[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.

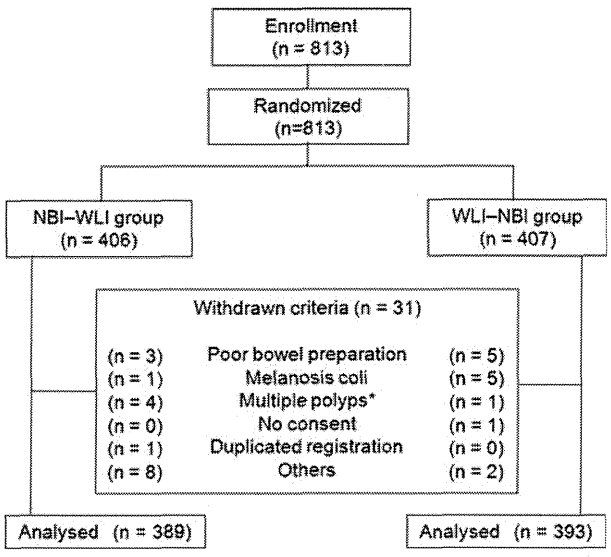

Fig. 1 CONSORT diagram. Overview of the study design. *Multiple polyps* (*asterisk*) many polyps unresectable in a single endoscopic examination, *NBI* narrow band imaging, *WLI* white light imaging

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

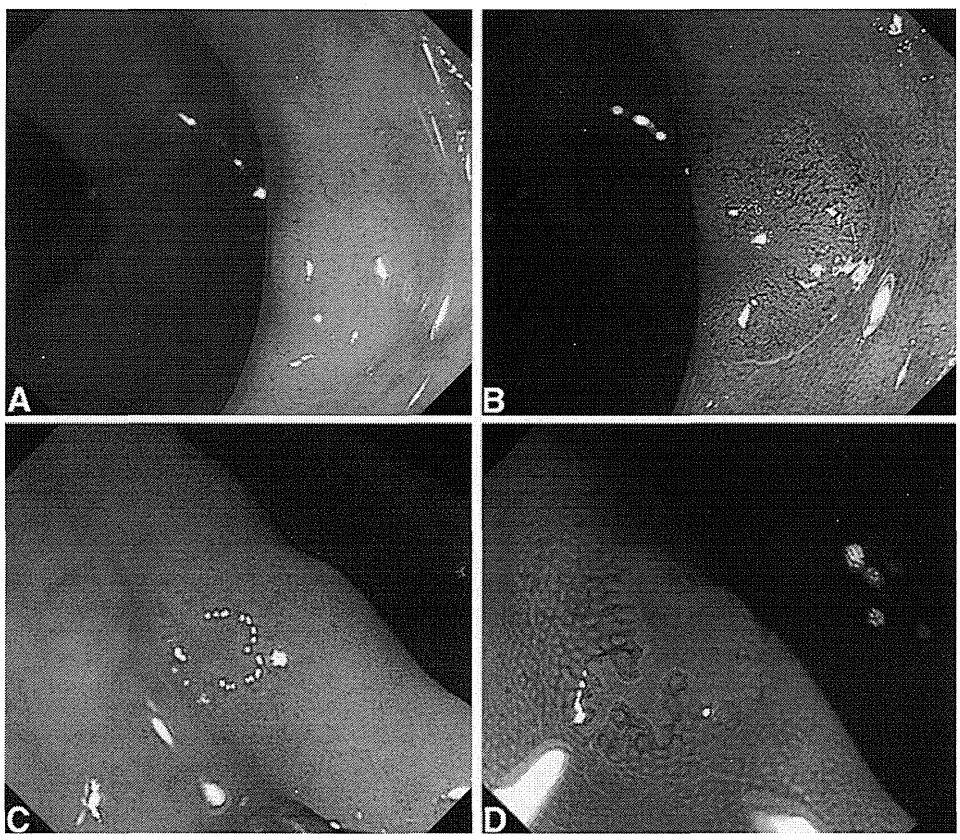

Fig. 2 A flat elevated lesion was detected in the transverse colon. The size of the lesion was 7 mm in diameter. The final histopathological diagnosis was adenoma with low-grade dysplasia (LGD). **a** The polyp was missed by WLI; **b** the same lesion was identified by subsequent NBI. **c, d** A depressed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

The use of computed tomographic colonography in predicting the difficulty of endoscopic treatment for large protruding neoplasms

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Dear Editor:

Submucosal fibrosis is considered a major hurdle in endoscopic submucosal dissection (ESD), which is an effective technique for treating colorectal neoplasms. Although it is relatively easy to predict the difficulty of endoscopic resection for laterally spreading tumors (LST), it is more difficult in the case of large protruding lesions (Paris type 0-Is, >20 mm in diameter) such as villous tumors, which are often eventually removed by multiple piecemeal resection. However, considering the high incidence of recurrent or residual tumors and the difficulty of precise histopathological evaluation, piecemeal endoscopic mucosal resection (EMR) should be avoided. Instead, when endoscopic resection is predicted to be difficult, laparoscopic assisted colectomy is a viable treatment option; therefore, the objective evaluation of fibrotic changes in the submucosal layer is important. Although this evaluation may be accomplished using endoscopic miniprobe ultrasonography (mEUS), which is effective in assessing the depth of invasion in both gastric cancer and colorectal neoplasms as well as that of submucosal fibrosis for flat or depressed lesions, its limited depth of penetration is a disadvantage in assessing protruding lesions. Moreover, the observation of lesions located on the oral side of folds using mEUS is also considered difficult, and a different method may be more suitable for identifying these cases.

Computed tomographic colonography (CTC) is currently an established technique for colorectal imaging that allows the evaluation of both endoluminal and transluminal features and has good diagnostic performance in T staging of colorectal cancer. Using CTC, images can be reconstructed in almost any plane and can be used to create three-dimensional images while maintaining diagnostic image resolution and without influencing the location of the lesion. It can also be used to evaluate both lesion morphology and intratumoral features, including those of protruding lesions and lesions located on the oral side of folds. Moreover, several studies have shown that the degree of fibrosis contributes to an enhancement pattern in contrast-enhanced CTC (CE-CTC). Thus, CE-CTC may potentially be used for evaluating the shape and morphological changes of the bowel wall, including the degree of fibrotic changes in the submucosal layer. In this letter, we describe the use of CTC in the identification of patients with intramucosal protruded-type neoplasm predicted to present endoscopic difficulties.

All patients who had undergone preoperative colonoscopy and same day CE-CTC at our institution from January 2006 to December 2008 were identified through retrospective analysis. After pretreatment colonoscopy and standard preparation, patients underwent CE-CTC examination for staging using a 64-multidetector row CT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). The scan range was from the abdomen to the pelvis, with the following parameters: 120 kV; 200–400 mA with automatic exposure control; 64 rows × 0.5 mm collimation; and helical pitch, 53 (pitch factor, 0.828). Anticholinergic drugs were injected intravenously immediately before each examination, and gas insufflation was performed via the anus with an

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automated CO_2 insufflator (Protocol; E-Z-EM, New York). For TNM staging, all patients were administered a total of 150 mL of contrast medium [Omnipaque (300 mg/mL); Daiichi-Sankyo Pharmaceuticals, Tokyo, Japan] intravenously with an autoinjector at a rate of 3.0 mL/s. The scan delays were set at 50 s (early phase) and 90 s (delayed phase) after the injection of the contrast medium. CE-CTC images were acquired for each patient in prone and supine positions and reviewed by an experienced radiologist for identifying "bundle-like low-density areas (BLDA)" in the submucosa, which were characterized as a lower density area than that of protruding intramucosal neoplasms in the early phase.

Patients with protruding intramucosal neoplasms larger than 20 mm in diameter were included in our study, whereas those with LSTs as per the endoscopic data were excluded. The 11 patients that met these criteria were divided into two groups according to the outcome of the endoscopic treatment: 6 cases of patients were included in group A, which comprised the difficult resections that had a piecemeal resected specimen with more than 10 pieces and/or a procedure time longer than 180 min, while group B included the remaining 5 cases. En bloc resection was achieved in 36% cases (4 out of 11), and the median duration of the procedure time was 95 min (interquartile range, 80–200 min). In group A, the median size of the lesions was 52.5 mm (range, 40–60), with 83% lesions located in the colon and 17% in the rectum. In group B, the lesions had a median size of 40 mm (range, 30–50 mm), and 80% was located in the rectum. No significant differences in the size or location of lesions were observed between the two groups (P=0.113 and P=0.067, respectively); however, the duration of the procedure was significantly longer in group A than group B (median time, 200 vs. 70 min; P=0.008). The rate of positive findings for BLDAs was 83% (five out of six) in group A and 20% (one out of five) in group B. Histopathological examination showed that the presence of BLDA corresponded to the presence of submucosal fibrosis.

Regarding clinical outcomes, en bloc resection was achieved in only 36% of the cases in this study. Although ESD was planned in nine cases, the procedure was abandoned and converted to piecemeal EMR in 56% (five out of nine) of these cases because of technical difficulties associated with submucosal fibrosis. As a previous Japanese multicenter study has reported that the en bloc resection rate of ESD for treatment of colorectal neoplasms was 88%, it appears that endoscopic treatment for large protruding lesions is more difficult than that for other colorectal neoplasms. Additionally, confounding factors other than submucosal fibrosis, such as location and lesion size, may have potentially contributed to the lack of success of endoscopic treatment in our study. In particular, group A included a greater number of colonic lesions; colonic lesion ESD is known to be technically more difficult to treat than rectal ESD. However, as there was no significant difference in lesion size between groups, submucosal fibrosis seemed to be the most important factor determining the difficulty of endoscopic treatment.

Our study has certain limitations. First, we reviewed only intramucosal neoplastic lesions that were treated endoscopically. Although the presence of submucosal fibrosis could be confirmed, precise correspondence between histological and CTC findings may be difficult to conclude in cases where patients require piecemeal resection. Comparing histological and CTC findings in surgically resected intramucosal neoplasms would enhance the accuracy and acceptance of preoperative BLDA assessment by CTC. Second, only a single experienced radiologist evaluated the presence of BLDA in our study, and our findings require validation by studies involving multiple radiologists. Third, our study was a pilot study with a small sample size; a prospective multicenter trial would provide further clarity regarding the utility of CTC in predicting difficulties in endoscopic resection. Despite these limitations, our study suggests that the presence of BLDA corresponds well with the presence of fibrosis in the submucosal layer and that CTC may be an effective tool for preoperatively estimating the difficulty of the endoscopic resection of large protruding tumors in the colon.

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GASTROENTEROLOGY

Time saving with narrow-band imaging for distinguishing between neoplastic and non-neoplastic small colorectal lesions

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Key words
colonoscopy, colorectal lesion, magnifying chromoendoscopy, narrow-band imaging.

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Abstract

Background and Aims: For colonoscopic examinations, the narrow-band imaging (NBI) system is more convenient and timesaving than magnifying chromoendoscopy (MCE). However, the time-saving aspects of NBI techniques have not been assessed. The present study compared interpretation times between NBI and MCE techniques in distinguishing between neoplastic and non-neoplastic small colorectal lesions.

Methods: Between January and March 2010, 693 consecutive patients who underwent colonoscopy at the National Cancer Center Hospital, Tokyo, Japan, were enrolled. When the first lesion was detected by conventional white-light observation, the patient was randomly assigned to undergo a sequence of NBI and MCE observations (group A: NBI–MCE, group B: MCE–NBI). The time to diagnosis with each modality (NBI, from changing to NBI until diagnosis; MCE, from the start of indigo carmine solution spraying until diagnosis) was recorded by an independent observer. The sensitivity, specificity, and diagnostic accuracy of the first modality used in each group (NBI or MCE) were assessed by referring to the histopathological data.

Results: Seventy-one patients with 137 lesions were randomized to group A, and 80 patients with 163 lesions to group B. The median interpretation times were 12 s (interquartile range [IQR]: 7–19 s) in group A, and 17 s (IQR: 12–24 s) in group B, the difference being significant ($P < 0.001$). No significant differences were observed between NBI and MCE in terms of sensitivity, specificity, and diagnostic accuracy.

Conclusions: NBI reduces the interpretation times for distinguishing between neoplastic and non-neoplastic small lesions during colonoscopies, without loss of diagnostic accuracy.

Introduction

The usefulness of narrow-band imaging (NBI) systems with magnification, for differentiating between neoplastic and non-neoplastic lesions in colonoscopy, has been commonly reported.[1–9] Prior to the development of NBI techniques, pit pattern analysis using magnifying chromoendoscopy (MCE) was considered to be the most reliable method, not only for differentiating between neoplastic and non-neoplastic lesions, but also for evaluating the invasion depth of early colorectal cancers.[10–15] Most previous studies showed high diagnostic accuracies of pit pattern analysis with MCE (> 90%), especially in the differentiation of neoplastic lesions from non-neoplastic ones.[10–12] Pit pattern analysis is, therefore, considered a gold standard for accurate endoscopic diagnosis of colorectal lesions. However, some studies have suggested that analysis of microcapillary vessel patterns of lesions using NBI with magnification shows almost the same diagnostic accuracy as pit pattern analysis.[1–6] Moreover, NBI is reputed to be convenient and time saving compared to MCE, and thus the NBI system has received increasing attention. Previous studies on the efficacy of NBI tended to emphasize only the merits of NBI's diagnostic capabilities, and did not precisely assess the duration of diagnostic interpretation times.[1–9] The primary aim of this study was to compare the interpretation times between NBI and MCE in distinguishing between neoplastic and non-neoplastic lesions. Furthermore, we attempted to determine diagnostic accuracy and the levels of agreement between NBI and MCE techniques in the analysis of identical lesions.

Methods

Patients

A total of 693 consecutive patients who underwent total colonoscopy at the National Cancer Center Hospital (NCCH), Tokyo, Japan, between January and March 2010, were considered eligible for enrolment in the study. Patients with familial adenomatous polyposis, inflammatory bowel disease, advanced colorectal

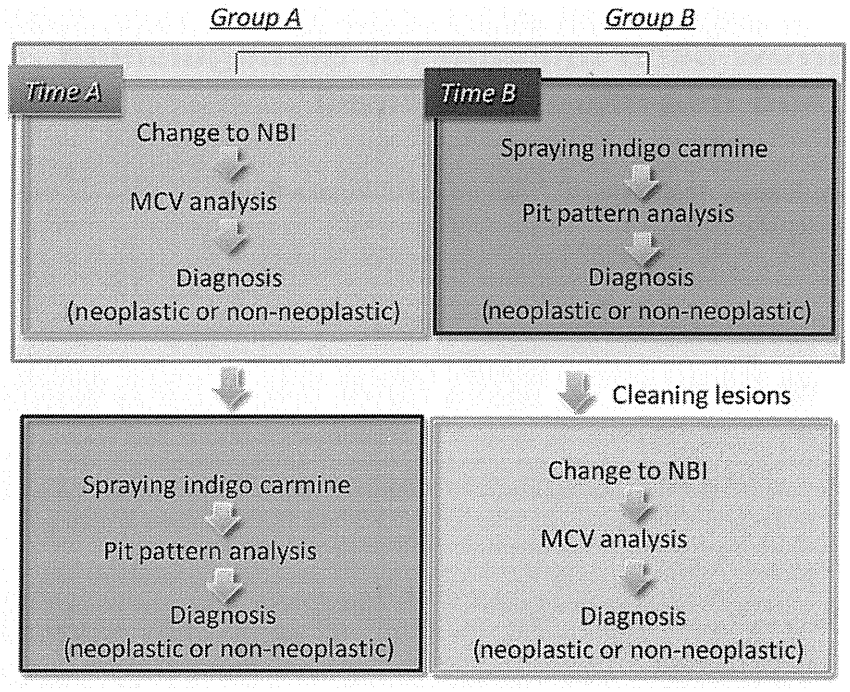

Figure 1 Flow chart of the colonoscopic diagnoses used in this study. MCV, microcapillary vessels; NBI, narrow-band imaging.

cancer, and poor colonoscopy preparation were excluded. The study was conducted prospectively, and the study protocol was approved by the NCCH institutional review board. Written, informed consent for diagnosis and treatment was obtained from all patients prior to the procedures. Lesions were detected in 151 patients and selected for study.

Colonoscopic examination

Patients prepared for colonoscopy by ingesting 2–3 L of polyethylene glycol-electrolyte solution on the morning of the examination day. Scopolamine butylbromide (10 mg) was administered intravenously to avoid bowel movement prior to examination in patients with no contraindication for this agent.

All examinations were performed using magnifying colonoscopes (CF-H260AZI or PCF-Q240ZI; Olympus Optical, Tokyo, Japan) and a standard videoendoscopic system (EVIS LUCERA system; Olympus Optical, Japan) with two light sources: one for the standard optical broadband filter, and the other for the NBI system (surface structure enhancement function, A-5 setting; and adaptive IHb color enhancement function, level 3 setting). During the procedure, whenever a lesion was detected by standard colonoscopy, analyses of capillary-vessel patterns with NBI magnification and analyses of pit patterns using MCE were performed. Patients were randomly assigned to first undergo observation with either NBI or MCE (group A: NBI–MCE, group B: MCE–NBI) (Fig. 1). For pit pattern analyses, indigo carmine (0.4%) was sprayed directly on the mucosal surface after washing with proteinase to remove any overlying mucous. The mucosal crypt patterns observed with chromoendoscopy were assessed using Kudo's classification.[16–18] In the case of NBI, four different microvascular architecture patterns were identified according to Sano's classification.[1,5,6,19]

After endoscopic evaluation, all detected lesions, unless contraindicated for endoscopic resection, were treated by biopsy, hot biopsy, snare polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD). All 11 endoscopists involved in the study had performed more than 200 colonoscopies with magnification, and had worked for more than 6 months at the NCCH. All endoscopists were familiar with NBI and MCE images, and received lectures throughout the course of the study during a weekly case conference meeting.

Assessments

The time to diagnosis with each modality (NBI, from changing to NBI until diagnosis; MCE, from starting the indigo carmine solution spraying until diagnosis) was recorded by an independent observer (Fig. 1). The sensitivity, specificity, and diagnostic accuracy of the first observation modality (NBI or MCE) in each group were assessed by referring to histopathological data.

Statistical analysis

Interpretation times of the two modalities were described by median values and interquartile ranges (IQR). Group medians were compared using the Wilcoxon rank sum test. Diagnostic performances for differentiating between neoplastic and non-neoplastic lesions were compared using the χ^2-test. All P-values were determined by two-tailed tests, and values of $P < 0.05$ were considered statistically significant. All calculations were performed using STATA software, version 10.0 (StataCorp, College Station, TX, USA).

Table 1 Clinical characteristics of patients and lesions

	Group A (n = 137/71 patients)	Group B (n = 163/80 patients)	P-value†
Age (mean ± SD) years	65.6 ± 10.7	65.1 ± 8.6	0.373
Gender (male/female)	50/21	54/26	0.699
Median size (IQR)	5 (3–7)mm	5 (3–7)mm	0.887
No. cases by location (%)			0.765
Right colon	70 (51)	83 (51)	
Left colon	42 (38)	60 (37)	
Rectum	15 (11)	20 (12)	
No. cases by macroscopic type (%)			0.386
Is/Isp, Ip	43 (31)	63 (38)	
Is + IIa	2 (2)	1 (1)	
IIa	92 (67)	98 (60)	
IIa + IIc	0 (0)	1 (1)	

†P-values represent the significance of the differences between the two groups. IQR, interquartile range; SD, standard deviation.

Table 2 Histopathological results

No. cases of neoplastic lesions (%)	
Tubular adenoma	216 (79)
Tubulo-villous adenoma	2 (1)
Well-differentiated adenocarcinoma	15 (6)
Sessile serrated adenoma	6 (2)
No. cases of non-neoplastic lesions (%)	
Hyperplastic polyp	28 (11)
Inflammatory polyp	3 (1)

Table 3 Diagnostic performances of magnifying chromoendoscopy (MCE) and narrow-band imaging (NBI), and the significance of the differences between them

	MCE	NBI	P-value
Sensitivity	93.7% (224/239)	94.1% (225/239)	0.863
Specificity	80.6% (25/31)	74.2% (23/31)	0.415
Accuracy	92.2% (249/270)	91.9% (248/270)	0.857

No. cases are in parentheses.

Results

Seventy-one patients with 137 lesions were randomized to group A, and 80 patients with 163 lesions to group B. The clinical features of the lesions detected in each group are presented in Table 1. There were no significant differences in age, sex, lesion size, location, and macroscopic type between the two groups.

In group A, the median interpretation times were 12 s (IQR: 7–19 s) at the first diagnosis by NBI (time A), and 17 s (IQR: 10–29.5 s) at the second diagnosis by MCE. In group B, the median interpretation times were 17 s (IQR: 12–24 s) at the first diagnosis by MCE (time B), and 11 s (IQR: 8–17 s) at the second diagnosis by NBI. Comparison of times A and B values indicated a significant difference in the interpretation time between NBI and MCE ($P < 0.001$).

Of the 270 colorectal lesions for which the histopathological findings were confirmed, 31 were hyperplastic or inflammatory polyps, six were sessile serrated adenomas (SSA), 218 were adenomas, and 15 were adenocarcinomas (Table 2). Interpretation of neoplastic lesions (adenoma, adenocarcinoma, and SSA) by NBI and MCE revealed sensitivities of 94.1% and 93.7%, respectively, specificities of 74.2% and 80.6% respectively, and diagnostic accuracies of 91.9% and 92.2%, respectively; none of these parameters showed significant differences between MCE and NBI (Table 3). Almost perfect intraobserver agreement was observed for the diagnoses of neoplastic lesions for each modality ($\kappa = 0.92$).

Discussion

The present study demonstrated that NBI can reduce the interpretation times for distinguishing between neoplastic and non-neoplastic lesions during colonoscopies. One of the advantages of using the NBI system is its relative simplicity, requiring only a single touch of a button to immediately change to the NBI mode from the conventional white-light observation mode. Moreover, the time required to differentiate between neoplastic and non-neoplastic lesions using the NBI system was statistically 4 or 5 s less than that for chromoendoscopic techniques. The extended interpretation time for MCE techniques was due to several factors, including: (i) the time required for spraying and suctioning indigo carmine solution; (ii) the time required to locate lesions in deep fold areas where fluid is easily retained, such as in the ascending colon; and (iii) the extra time required in cases where the patient has strong bowel movement or multiple lesions. The time saved using NBI was only 4 or 5 s per lesion, and the clinical benefit was rather small. However, the time saved would be particularly useful for the examination of patients with multiple lesions or with relatively poor preparation. In addition, time-saving modalities are important in cases where the lesions are located in curvy areas, such as the hepatic and splenic flexure, or when it is difficult to maneuver the colonoscope due to paradoxical movement.

Regarding the diagnostic performance for differentiating between neoplastic and non-neoplastic lesions, the NBI and MCE techniques showed almost the same values for sensitivity, specificity, and diagnostic accuracy, as determined in previous studies.[1–6,10–12] Our data were obtained in a prospectively-designed study, and its applicability is limited to the roles of MCE and NBI in differentiating between neoplastic and non-neoplastic lesions.

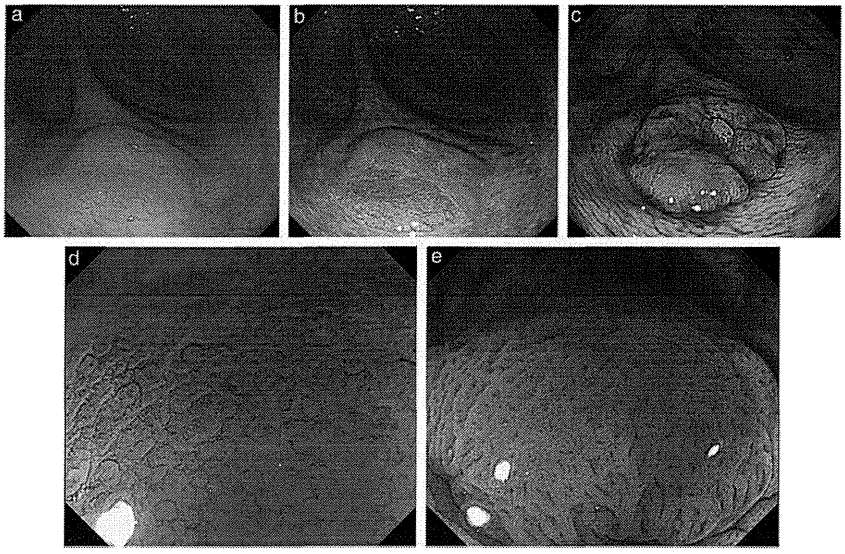

Figure 2 Endoscopic images of a case of sessile serrated adenoma/polyp. Regular capillary vessel surrounding round crypts was identified with magnifying narrow-band imaging. Slight dilation of crypts or inhomogeneous pits was recognized with magnifying chromoendoscopy.

We should note that, despite its longer interpretation time, chromoendoscopy using indigo carmine dye spraying is not without value in endoscopic examinations. Treatment strategies for neoplastic lesions require detailed assessments of the configurations of lesions, for which MCE is well suited. For example, flat and depressed types of lesions, which characterize laterally-spreading tumors (LST), are likely precursors of advanced carcinoma; possible treatments are broadly divided into conventional EMR, piecemeal EMR, and ESD. In particular, LST non-granular lesions showing a very flat and smooth configuration with pseudopodia-like appearances larger than 20 mm in size are considered to be a definite indication for ESD because of the high risk of submucosal invasion;[20–22] indigo carmine dye spraying is essential to clarify these features.

For diagnostic performance, the specificity of NBI is slightly lower than that of MCE, although the differences observed in this study were not statistically significant; this might be due to the presence of SSA cases in this study. Most SSA might be diagnosed as non-neoplastic lesions by NBI, but as neoplastic lesions by MCE. SSA are histologically characterized as follows: dilation of crypts, branching, presence of horizontal glands at the base, presence of mature mucinous cells at the base of crypts etc.[23,24] Dilation of crypts or inhomogeneous pits reflecting histopathologically-evident atypia can be observed by MCE (Fig. 2). The shapes of crypts are similar to the hyperplastic polyps diagnosed on the basis of type II pit patterns (almost homogeneous stellar of papillary pits) by Kudo's classification; therefore, we can distinguish between SSA and hyperplastic polyps from the minor differences in pit pattern. However, some cases showed relatively dilated microcapillary vessels surrounding small crypts, rather than normal mucosa or typical small hyperplastic polyps characteristic of SSA. A clear definition suggesting the difference in capillary vessel pattern between SSA and hyperplastic polyps has not been provided yet, which resulted in non-neoplastic lesion diagnoses by NBI (Fig. 2). SSA thus need to be independently confirmed; the NBI findings for SSA might offer insights into a subset of colorectal adenocarcinomas characteristic of neoplastic lesion, but more detailed study is needed to clarify the meaning of NBI findings.

There are several limitations to this study. First, this study was conducted at a single medical centre, where we usually apply Sano's classification to interpret microcapillary vessel patterns. However, other classification systems for NBI have been suggested in Japan, including the simultaneous evaluation of mucosal surface patterns and microcapillary vessels. In this approach, the NBI image settings might be slightly different than those in the present study, leading to slightly different results. Second, the endoscopists who performed the colonoscopies in this study were proficient in both NBI and MCE. Thus, the general efficacy of NBI requires revalidation studies, including those with general endoscopists. Third, all diagnoses were performed using magnifying endoscopy, but there might be some institutions where colonoscopies without magnification are performed in routine examinations. Therefore, the applicability of our results to endoscopic examinations without magnification is unclear.

In conclusion, NBI can reduce the interpretation time required for distinguishing between neoplastic and non-neoplastic lesions during colonoscopies without loss of diagnostic accuracy. Moreover, the differential diagnoses for a lesion by NBI are the same as those obtained by MCE. These results suggest that NBI can replace MCE as a diagnostic tool for assessing colorectal neoplasms.

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Research Article

Visualization of Laterally Spreading Colorectal Tumors by Using Image-Enhanced Endoscopy

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Laterally spreading tumors may sometimes evade detection by colonoscopy. This study aimed to evaluate the use of image-enhanced endoscopy for visualizing laterally spreading tumors of the nongranular type. We reviewed consecutive patients with 47 non-granular-type laterally spreading tumors that had been examined using white-light imaging, autofluorescence imaging, narrow-band imaging, and chromoendoscopy with indigo carmine. The quality of visualization was evaluated using a 5-point scale by less- and more-experienced endoscopists. Autofluorescence imaging provided significantly better visualization than white-light imaging for both less-experienced and experienced endoscopists. On the other hand, no significant differences were observed between the quality of visualization provided by white-light imaging and narrow-band imaging for less-experienced endoscopists. Autofluorescence imaging provides high-quality visualization of non-granular-type laterally spreading tumors on still images. Multicenter trials should be conducted to confirm the usefulness of autofluorescence imaging in detecting laterally spreading colorectal tumors.

1. Introduction

Colorectal carcinoma is one of the most common cancers worldwide, and its prevalence is steadily increasing in Japan [1]. Colonoscopy is considered the gold standard for the detection of neoplastic lesions at risk of progression to colorectal carcinoma. However, according to the results of back-to-back colonoscopies by Rex et al., the miss rate for adenomas ≥1 cm was 6% [2]. Laterally spreading tumors (LSTs) constitute a subset of nonpolypoidal colonic lesions, which are characterized by lateral and circumferential extension along the colonic wall rather than vertical growth [3]. LSTs are further classified based on their macroscopic appearance. The granular type LST (LST-G) is defined by the presence of aggregates of even or uneven nodules on the surface, whereas the non-granular-type LST (LST-NG) has a smooth surface lacking the granulonodular formations [4, 5]. Owing to the flat shape of LSTs, the miss rate for these tumors might be higher than the 6% reported by Rex et al. In addition, LSTs, particularly the NG type, have a higher potential for malignancy; nearly 30% of LST-NGs are associated with lymph follicular or multifocal submucosal invasion [6]. A reduction in the miss rate for LST-NG could therefore contribute to colorectal cancer prevention. Emerging data suggest that the use of image-enhanced endoscopy (IEE) such as autofluorescence imaging (AFI) and narrow-band imaging (NBI) may lead to improvements in polyp detection rates, although this notion remains controversial [7–15]. In our experience, we have encountered many LST-NG lesions that were better visualized by IEE than by white-light imaging (WL). The aim of this study was to evaluate the quality of visualization of LST-NG provided by IEE.

2. Methods

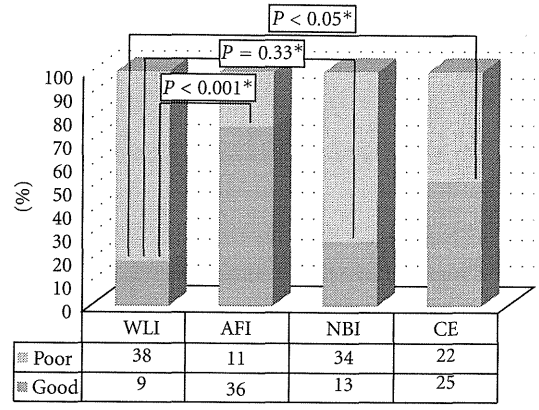
From September 2009 to April 2011, consecutive patients with LST-NG lesions resected by endoscopic submucosal

Table 1: Characteristics of lesions.

Number of lesions	47
Number of patients	45
Sex	
Male	31
Female	24
Age (years)	
Median	69
Range	50–80
Tumor size (mm)	
Median	30
Range	20–60
Tumor location	
Cecum	1
Colon	39
Rectum	7
Histopathology	
Adenoma	5
m-ca	24
sm superficial (sm1*)	11
sm deep (sm2-3)	7

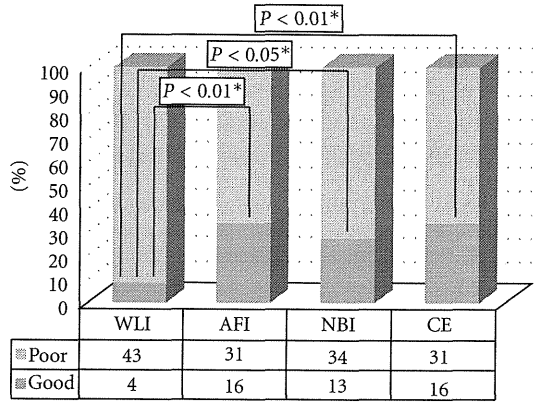
*sm1 : sm < 1000 μm.

dissection (ESD) in our institution were included in this study. The inclusion criteria for performing ESD on LST-NGs were as follows: (1) evidence of a noninvasive pattern [15–17] and (2) lesions larger than 20 mm that were difficult to resect enbloc by using conventional EMR [18]. First, endoscopic examinations were performed using the white-light mode of the AFI videoendoscope system to identify LST-NG lesions, once lesions were detected, the colonoscopist conducted AFI and NBI examinations by switching first to the AFI mode followed by the NBI mode, and finally lesions were examined by chromoendoscopy (CE) using the white-light mode. AFI colonoscopes (EVIS CF-FH260AZI; Olympus Medical Systems, Tokyo, Japan), light sources (EVIS CLV-260SL; Olympus Medical Systems), and video processors (EVISLUCERA CV-260SL; Olympus Medical Systems) were used in this study. The AFI videoendoscope system is a novel illumination method that produces real-time pseudocolor images. Neoplastic lesions involve a thickening of the mucosal layer and increased hemoglobin so such lesions emit weaker autofluorescence compared to nonneoplastic lesions; therefore nonneoplastic lesion appears green, while neoplastic lesion has a magenta image [7]. The AFI system allowed for immediate switching from WL to AFI and NBI with a button on the control head of the endoscope. CE was performed using 0.4% indigo carmine. Images of the lesions from WL, NBI, AFI, and CE without magnification were captured and electronically archived in the electronic medical records of our hospital. The images were selected by an experienced endoscopist blinded to this study. The WL, NBI, AFI, and CE images for each lesion were downloaded. The images of all the lesions were randomly arranged, and a Microsoft PowerPoint presentation was created. These images did not contain any information to identify the



*Chi-square test

Figure 1: Visualization of LST-NG in group A.



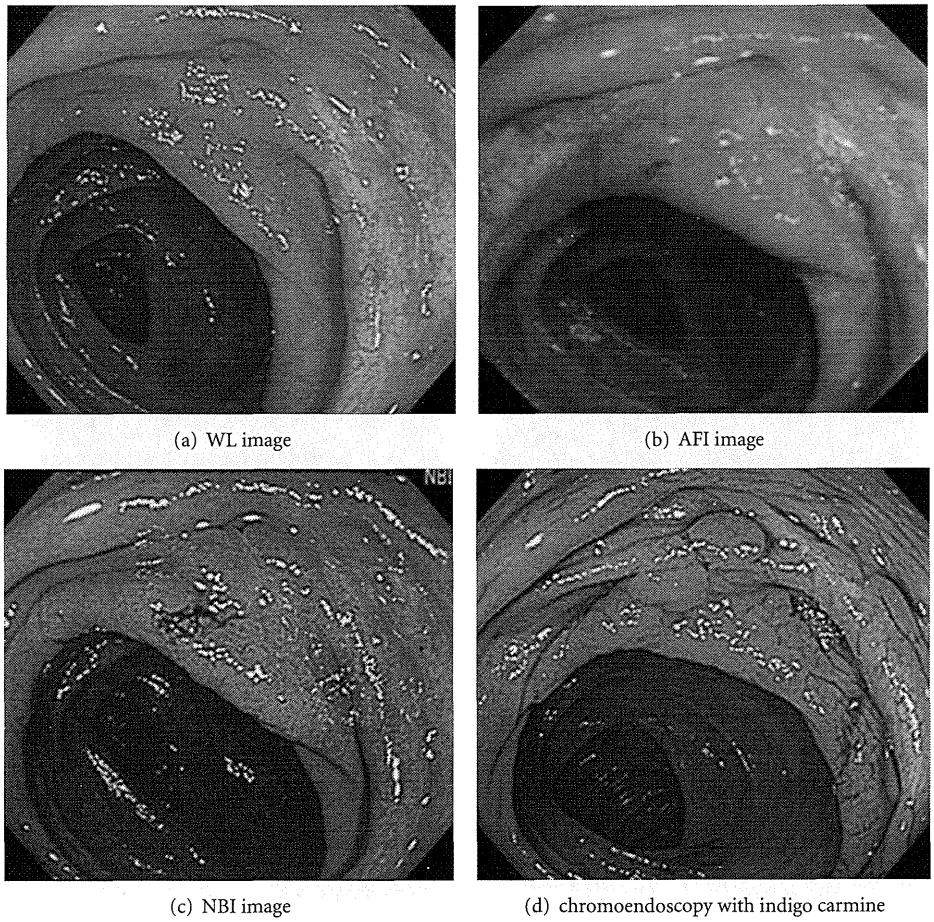
*Fisher's exact test

Figure 2: Visualization of LST-NG in group B.

patient or the lesion. The PowerPoint presentations were sent to the respective raters for their independent evaluation. The images were assessed by 2 groups of endoscopists (A and B). Group A comprised 2 physicians with no previous experience in IEE, and group B comprised 2 endoscopists, each of whom had analyzed over 100 cases by using IEE. Each endoscopic image was assessed and given a global rating for visualization based on the ability to detect the lesion and the clarity of the tumor margins. The images were rated by the endoscopists on a 5-point scale as follows: 5, very well visualized; 4, well visualized; 3, moderately well visualized; 2, poorly visualized; 1, very poorly visualized. The ratings of the images were analyzed separately for groups A and B. For each group of raters, the quality of visualization of lesions that received a score of 4 or more from both the raters was classified as "good". The quality of visualization of lesions with a score below 4 was classified as "poor."

3. Statistical Analysis

Statistical analysis was performed using SPSS for Windows (SPSS, Release 6.0; SPSS Inc., Chicago, Ill, USA, 1993). Statistical significance was defined as a P-value less than 0.05.



(a) WL image (b) AFI image

(c) NBI image (d) chromoendoscopy with indigo carmine

FIGURE 3: LST-NG lesions categorized as "wellvisualized" using AFI. Location: Transverse colon. Size of the lesion: 45 mm. Macroscopic type: IIa (LST-NG). Pathological findings: well-differentiated adenocarcinoma, low-grade atypia, Pm.

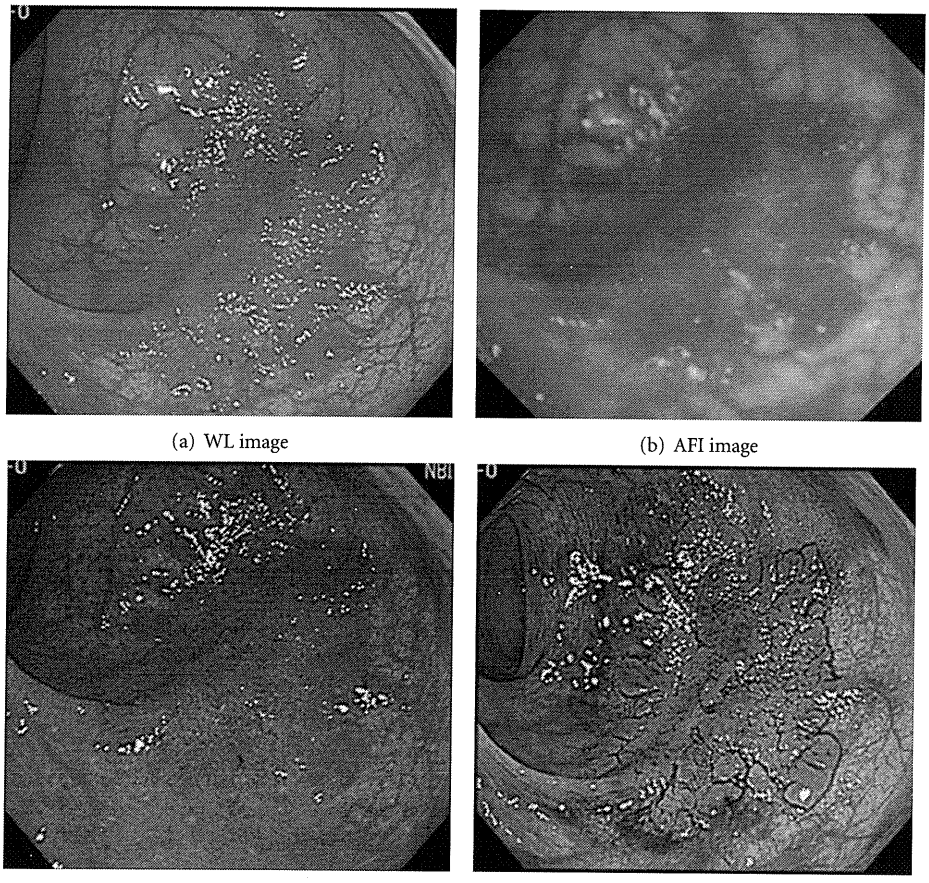
4. Results

In all, 49 LST-NG lesions in 47 patients were included in this study. Two patients with lesions were excluded from this study, because the lesions were not observed in the same field in each of the 4 modalities. Finally, a total of 47 LST-NG lesions in 45 patients were evaluated (Table 1). Of the 47 lesions analyzed in group A, the quality of visualization was categorized as "good" for 6 lesions using AFI, 13 using NBI, and 25 using CE. AFI (36/47) provided significantly better visualization than WL (9/47) ($P < 0.001$). Similarly, there was a significant difference between the quality of visualization using CE (25/47) and WLI (9/47) ($P < 0.05$). There was no significant difference, however, between WLI (9/47) and NBI (25/47) (Figure 1). Regarding AFI visualization, there was no significant difference in the macroscopic subtype, tumor location, or underlying histology between well-visualized and poorly visualized lesions, but well-visualized lesions were larger than the poorly visualized lesions (Table 2).

In group B, the quality of visualization was assessed as "good" for 4 lesions by using WLI, 16 lesions by using AFI, 13 lesions by using NBI, and 16 lesions by using CE. There was a significant difference in the frequency of well-visualized lesions between AFI (16/47) and WLI (4/47) ($P < 0.001$). Similarly, a significant difference in visualization quality was observed between CE (16/47) and WLI (16/47) ($P < 0.01$) and between NBI (13/47) and WLI (4/47) ($P < 0.05$) in group B (Figure 2). Regarding AFI, there was no significant difference in the macroscopic subtype, tumor location, or underlying histology between well-visualized and poorly visualized lesions. Well-visualized lesions were larger than the poorly visualized ones (Table 3).

5. Discussion

Based on the results of our study, AFI provides good-quality visualization of LST-NG lesions, not only for experienced endoscopists but for less-experienced endoscopists as well. The utility of AFI for the detection of colorectal tumors still remains controversial, with studies reporting mixed results [7–9, 15, 19]. In this study, 2 LST-NG lesions were determined to be well visualized by 4 endoscopists (Figures 3 and 4.). As Figures 1 and 2 show, we observed LST-NG lesions that were better visualized using AFI than the other methods. The relationship between visualization and



(a) WL image (b) AFI image

(c) NBI image (d) Chromoendoscopy with indigo carmine

FIGURE 4: LST-NG lesions categorized as "wellvisualized" by using AFI. Location: lower rectum. Size of the lesion: 45 mm. Macroscopic type: IIa (LST-NG). Pathological findings: well and moderately differentiated adenocarcinoma, pSM (350 um).

detection is uncertain. However, better visualization may enable improved detection of LST lesions, especially those of the NG type, which have been shown to be difficult to detect with CE [4]. It is particularly important to improve the detection rate of LST-NGs, because they are more likely to harbor malignancy; nearly 30% of LSTs of the NG type involve lymph follicular or multifocal submucosal invasion [6]. Though LST-NG lesions are less prevalent than polypoidal lesions, their greater malignant potential necessitates reliable detection methods. This study suggests that AFI is superior to WLI for the detection of LST-NG lesions at least on still images. In the present study, there was no significant difference in the quality of visualization of LST-NGs between WLI and NBI for the less-experienced endoscopists.

We also evaluated LST-G lesions in the same fashion as for the LST-NGs. As shown in Figures 5 and 6, AFI also provided good-quality visualization of LST-G lesions for the less-experienced endoscopists, despite the lack of a significant difference in visualization quality between WLI and AFI for the experienced endoscopists. This result indicates that an advantage of AFI might be that it simplifies observations for less-experienced endoscopists. We also compared the backgrounds of the LST-NG lesions between those with good versus poor visualization quality by using AFI. There were no significant differences between lesions that had good versus poor visualization quality with respect to macroscopic

TABLE 2: Backgrounds of the LST-NG lesion evaluated by AFI in group A.

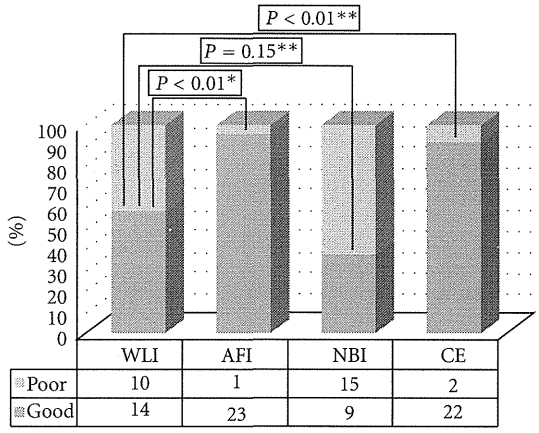
	Quality of visualization		
	Good	Poor	P
Macroscopic type			
Flat elevated	32	9	0.30*
Flat or flat depressed	4	2	
Lesion size (mm)			
Median	25	35	<0.05**
Range	20–50	20–60	
Location			
Rectum	6	1	0.34*
Cecum or colon	30	10	
Pathological finding			
Adenoma	4	2	0.30*
Adenocarcinoma	32	9	

*Fisher's exact test.
**Mann-Whitney test.

Table 3: Characterization of LST-NG lesions by AFI in group B.

	Quality of visualization		
	Good	Poor	P
Macroscopic type			
Flat elevated	16	25	0.07*
Flat or flat depressed	0	6	
Lesion size (mm)			
Median	25	30	<0.05**
Range	20–45	20–60	
Location			
Rectum	2	5	0.32*
Cecum or colon	14	26	
Pathological finding			
Adenoma	4	2	0.08*
Adenocarcinoma	12	29	

*Fisher's exact test.
**Mann-Whitney test.



*Fisher's exact test
**Chi-square test

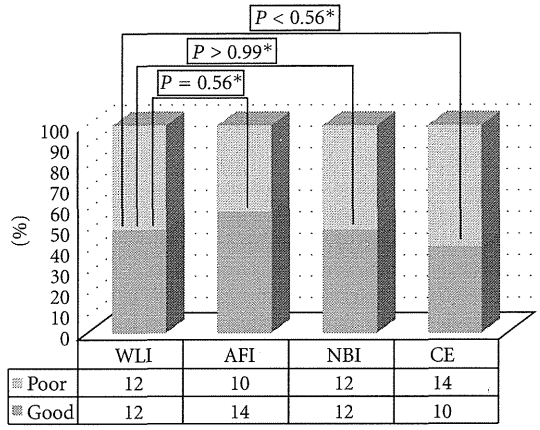
Figure 5: Visualization of LST-G in group A.

type, location, or pathological findings. However, the well-visualized lesions were larger than the poorly visualized lesions in groups A and B. To obtain a whole image of a large lesion, it is necessary to maintain sufficient distance between the tip of the scope and the lesion, which may affect the visibility of the lesion.

This study had several limitations. Only still images were evaluated, and it is uncertain if these findings can be applied to real-time video endoscopy. A relatively small sample precludes any multivariate analysis. Larger studies are needed to define the factors influencing the quality of visualization.

6. Conclusion

AFI provides good-quality visualization of LST-NG lesions on still images. However, to confirm the detectability of LST-NG lesions by using AFI, multicenter trials should be performed.



*Chi-square test

Figure 6: Visualization of LST-G in group B.

Conflict of Interests

All authors have no conflict of interests or financial ties to disclose.

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