecum, ascending colon, and transverse colon, because of a previous report of positive adenoma detection with NBI in this region, and to reduce the patient's discomfort during insertion and withdrawal.

Randomization

Random assignment was performed in each case by an investigator using a computer-aided system on the Medical Research Support website (Kyoto, Japan). A minimization algorithm was used to balance the selection of the primary

examination, according to the following 4 stratification variables: institution, age (<60 and ≥60 years), gender, and indication for colonoscopy.

Endoscopic equipment and setting

All procedures were performed up to the cecum by using a high-definition colonoscope (CF-H260AZI; Olympus Optical). A video endoscope system (EVIS LUCERA SPECTRUM; Olympus Optical) was used without a magnifying system. The NBI settings were fixed at surface structure enhancement level A-5 and adaptive index of hemoglobin color enhancement level 3. Twenty-seven endoscopists, each of whom had performed more than 5000 colonoscopies and more than 500 NBI colonoscopies, participated in this study.

Endoscopic procedure

For bowel preparation, 2–3 L of polyethylene glycol solution was administered in the morning on the day before the procedure. Scopolamine butylbromide (10 mg) was administered in the absence of contraindications, and midazolam (0.03 mg/kg) and/or pethidine hydrochloride (35 mg) was used for conscious sedation only when a patient complained of discomfort or pain. An examiner assessed the quality of bowel preparation according to the extent of mucosal visualization after suction of the fluid residue, as follows: excellent (approximately 100 % mucosal visualization following suction of fluid residue); good (approximately 90 % mucosal visualization); fair (less than 90 % mucosal visualization); poor (large amounts of solid fecal matter were found) [27]. The endoscopists who participated in the study were blinded to the indication for the procedure and and to the findings of previous colonoscopy.

In the NBI–WLI group, the colonoscope was withdrawn from the cecum to the splenic flexure with NBI, reinserted into the cecum, and then withdrawn again to the splenic flexure with WLI; in the WLI–NBI group, the same steps were performed with WLI first and then with NBI. The same endoscopist performed the primary and secondary examinations for the same patient. Patients were maintained in a supine position during NBI–WLI and WLI–NBI examinations, because changing the position did not influence the detection and miss rate [28].

In the primary examination, the endoscopists diagnosed lesions using the image obtained upon the detection of the lesion. At the same time, lesions less than 20 mm in diameter that were diagnosed as adenomas were removed endoscopically, and all lesions that were diagnosed as hyperplastic polyps were biopsied. All endoscopic treatments were performed using WLI. The same procedure was followed for the secondary examination. Adenoma lesions more than 20 mm in diameter were observed with both NBI and WLI and were removed by endoscopic mucosal resection or endoscopic submucosal dissection on another day in the hospital.

We did not use chromoendoscopy during the NBI or WLI because it elevates the adenoma detection rate; however, when observation with chromoendoscopy was diagnostically required, it was performed after the secondary examination.

In the primary examination, all lesions diagnosed as adenomas were removed by hot biopsy, snare polypectomy, endoscopic mucosal resection on the same day, or endoscopic submucosal dissection on another day, and all lesions diagnosed as hyperplastic polyps were biopsied. The location of each lesion was defined according to landmarks such as the hepatic flexure and splenic flexure. The lesion size was estimated by using open endoscopic biopsy forceps and/or a snare. Macroscopically, the lesions were classified according to the Paris classification of superficial gastrointestinal lesions [29]. We measured the total observation time, excluding mucosal washing, the diagnostic time, and the therapeutic time using a stopwatch. A doctor who was not the examiner, or a nurse, operated the stopwatch.

Histologic examination

All resected and biopsy specimens were retrieved, immediately fixed in 10 % buffered formalin solution, and examined histologically by hematoxylin and eosin staining. Experienced gastrointestinal pathologists blinded to the endoscopic diagnosis determined the histopathological diagnosis according to the World Health Organization (WHO) criteria [30]. Only traditional serrated adenoma (TSA) was included in the category of serrated adenoma.

Statistical analysis

The primary outcome measure was the detection rate of non-advanced adenoma lesions [adenoma with low-grade dysplasia (LGD)] and advanced adenoma lesions [adenoma of ≥10 mm or with villous histology in 25 % of polyps or with high-grade dysplasia (HGD) and submucosal invasive cancer] in the primary examination. Assuming an adenoma detection rate of 61 % in the right colon with WLI, from the pilot study at the National Cancer Center Hospital East and an increase of 16 % in the detection rate with NBI [17], the necessary sample number was calculated to be 369 patients in each group, 738 patients in total. Hence, 400 patients were required in each group for the probability of an α error to be 0.05 with a power of 0.80 (reflecting a β error of 0.2). The secondary outcome measure was the

adenoma miss rate in the primary examination; we defined a missed adenoma lesion as one detected only during the secondary examination.

Nominal and ordinal variables are expressed as frequencies and percentages. Continuous variables are expressed as means and standard deviations (age, adenoma lesions per patient) or medians and ranges (withdrawal time). Continuous data were compared by using the Mann–Whitney *U*-test. Pearson's χ^2test or Fisher's exact test was used to analyze categorical data and compare proportions. SPSS version 11 (SPSS, Chicago, IL, USA) was used for the statistical analyses. All statistical tests were two-tailed and significance was defined as $p < 0.05$.

Results

Group characteristics

Between October 2008 and March 2010, 813 patients were enrolled in this study. Of the 813 enrolled patients, 406 and 407 patients were randomly assigned to the NBI–WLI and WLI–NBI groups, respectively (Fig. 1). Three patients were withdrawn just before the primary examination, because of refusal to participate in the study ($n = 1$) and cardiac arrhythmia ($n = 2$). The colonoscope reached the cecum in 809 (99.9 %) of the remaining 810 study patients. Then 27 patients were withdrawn because of poor bowel preparation ($n = 8$), melanosis coli ($n = 6$), multiple polyps unresectable in a single endoscopic examination ($n = 5$), advanced cancer ($n = 4$), duplicated registration ($n = 1$), and other factors ($n = 3$). Finally, we analyzed 389 and 393 patients in the NBI–WLI and WLI–NBI groups, respectively.

The characteristics of the groups are listed in Table 1. The 782 analyzed patients included 553 (70 %) men, and the mean patient age was 63.2 ± 10.1 years. The indications for colonoscopy were polyp surveillance ($n = 553$), screening ($n = 183$), any abdominal symptoms ($n = 45$).and family history of colorectal cancer ($n = 1$). The bowel preparation was described as excellent, good, and fair in 246, 439, and 97 patients, respectively. The groups did not differ significantly in gender, age, indication for colonoscopy, bowel preparation, or institution. No complications occurred with the endoscopic treatment.

Table 2 shows the total observation times of the examinations. The observation times did not differ significantly between the groups.

Detection rates

The numbers of patients with lesions detected by primary NBI and WLI, including adenoma and hyperplastic polyp lesions, were 191 and 187, respectively (Table 3). The detection rate of adenoma lesions did not differ significantly between primary NBI and primary WLI (42.4 vs. 42.5 %). When we compared the detection rates of primary NBI and WLI by adenoma characteristics, the percentages of patients were not significantly different in terms of the number of lesions, non-advanced or advanced adenoma, and polypoid or flat and depressed adenoma.

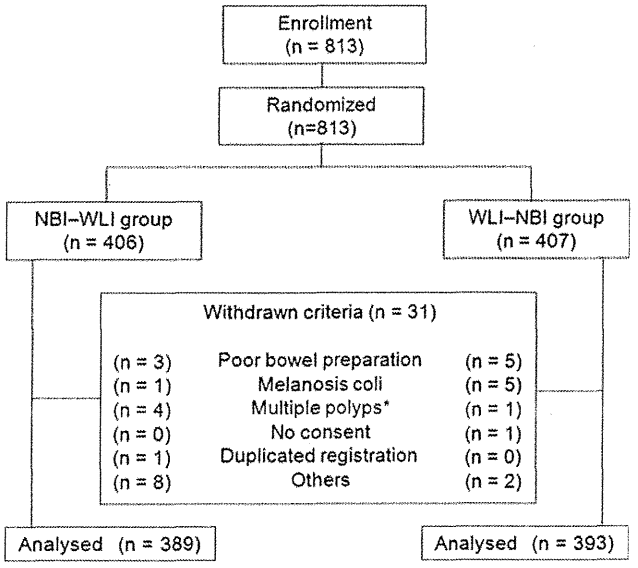

Fig. 1 CONSORT diagram. Overview of the study design. *Multiple polyps* (*asterisk*) many polyps unresectable in a single endoscopic examination, *NBI* narrow band imaging, *WLI* white light imaging

Table 1 Patient characteristics

Characteristic	NBI–WLI group ($n = 389$)	WLI–NBI group ($n = 393$)	p
Male gender	267 (69)	277 (70)	0.57
Mean (SD) age (years)	63.2 (10.2)	63.3 (9.9)	0.58
Indication for colonoscopy			0.67
Polyp surveillance	280	273	
Screening	88	95	
Any abdominal symptom	21	24	
Family history of CRC	0	1	
Bowel preparation			0.25
Excellent	115	131	
Good	219	220	
Fair	55	42	

Data represent the number of patients (%) unless indicated otherwise
NBI narrow band imaging, *WLI* white light imaging, *CRC* colorectal cancer

Table 2 Observation time

Time (s)	NBI–WLI group			WLI–NBI group			Primary imaging			Total		
	NBI	WLI	*p*	WLI	NBI	*p*	NBI	WLI	*p*	NBI	WLI	*p*
Median	210	164	0.67	180	180	0.98	210	180	0.76	190	180	0.78
Range	59–1112	52–1230		60–1200	20–1200		59–1112	60–1200		20–1200	52–1230	

NBI narrow band imaging, *WLI* white light imaging

Table 3 Detection rates of primary NBI and WLI

	Primary NBI ($n = 389$)	Primary WLI ($n = 393$)	*p*
Patients with any lesion	191 (49.1)	187 (47.6)	0.67
Patients with adenoma lesions	165 (42.4)	167 (42.5)	0.98
Mean (SD) no. of lesions per patient	0.79 (1.23)	0.79 (1.27)	0.98
Patients with 1–2 lesions	135 (34.7)	133 (33.8)	0.88
Patients with ≥3 lesions	30 (7.7)	34 (8.7)	
Patients with non-advanced adenoma[a]	106 (27.2)	112 (18.5)	0.59
Patients with advanced adenoma[a]	59 (15.2)	55 (14.0)	
Patients with polypoid adenoma only	30 (7.2)	45 (11.5)	0.06
Patients with flat and depressed adenoma	135 (34.1)	122 (31.0)	

Data represent the number of patients (%) unless indicated otherwise

[a] Advanced adenoma: adenomas ≥10 mm or with villous histology in 25 % of the polyps or with high-grade dysplasia or invasive cancer

Characteristics of the detected adenoma lesions

The total numbers of adenoma lesions detected by primary NBI and WLI were 306 and 310, respectively (Table 4), and those identified by secondary WLI and NBI were 83 and 119, respectively. The adenoma miss rates of primary NBI and WLI were significantly different (21.3 vs. 27.8 %; $p = 0.03$). In terms of location, there was no significant difference in the detection rate. Morphologically, polypoid lesions were detected significantly more often by primary NBI ($p = 0.006$). Further, 4-mm or smaller lesions ($p = 0.04$) and LGD ($p = 0.04$) were detected significantly more often by primary NBI. There was no significant difference in the detection rate for advanced adenoma. Figure 2 shows representative images of polyps detected by one imaging technique and missed by the other.

Discussion

The present study was the first randomized tandem colonoscopy trial in a multicenter setting for comparing the adenoma detection and miss rates of NBI and WLI. The results did not show any objective advantage of NBI over WLI in terms of improved detection of adenoma lesions in primary colonoscopy; however, NBI had a lower adenoma miss rate in the proximal colon than WLI by tandem colonoscopy.

The results of previous randomized trials comparing the adenoma detection rate of colonoscopy with NBI against that of colonoscopy without NBI are controversial. For example, Uraoka et al. [17] reported that the total number of adenoma lesions detected by colonoscopy with NBI was significantly higher than that detected by high-definition colonoscopy alone ($p = 0.02$) and adenomatous lesions in the right colon were identified more often by NBI ($p = 0.02$). Similarly, Inoue et al. [16] noted a significantly higher number of patients with detected diminutive (<5 mm) adenomas ($p = 0.011$) and lesions in the distal colon ($p = 0.02$) in their NBI group than in their control group. On the other hand, Rex and Helbig [18] reported no significant difference in the percentage of patients with adenomas detected by WLI versus NBI ($p = 0.68$). Further, Adler et al. [21] reported no significant difference between their NBI and their control groups in terms of the general adenoma detection rate (0.32 vs. 0.34 %). We attribute these varied results to differences in factors such as the NBI systems, endoscope and imaging settings, and the learning curves among the studies.

Differences in the NBI systems can be explained by differences between the optical-electronic technologies employed in video endoscopes in the previous studies: a sequential system (LUCERA) was used in the studies conducted in Japan and the United Kingdom, whereas a non-sequential system (EXERA II) was used in the other Western studies. Though we used only the LUCERA system in the present study, the present study was also a negative study of the rate of adenoma detection. Hence, we consider that the video endoscope system alone is not a reason for the negative study in the adenoma detection rate of NBI.

Darkness and noise of the viewing screen cause problems in NBI without high-definition colonoscopy, and

Table 4 Clinicopathologic characteristics of adenoma lesions detected during primary and secondary examinations

Characteristic	Primary		Secondary		*p*
	NBI	WLI	WLI	NBI	
Adenoma lesions	306 (78.7)	310 (72.2)	83 (21.3)	119 (27.8)	0.03
Location					
Cecum	57 (90.5)	49 (89.1)	6 (9.5)	6 (10.9)	0.80
Ascending colon	120 (78.9)	129 (71.7)	32 (21.1)	51 (28.3)	0.13
Transverse colon	129 (74.1)	132 (68.0)	45 (25.9)	62 (32.0)	0.20
Morphology					
Polypoid	136 (89.5)	139 (78.1)	16 (10.5)	39 (21.9)	0.006
Ip	8 (88.9)	12 (100)	1 (11.1)	0	0.24
Isp	13 (100)	15 (83.3)	0	3 (16.7)	0.12
Is	115 (88.5)	112 (75.7)	15 (11.5)	36 (24.3)	0.006
Flat and depressed	170 (72.0)	171 (68.6)	67 (28.0)	80 (31.4)	0.42
IIa	167 (71.4)	167 (68.2)	67 (28.6)	78 (31.8)	0.45
IIa + IIc	3 (100)	3 (75.0)	0	1 (25.0)	0.35
IIc	0	1 (50.0)	0	1 (50.0)	–
Size (mm)					
1–4	148 (74.4)	154 (65.3)	51 (25.6)	82 (34.7)	0.04
5–9	108 (79.4)	109 (76.8)	28 (20.6)	33 (23.2)	0.59
≥10	50 (92.6)	47 (92.2)	4 (7.4)	4 (7.8)	0.93
Histopathological findings					
TSA	7 (77.8)	12 (85.7)	2 (22.2)	2 (14.3)	0.62
LGD	277 (77.7)	283 (70.9)	80 (22.3)	116 (29.1)	0.04
LGD with villous	2 (100)	0	0	0	–
HGD	12 (93.3)	7 (92.9)	1 (6.7)	1 (7.1)	0.72
HGD with villous	2 (100)	6 (100)	0	0	–
Invasive cancer	6 (100)	2 (100)	0	0	–

Data represent the number of lesions (%)

NBI narrow band imaging, *WLI* white light imaging, *TSA* traditional serrated adenoma, *LGD* adenoma with low-grade dysplasia, *HGD* adenoma with high-grade dysplasia

these problems are usually solved by using high-definition colonoscopy. In addition, the wider colorectal lumen than the esophageal lumen in NBI is considered to be a reason for the screen darkness. An NBI setting different from that used in esophageal observation by high-definition colonoscopy is, therefore, indispensable for polyp detection in the colon and rectum. Uraoka et al. [25, 26] have reported that the A-5 image setting of the surface structure enhancement function, together with the level 3 adaptive index of hemoglobin color enhancement function, seem to be the most suitable settings for the detection of colorectal adenomas. In accordance with these findings, we used only high-definition colonoscopy to compare WLI with NBI and we applied surface structure enhancement level A-5 and adaptive index of hemoglobin color enhancement level 3 for NBI.

Our study results did not show a significant difference between NBI and WLI in the primary outcome measure but results were significantly different in the secondary outcome measure. Specifically, we found no significant difference in the adenoma detection rates by primary NBI versus primary WLI. We consider these results reliable because there was no significant difference in the bowel preparation results or total observation times between the groups. Only expert colonoscopists performed the procedures in this study; therefore, it is necessary to clarify the usefulness of NBI for adenoma detection by all colonoscopists, including novices, in the future. Further, the detection rates of adenoma lesions by primary NBI and WLI were 78.7 and 72.2 % when we considered the detection rate of adenoma lesions by both primary and secondary examinations to be 100 %. In other words, the adenoma miss rates by primary NBI and WLI were 21.3 and 27.8 % ($p = 0.03$). The higher miss rate of WLI is similar to that reported previously. [5–7] Furthermore, Kaltenbach et al. [20] reported that NBI did not improve the colorectal adenoma miss rate compared to WLI in a randomized controlled trial using tandem colonoscopy (NBI–WLI vs. WLI–WLI; 12.6 vs. 12.1 %, respectively). Their adenoma miss rate using WLI was lower than the adenoma miss rate of 10–30 % reported in other studies. However, when we compared our results with their findings, it was evident that our miss rate was high. The differences between the study of Kaltenbach et al. and our

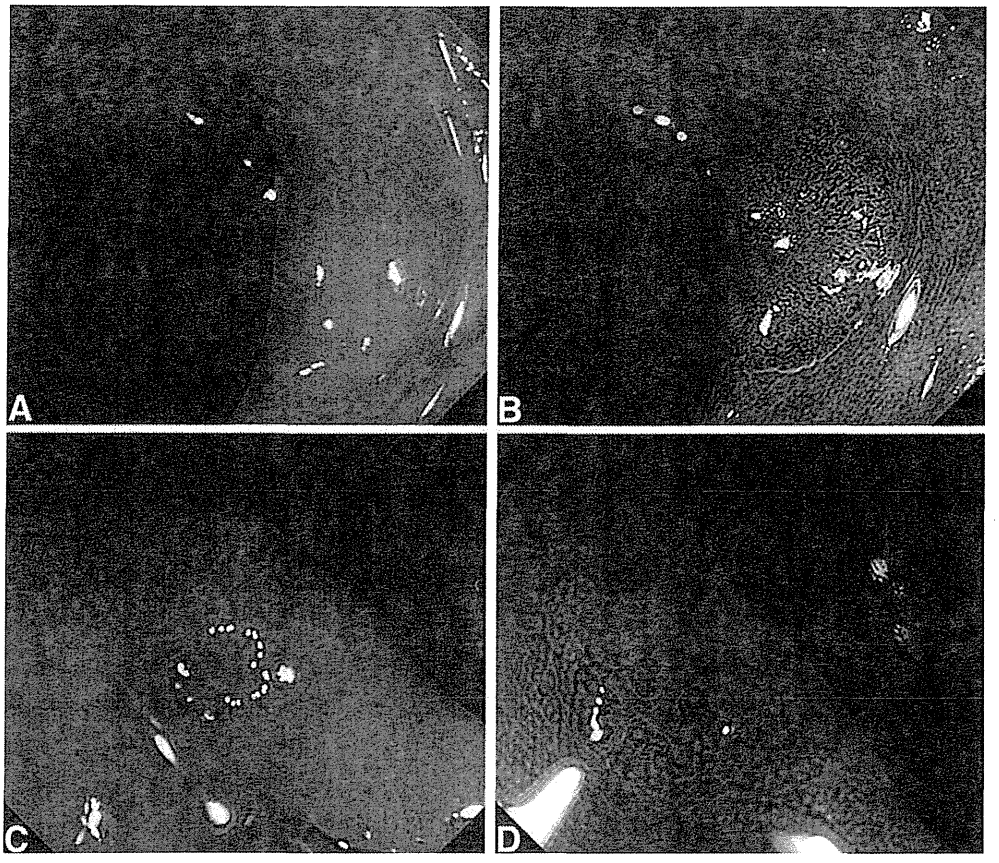

Fig. 2 A flat elevated lesion was detected in the transverse colon. The size of the lesion was 7 mm in diameter. The final histopathological diagnosis was adenoma with low-grade dysplasia (LGD). **a** The polyp was missed by WLI; **b** the same lesion was identified by subsequent NBI. **c, d** A depressed lesion was detected in the transverse colon. The size of the lesion was 5 mm in diameter. The final histopathological diagnosis was LGD. **c** The polyp was missed by WLI; **d** the same lesion was identified by subsequent NBI

study are the use of LUCERA versus EXERA II and the single-center versus multicenter design. Furthermore, we believe that a difference in the resolution of NBI and WLI may have influenced the results, because we were able to detect small lesions with NBI.

In line with previous reports [16, 17], we found that significantly higher numbers of small lesions (<5 mm) and/or LGD lesions were detected by NBI than by WLI16, 17. Further, nearly all the adenoma lesions we detected were flat elevated or polypoid in shape, and two were depressed. Depressed lesions are considered to have a higher malignant potential than polypoid ones of similar size [31–34]. The superiority of NBI over WLI in the detection of depressed lesions was not proven in the present study; however, we believe NBI is a promising modality for detecting small neoplastic lesions. The advantage of NBI endoscopy is simply to get the NBI view when we use a one-touch electrical button and to avoid indigo carmine dye-spraying. In addition, we can diagnose a lesion at the same time as it is detected. In the colorectal region, NBI is useful for differentiating non-neoplastic from neoplastic lesions, and magnifying NBI is effective for determining the depth of invasion in early neoplasms [35–37].

In the present study, we could not evaluate serrated lesions because the pathological diagnosis of serrated lesions (particularly, sessile serrated adenoma) is not yet unified among Japanese pathologists. The number of TSAs detected by primary NBI and WLI were 7 and 12, respectively, and those identified by secondary WLI and NBI were 2 and 2, respectively. The miss rates of primary NBI and WLI for these lesions were not significantly different (22.2 vs. 14.3 %; $p = 0.62$).

This study has several limitations. First, the procedures were conducted only in the right colon, because Uraoka et al. [17] reported higher adenoma detection rates with NBI in the right colon, and a higher adenoma miss rate has been reported in the right colon than in the left colon [5]. Further, because complete back-to-back colonoscopy is sometimes uncomfortable for patients without sedation, we defined the region from the cecum to the splenic flexure as the target area in our study. Another limitation is that WLI was used for colonoscope insertion in both the study groups, which could have

influenced the NBI results if some lesions were identified during insertion. However, we used the same imaging condition and study design for tandem colonoscopy in both the groups. Moreover, the detected lesions were removed endoscopically using WLI, because of the darkness of the screen with NBI. We cannot entirely exclude the possibility that some switches of endoscopic treatment influenced the detection rates in both the groups. Endoscopic treatment is, however, usually focused on the small area in which the polyp is located and the examiner likely concentrates on the endoscopic treatment rather than on the detection of additional lesions. Another limitation is that both the NBI and WLI examinations were performed by the same endoscopist. There may be investigator bias. However, we believe this does not substantially influence the results, because this was a multicenter trial and the endoscopists performed procedures for both the NBI–WLI and WLI–NBI groups. Another limitation is that, in the distinction between neoplasia and non-neoplasia, NBI may be expected to have a small advantage. In the present study, expert colonoscopists examined the lesions; such experts are able to distinguish between neoplasia and non-neoplasia using WLI as well as NBI. Furthermore, because all detected non-neoplastic lesions were removed or biopsied, the difference between NBI and WLI with respect to the distinction between neoplasia and non-neoplasia would not have affected the overall adenoma detection rate. Therefore, we believe that the primary endpoint of the adenoma detection rate was not affected by this discrepancy. Finally, the current NBI systems have problems such as darkness and noise. Even if these systems are used with high-definition colonoscopy, the brightness of the screen is still not sufficient. Further, NBI system-related improvement is necessary for enhanced adenoma detection.

In conclusion, NBI does not have a higher adenoma detection rate during primary colonoscopy than WLI, but it has a lower adenoma miss rate in the proximal colon by tandem colonoscopy. NBI can be expected to represent a suitable modality for screening colonoscopy, because the miss rate is low.

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Conflict of interest The authors declare that they have no conflict of interest.

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SPECIAL REPORT

MID-TERM PROGNOSIS AFTER ENDOSCOPIC RESECTION FOR SUBMUCOSAL COLORECTAL CARCINOMA: SUMMARY OF A MULTICENTER QUESTIONNAIRE SURVEY CONDUCTED BY THE COLORECTAL ENDOSCOPIC RESECTION STANDARDIZATION IMPLEMENTATION WORKING GROUP IN JAPANESE SOCIETY FOR CANCER OF THE COLON AND RECTUM

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We carried out a retrospective questionnaire survey of 792 submucosal colorectal carcinoma (CRC) cases from 15 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in Japanese Society for Cancer of the Colon and Rectum. In these cases, endoscopic resection (ER) and surveillance was carried out without additional surgical resection. Local recurrence or metastasis was observed in 18 cases. Local submucosal recurrence was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth less than 1000 μm, which has other risk factors for metastasis. Metastatic recurrence was observed in the lung, liver, lymph node, bone, adrenal glands, and the brain; in some cases, metastatic recurrence was observed in multiple organs. Death due to primary disease was observed in six cases. The average interval between ER and recurrence was 19.7 ± 9.2 months. In 16 cases, recurrence was observed within 3 years after ER. Thus, validity of ER without additional surgical resection for cases with the conditions that the depth of submucosal invasion is less than 1000 μm and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement was proven.

Key words: endoscopic resection, prognosis, recurrence, submucosal colorectal carcinoma.

INTRODUCTION

In the Guidelines for Colorectal Cancer Treatment, 1st Edition, 2005 by Japanese Society for Cancer of the Colon and Rectum (JSCCR),[1] the curative conditions after endoscopic resection (ER) for submucosal colorectal carcinoma (CRC) state that 'if a lesion is completely resected by ER, the depth of submucosal invasion is less than 1000 μm, and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement, the possibility of lymph node (LN) metastasis will be extremely low so that the surveillance is allowed without additional surgical resection.' This statement has generated a certain consensus. However, these conditions were established on the basis of the analysis of submucosal CRC cases obtained from surgical resection,[2] and there are very few reports of cases in which surveillance after ER for submucosal CRC was carried out extensively.

In the present study, we obtained information on the non-surgical submucosal CRC cases with surveillance after ER; this information was obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. Using the information for these cases, we analyzed the risk factors for recurrence, the interval between ER and recurrence, and the recurrence pattern (local or metastatic). In this report, we have introduced data that can be used to verify the validity of the curative conditions after ER for submucosal CRC.

QUESTIONNAIRE SURVEY METHOD

The retrospective questionnaire survey was carried out for submucosal CRC cases obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. In these

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Table 1. Facilities that answered the questionnaire

Kitasato University East Hospital
Hiroshima University Hospital
National Cancer Center East Hospital
Asahikawa City Hospital
Jichi Medical University Hospital
National Cancer Center Hospital
Osaka Medical Center for Cancer and Cardiovascular Diseases
Nagoya City University Hospital
Kobe University Hospital
Fukuoka University Chikushi Hospital
Showa University Northern Yokohama Hospital
Cancer Institute Hospital Ariake
Tokyo University Hospital
Kyusyu University Hospital
Juntendo University Hospital

cases, surveillance had been carried out after ER without additional surgical resection for various reasons.

The following factors were surveyed: age of the patient at the initial ER, gender, tumor size, location, macroscopic type, ER technique (en bloc or piecemeal resection), histological margin (lateral or vertical), histological grade, histological grade at the deepest invasive portion, depth of submucosal invasion (μm), lymphatic/venous involvement, follow-up period after ER, existence of recurrence, recurrence pattern, and vital prognosis. Tumor size, location, macroscopic type, histological margin, histological grade, depth of submucosal invasion and lymphatic/venous involvement were recorded according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 7th Edition, Revised Version by JSCCR[3]. Further, we directly used the clinical and histopathological findings stated in the questionnaire.

QUESTIONNARIE SURVEY RESULTS

Among the 28 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR, 15 institutions participated in this questionnaire survey (response rate, 53.6%) (Table 1). The information for 792 patients (556 male and 236 female) was collected from these 15 institutions. The average age of the patients was 72.9 ± 12.3 years (range, 19–93 years). The lesions were located in the cecum (25 cases), ascending colon (91 cases), transverse colon (77 cases), descending colon (56 cases), sigmoid colon (339 cases), and rectum (204). The average size of the lesions was 16.2 ± 8.2 mm (3–60 mm). The macroscopic type of the lesions showed that there were 0-Ip (209 cases), 0-Isp (197 cases), 0-Is (142 cases), 0-IIa (141 cases), 0-IIa + IIc (76 cases) and 0-IIc (27 cases). En bloc resection was carried out in 569 cases, and piecemeal resection was carried out in 114 cases; the ER technique was not mentioned in 109 cases. The histological lateral margin-positive was reported in 50 cases and was negative in 504 cases; the lateral margin was not mentioned in 238 cases. The histological vertical margin-positive was reported in 34 cases and was negative in 563 cases; the vertical margin was not mentioned in 195 cases. With regard to the histological grade, 724 lesions were graded as well differentiated adenocarcinoma, 63 were graded as moderately differentiated adenocarcinoma, two were graded as poorly differentiated adenocarcinoma, and the histological grade was not mentioned in three cases. The average depth of submucosal invasion was 1388 ± 1546 μm (5–10 000 μm); submucosal invasion less than 1000 μm was observed in 324 cases; deeper than 1000 μm was observed in 315 cases; and the depth of submucosal invasion was not mentioned in 153 cases. The average follow-up period was 38.7 ± 83.0 months, and recurrence was observed in 18 cases (2.3%). The recurrence rate for the cases that underwent en bloc resection was 2.5% (14/569) and that for the cases that underwent piecemeal resection was 3.5% (4/114); there was no significant difference between these two techniques. In 368 cases, the lesion satisfied the curative conditions after ER for submucosal CRC, whereas the lesion did not satisfy the curative conditions after ER for submucosal CRC in 302 cases; the relationship between the lesion and the curative conditions after ER for submucosal CRC was not mentioned in 122 cases.

HISTOPATHOLOGICAL RISK FACTORS FOR RECURRENCE

Among the 792 cases with surveillance after ER for submucosal CRC, information on all factors related to the histopathological findings was obtained in 387 cases (48.9%). These cases were re-examined to determine the relationship between the following factors and recurrence: histological grade, histological grade at the deepest invasion portion, existence of budding,[4] submucosal invasive depth of 1000 μm, lymphatic involvement, and venous involvement.

Among these 387 patients, there were 275 males and 112 females. The average age of the patients was 64.4 ± 11.2 years (19–93 years). The average tumor size was 15.7 ± 8.3 mm (4–60 mm). The lesions were located in the cecum (6 cases), ascending colon (47 cases), transverse colon (37 cases), descending colon (40 cases), sigmoid colon (174 cases), and rectum (83 cases). Macroscopic type of the lesions revealed 0-Ip (138 cases), 0-Isp (105 cases), 0-Is (43 cases), 0-IIa (45 cases), 0-IIa+IIc (24 cases), 0-IIc (9 cases), and other type (23 cases). The average follow-up period after ER was 39.5 ± 36.7 months (3–174 months). Further, recurrence was observed in 10 cases. There were no intramucosal recurrent cases.

Using univariate analysis, each of the following factors was confirmed to be significantly related to recurrence: existence of budding,[4] submucosal invasion depth deeper than 1000 μm, and lymphatic/venous involvement (Table 2). Multivariate analysis using logistic-regression analysis was carried out using these four factors. Consequently, submucosal invasion depth deeper than 1000 μm and lymphatic involvement were indicated as the factors with high odds ratios, and only lymphatic involvement was considered as an independent risk factor for recurrence (Table 3).

CLINICOPATHOLOGICAL CHARACTERISTICS OF THE CASES SHOWING RECURRENCE

The 18 cases (11 male and 7 female) of recurrence are shown in Table 4. The average age of the patients was

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Table 2. Recurrence rate after ER for submucosal CRC in relation to pathological features ($n = 387$)

Pathological features	*n*	Recurrence positive (%)	*P* value
Histological grade			
well or mod	387	10 (3)	
por or muc	0		–
Histological grade at the deepest invasive portion			
well or mod	367	9 (2)	
por or muc	11	1 (9)	0.2756
Budding			
Positive	42	4 (10)	
Negative	345	6 (2)	0.0015
Depth of submucosal invasion (μm)			
<1000	220	1 (0.5)	
≧1000	167	9 (5)	0.0016
Lymphatic involvement			
Positive	29	5 (17)	
Negative	358	5 (1)	0.0002
Venous involvement			
Positive	18	3 (17)	
Negative	369	7 (2)	0.0070

CRC, colorectal carcinoma; ER, endoscopic resection; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; well, well differentiated adenocarcinoma.

Table 3. Multivariate analysis of risk factors for recurrence after ER for submucosal CRC ($n = 387$)

Risk factors	Odds ratio	(*P*-value)	95%CI
Depth of submucosal invasion ≧1000 μm	7.014	(0.0753)	0.820–60.01
Lymphatic involvement positive	6.363	(0.0139)	1.457–27.79
Budding positive	2.258	(0.3466)	0.414–12.31
Venous involvement positive	2.275	(0.3446)	0.634–11.64

CRC, colorectal carcinoma; ER, endoscopic resection.

69.2 ± 7.2 years. The lesions were located in the cecum (2 cases), ascending colon (2 cases), sigmoid colon (6 cases), and the rectum (8 cases). The average size of the lesions was 19.7 ± 9.2 mm. The macroscopic type of the lesions revealed 0-Ip (6 cases), 0-Isp (4 cases), 0-Is (3 cases), 0-IIa (3 cases), 0-IIa+IIc (1 case), and another type (1 case). En bloc resection was carried out in 14 cases, and piecemeal resection was carried out in four cases. Histological lateral margin-positive was reported in eight cases, and histological vertical margin-positive was reported in eight cases. Among the 15 cases in which the depth of submucosal invasion was reported, the depth was <1000 μm in one case and ≧1000 μm in 14 cases.

Local intramucosal recurrence was observed in four cases with a histological positive lateral margin. Among these four cases, metastatic recurrence was observed in two cases (lung metastasis was observed in one case, and the details were unknown in one case). However, as the details of the vertical margin were unknown, the exact depth of submucosal invasion could not be measured. Among the 18 cases in which the submucosal invasive carcinoma showed recurrence, local recurrence in the form of submucosal carcinoma was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth <1000 μm; however, these cases had lymphatic involvement and a positive vertical margin. Among the cases in which metastatic recurrence was observed in the organs, recurrence was observed in the lung (5 cases), liver (4 cases), LN (4 cases), bone (2 cases), adrenal gland (1 case), and brain (1 case); in some cases, metastatic recurrence was observed in multiple organs. Among the eight cases in which the patients died, death due to the primary disease was observed in six cases, death due to other diseases was observed in one case, and there were no details regarding the death in one case.

The average interval between ER and recurrence was 19.7 ± 9.2 months. Among the 18 cases in which recurrence was observed, 16 cases showed recurrence within 3 years after ER. Among the 18 cases in which recurrence was observed, in all cases the lesions did not satisfy the curative conditions after ER for submucosal CRC.

RELATIONSHIP BETWEEN DEPTH OF SUBMUCOSAL INVASION AND POSITIVE RATE OF VERTICAL MARGIN IN EACH MACROSCOPIC TYPE OF SUBMUCOSAL CRC

We examined the relationship between depth of submucosal invasion and positive rate of vertical margin according to the

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