Table 3 - Interobserver and intraobserver variabilities. (κ-value)

	HI-YS	HI-TM	YS-TM
Interobserver variabilities	**0.68**	**0.67**	**0.72**

	HI	YS	TM
Intraobserver variabilities	**0.79**	**0.76**	**0.75**

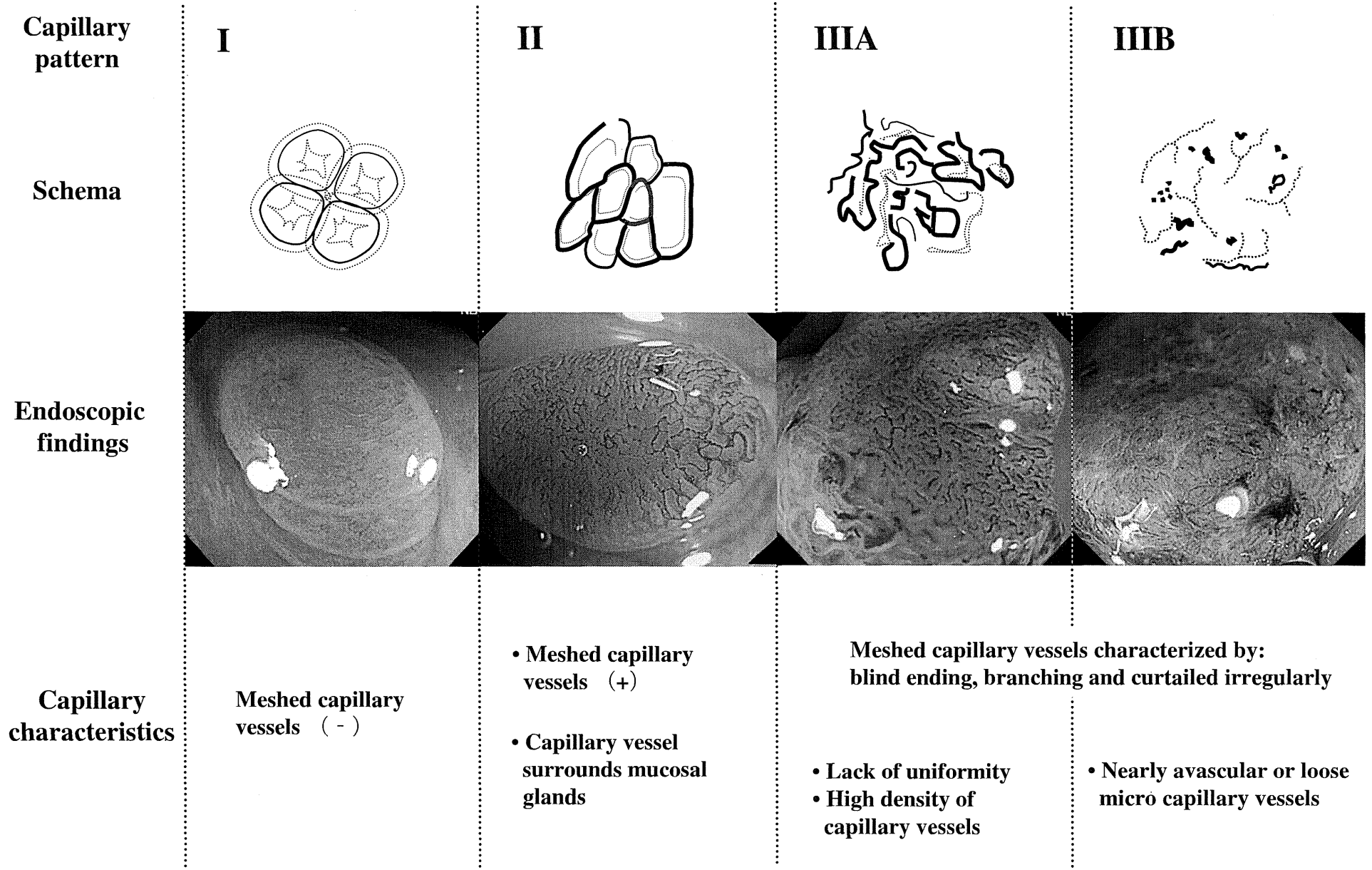
Capillary pattern
I
II
IIIA
IIIB
Schema
Endoscopic findings
Capillary characteristics
Meshed capillary vessels (-)
• Meshed capillary vessels (+)
• Capillary vessel surrounds mucosal glands
Meshed capillary vessels characterized by: blind ending, branching and curtailed irregularly
• Lack of uniformity
• High density of capillary vessels
• Nearly avascular or loose micro capillary vessels

Figure 1

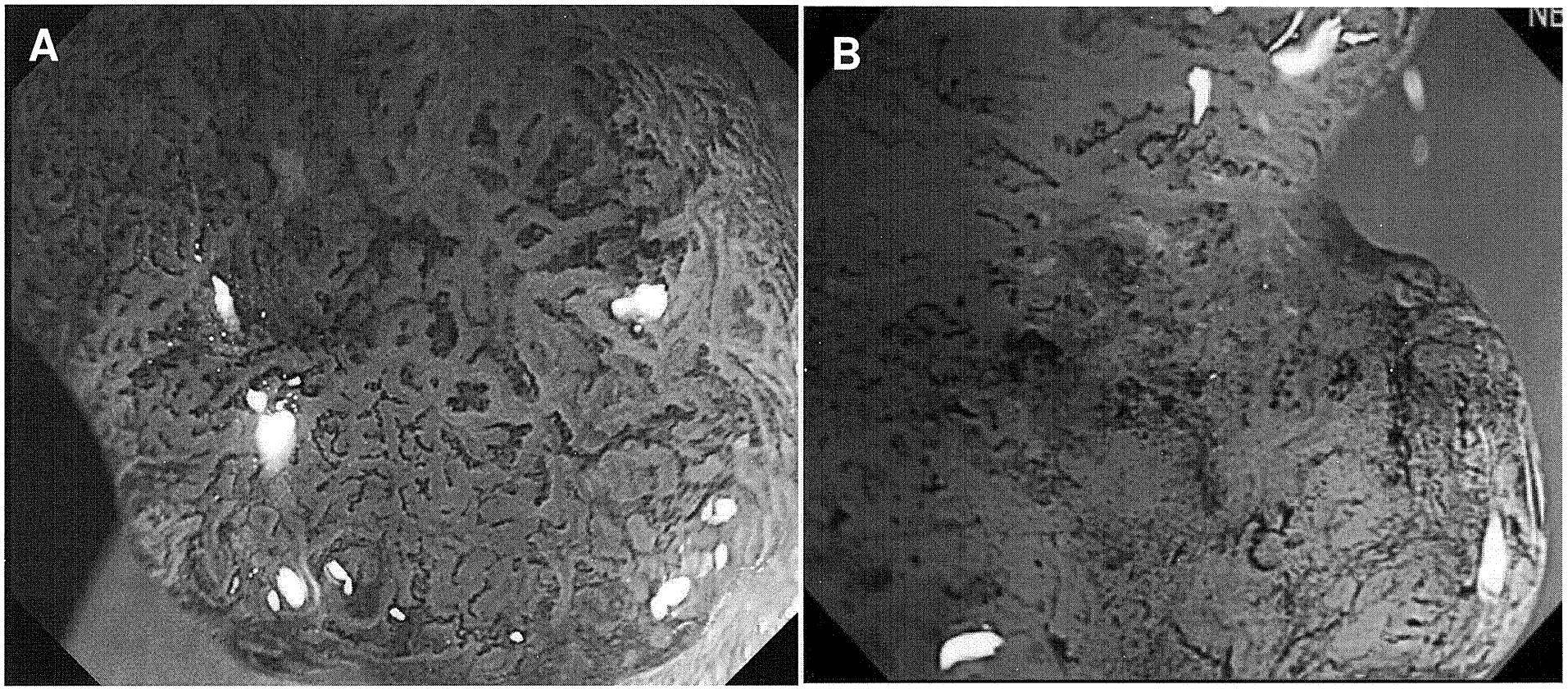

Figure 2

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i14.1727

World J Gastroenterol 2010 April 14; 16(14): 1727-1734
ISSN 1007-9327 (print)

ORIGINAL ARTICLE

Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer

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Received: November 30, 2009 Revised: January 20, 2010
Accepted: January 27, 2010
Published online: April 14, 2010

Abstract

AIM: To evaluate the surface microvascular patterns of early colorectal cancer (ECC) using narrow-band imaging (NBI) with magnification and its effectiveness for invasion depth diagnosis.

METHODS: We studied 112 ECC lesions [mucosal/submucosal superficial (m/sm-s), 69; sm-deep (sm-d), 43] ≥ 10 mm that subsequently underwent endoscopic or surgical treatment at our hospital. We compared microvascular architecture revealed by NBI with magnification to histological findings and then to magnification colonoscopy pit pattern diagnosis.

RESULTS: Univariate analysis indicated vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion. Multivariate analysis showed sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1] and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1). Both of these findings when combined were an indicator of sm-d invasion with sensitivity, specificity and accuracy of 81.4%, 100% and 92.9%, respectively. Pit pattern diagnosis sensitivity, specificity and accuracy, meanwhile, were 86.0%, 98.6% and 93.8%, respectively, thus, the NBI with magnification findings of non-dense vessel density and negative vessel regularity when combined together were comparable to pit pattern diagnosis.

CONCLUSION: Non-dense vessel density and/or negative vessel regularity observed by NBI with magnification could be indicators of ECC sm-d invasion.

Key words: Colorectal neoplasms; Narrow-band imaging; Microvasculature

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Fukuzawa M, Saito Y, Matsuda T, Uraoka T, Itoi T, Moriyasu F. Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer. *World J Gastroenterol* 2010; 16(14): 1727-1734 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i14/1727.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i14.1727

INTRODUCTION

Magnified colonoscopy and the development of pit pattern diagnosis[1] not only permits us to distinguish neoplastic from non-neoplastic colorectal lesions[2-5], but also helps to assess the invasion depth of early colorectal cancers (ECC)[6-9]. Similarly, vascular findings on the surface of gastric lesions have also been observed by

magnification endoscopy, and the usefulness in predicting the histological nature of such lesions and assessing their invasion depth has also been reported in the upper gastrointestinal (GI) tract[10-12].

The recently developed narrow-band imaging (NBI) system is a noninvasive optical technique that uses reflected light that provides clearer images of surface microvascular architecture than the conventional observation modality[13]. To date, the use of magnification endoscopy with the NBI system has been studied in the upper GI tract[14-20] and the suitability of this new modality for differentiating neoplastic from non-neoplastic lesions and its potential for pit pattern diagnosis have also been reported for the lower GI tract[21-30].

As previously indicated, colorectal lesions with mucosal (m) or submucosal (sm) superficial invasion < 1000 μm (sm-s) have an extremely low risk of lymph-node metastasis and are good candidates for endoscopic treatment[31]. It is helpful therefore, to differentiate endoscopically between m/sm-s and deeper sm invasion (sm-d ≥ 1000 μm) lesions. There have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases, however, a number of questions remain regarding the comparative effectiveness of a diagnosis based on NBI observation and one using pit pattern analysis by dye chromoendoscopy for determining invasion depth.

Using magnification colonoscopy with the NBI system, we evaluated the characteristics of the surface microvascular architecture of ECC and investigated the effectiveness of this new optical modality for the diagnosis of invasion depth. In addition, we evaluated the comparative relationship between NBI with magnification and pit pattern diagnoses.

MATERIALS AND METHODS

NBI system

NBI is a novel technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. It is based on the phenomenon that the depth of light penetration depends on its wavelength, with a short wavelength penetrating only superficially and a longer wavelength penetrating into deeper layers. In the NBI mode, optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon arc lamp and a red/green/blue rotation filter. Thin blood vessels such as capillaries on the mucosal surface can be seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels located in the deep layer of the mucosa can be observed at 540 nm. Current NBI technology limits mucosal surface light penetration, thereby enhancing visualization of the fine capillary vessel structure on the surface layer.

Patients and evaluation methods

We studied a total of 112 ECC lesions ≥ 10 mm analyzed with NBI with magnification colonoscopy examination, which then underwent endoscopic or surgical treatment at the National Cancer Center Hospital between January 2006 and February 2007. All colonoscopies were performed with a PCF-Q240ZI or CF-H260AZI endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) by three experienced endoscopists (MF, YS, TM) each of whom had annually performed more than 1000 magnifying chromoendoscopy examinations and at least 500 NBI examinations per year. Endoscopic images of each lesion were taken in the following order: conventional colonoscopy, NBI with magnification, chromoendoscopy and magnification chromoendoscopy. When a lesion was detected by conventional colonoscopy, its surface was washed with proteinase to remove excess mucus. Magnification NBI views of the microvascular architecture concentrated on those portions of the lesion where invasion seemed to have permeated the deepest regions, such as depressed areas and large nodules[32,33].

After completion of NBI with magnification, the pit pattern of each lesion was assessed with magnification chromoendoscopy performed using 0.4% indigo-carmine (IC) dye spraying. When high magnification observation with IC dye did not permit us to determine adequately the surface structure for pit pattern analysis, 0.05% crystal violet was applied for staining[7]. The visible pit pattern was then assessed during the course of the examination by the endoscopist conducting the procedure. All lesions were resected subsequently endoscopically or surgically and histological diagnosis was performed by three experienced pathologists based on the Vienna classification[34,35]. The depth of sm invasion was determined as being either sm-s < 1000 μm or sm-d ≥ 1000 μm[31]. After pathological diagnosis was completed on all resected lesions, three endoscopists (Fukuzawa M, Saito Y and Matsuda T) who performed the examination individually reviewed the endoscopic images of the NBI findings that were taken prior to treatment. All endoscopic images were chosen by one of these endoscopists. Their evaluation of the NBI images of the m/sm-s and sm-d lesions focused on the suspected areas, respectively, of higher grade dysplasia and deepest suspected invasion. Each characteristic of microvascular architecture was finally determined based on the agreement of at least two of the three reviewing endoscopists. Microvascular findings with a high frequency of sm-d were assessed as to whether those were significant sm-d indicators by univariate and multivariate analysis. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for each microvascular architectural feature observed during NBI, as well as every pit pattern diagnosis determined by magnification chromoendoscopy. We then compared the various types of microvascular architecture characteristics revealed by NBI with magnification to the chromoendoscopy pit pattern diagnoses.

The protocol for this study was approved by our institutional review board and all patients gave written informed consent.

Chromoendoscopy with magnification

Our pit pattern evaluation method relied on the clinical classification system proposed by Fujii *et al*[7] and Matsuda *et al*[8], with reference to the Kudo Classification System. Lesions were categorized into noninvasive and invasive

patterns. The noninvasive pattern included regular crypts with or without a demarcated area (e.g. depression, large nodule, or reddened area) and irregular pits without a demarcated area, and are usually observed in Kudo's types IIIS, IIIL, IV and VI without demarcated areas (e.g. adenomatous polyps, m and sm-s cancers), with endoscopic resection being the appropriate treatment. The invasive pattern was characterized by irregular and distorted crypts in a demarcated area, as observed in Kudo's type VN and VI with a demarcated area (e.g. sm-d), and should be treated by surgical resection. As indicated, Kudo's type VI can be observed in either noninvasive or invasive patterns. Those differences are dependent on the presence or absence of a demarcated area.

Microvascular architecture of ECC

Microvascular architectural images taken during magnification colonoscopy with NBI were reviewed retrospectively by three endoscopists who referenced the microvascular architectural features of superficial esophageal carcinoma[15], and included the following characteristics: (1) caliber, narrow or wide; (2) caliber regularity, positive or negative; (3) meandering, positive or negative; (4) vessel regularity, positive or negative; (5) vessel length, short or long; and (6) vessel density, non-dense or dense. These characteristics were evaluated by comparing the NBI with magnification images to representative photographs of model examples (Figure 1).

Statistical analysis

We compared microvascular architecture as revealed by NBI with magnification to histological findings using the χ^2 test of independence or Fisher's exact test for univariate analysis. Variables with a P value of < 0.05 in our univariate analysis were subsequently included in a logistic regression multivariate analysis. The StatView program, version 5.0 (SAS Institute, Cary, NC, USA), was used for data analysis and $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological features of patients and lesions

The clinicopathological details of the patients and colorectal lesions involved in this study are shown in Table 1.

Table 1 Clinicopathological features of evaluated colorectal lesions

	m/sm-s	sm-d
Lesions (n = 112)	69	43
Gender (male/female)	42/27	24/19
Age (range, yr)	63.2 (37-79)	62.5 (32-80)
Location		
Right colon	29	15
Left colon	18	12
Rectum	22	16
Morphology[1]		
Ip/Is/Isp	21	18
IIa/IIa + IIc/IIc	10	16
LST-G	20	5
LST-NG	18	4
Mean size (range, mm)	32.3 (10-100)	24.4 (10-90)

[1]Update on the Paris classification of superficial neoplastic lesion in the digestive tract[36]. LST-G: Laterally spreading tumor-granuler type; LST-NG: Laterally spreading tumour-non granular type; m/sm-s: Mucosal/submucosal superficial; sm-d: Submucosal-deep.

Univariate analysis

Univariate analysis indicated characteristics involving vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion (Table 2).

Multivariate analysis

Multivariate analysis demonstrated that sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13 133.1]; and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1) (Table 2). The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate for each characteristic are shown in Table 3. The two vascular findings that were confirmed by multivariate analysis had the highest values for specificity, PPV and accuracy (non-dense vessel density: specificity 0.99, PPV 0.95, accuracy 90.2%; negative vessel regularity: specificity 0.99, PPV 0.95, accuracy 90.2%).

Pit pattern diagnosis

The pit patterns of 21 m/sm-s lesions were evaluated following IC dye spraying, whereas the pit patterns of the other 48 m/sm-s lesions and all 43 sm-d lesions were assessed after crystal violet staining. We subsequently calculated the sensitivity, specificity, PPV, NPV and accuracy in differentiating m/sm-s from sm-d for: (1) the pit patterns that were diagnosed as being invasive; and (2) the NBI with magnification characteristic findings of (a) non-dense vessel density and/or negative vessel regularity and (b) non-dense vessel density and negative vessel regularity, which were both considered to be indicators for sm-d invasion. Pit pattern analysis sensitivity, specificity, PPV, NPV and diagnostic accuracy were 0.86 (95% CI: 0.72-0.95), 0.99 (0.92-0.99), 0.97 (0.86-0.99), 0.92 (0.83-0.97) and 93.8%, respectively. The NBI with magnification characteristic findings of non-dense vessel density and negative vessel regularity were comparable to pit pattern diagnosis results [0.81 (0.67-0.92), 1.00 (0.95-1.00), 1.00 (0.90-1.00), 0.90 (0.81-0.95), 92.9%] (Table 4). Seven of the lesions in this study were incorrectly diagnosed using pit pattern analysis including six sm-d lesions mistakenly diagnosed as m/sm-s invasion depth. In two of these cases, however, both non-dense vessel density and negative vessel regularity had also been observed by magnification NBI, which suggests its potential use as a supplementary diagnostic tool to pit pattern diagnosis (Figures 2 and 3).

DISCUSSION

It has been reported previously that observation of intra-

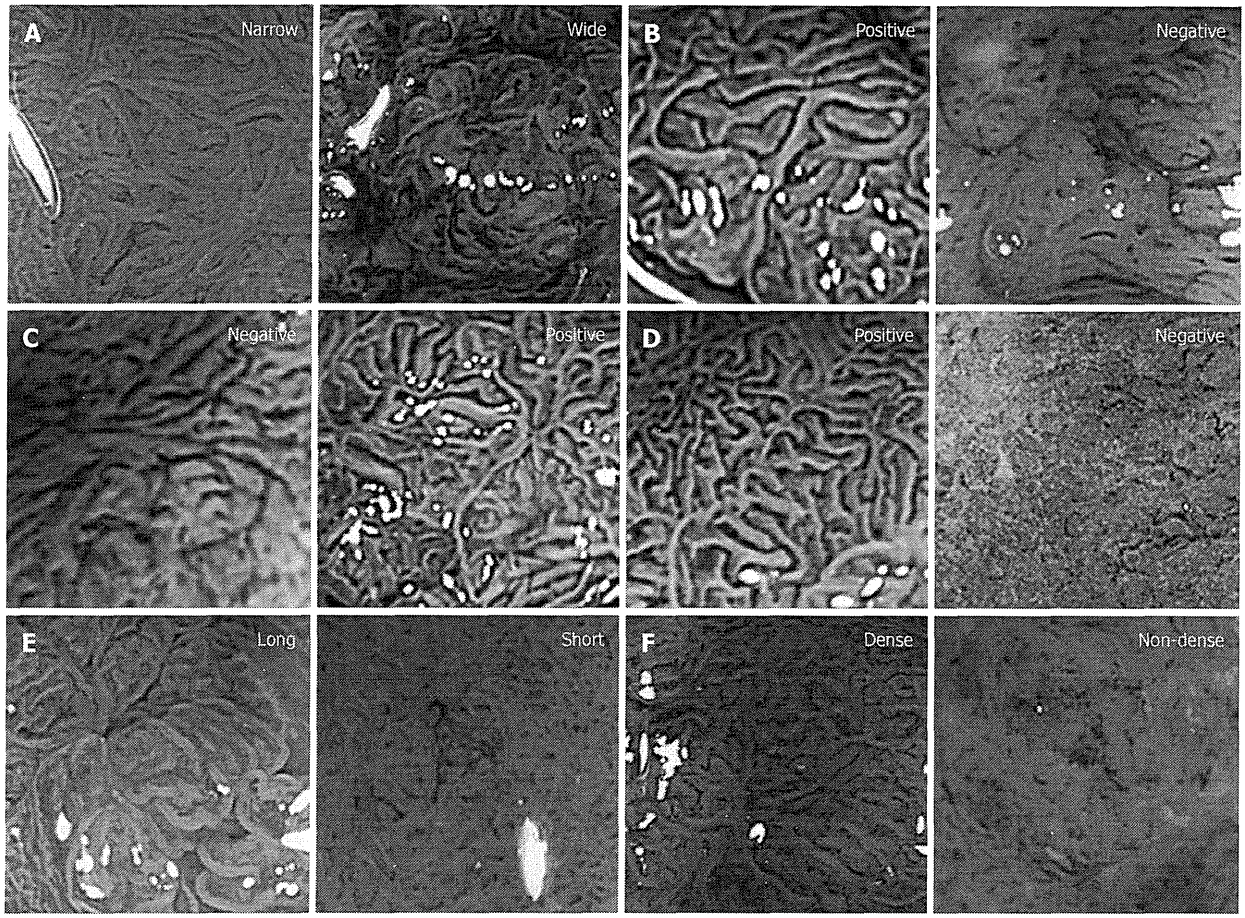

Figure 1 Microvascular architecture. A: Caliber, narrow: Capillaries are narrow diameter. Caliber, wide: Capillaries are wide diameter; B: Caliber regularity, positive: Capillaries are uniform thickness. Caliber regularity, negative: Capillaries are unequal thickness; C: Meandering, negative: Capillaries are linear. Meandering, positive: Capillaries are meandering; D: Vessel regularity, positive: Capillaries surround mucosal glands regularly. Vessel regularity, negative: Capillaries irregularly branching; E: Vessel length, long: Long capillaries. Vessel length, short: Short capillaries; F: Vessel density, dense: Dense capillaries. Vessel density, non-dense: Sparse capillaries.

Table 2 Microvascular architecture & invasion depth

Variables			Univariate analysis *P*-value[1]	Multivariate analysis		
				P-value[1]	Odds ratio	95% CI
		Non-dense/dense				
Vessel density	m/sm-s	1/68	< 0.001	0.001	402.5	12.4-13133.1
	sm-d	33/10				
		Negative/positive				
Vessel regularity	m/sm-s	8/61	< 0.001	0.038	15.9	1.2-219.1
	sm-d	38/5				
		Negative/positive				
Caliber regularity	m/sm-s	44/25	< 0.001	0.056	17.3	0.9-323.4
	sm-d	42/1				
		Short/long				
Vessel length	m/sm-s	20/49	< 0.001	0.161	0.2	0.01-2.10
	sm-d	37/6				
		Positive/negative				
Meandering	m/sm-s	49/20	0.002	0.110	0.1	0.01-1.60
	sm-d	41/2				
		Wide/narrow				
Caliber	m/sm-s	62/7	NS			
	sm-d	41/2				

[1]χ^2 or Fisher's test. 95% CI: 95% confidence interval; NS: Not significant.

papillary capillary loops by magnification endoscopy is useful in the diagnosis of invasion depth of superficial esophageal cancer[10,11]. The intra-papillary capillary loops can be seen in the normal esophageal mucosa by mag-

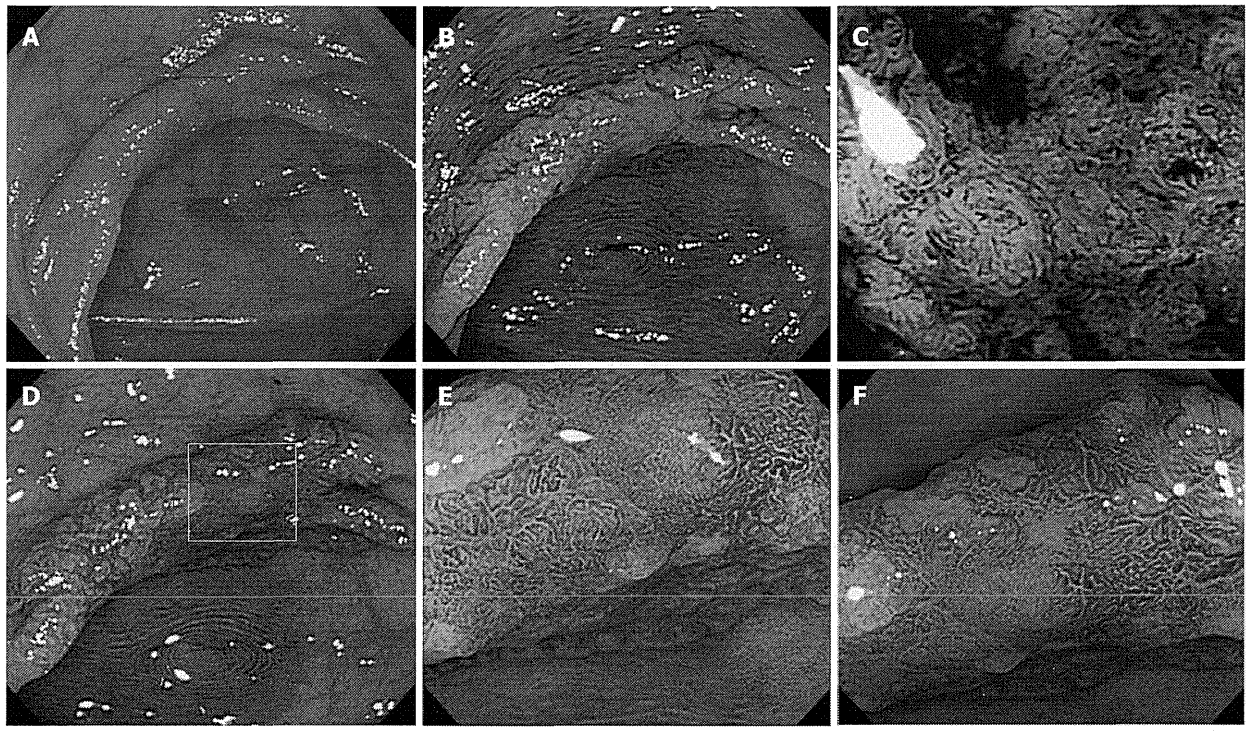

Figure 2 35 mm laterally spreading tumor, non-granular (LST-NG) type, located in the ascending colon. A: Conventional colonoscopy image; B: Conventional colonoscopy image following 0.4% IC dye spraying; C: Narrow-band imaging (NBI) with magnification image at center of the lesion enclosed by the red box in A. Microvascular architecture consisted of non-dense vessel density and negative vessel regularity; D: Crystal violet staining image; E: Magnification view of the portion enclosed by the red box in D revealed a noninvasive pattern; F: Magnification view of the portion enclosed by the yellow box in D also revealed a noninvasive pattern, such the estimated depth was intramucosal and this LST-NG lesion was treated by endoscopic submucosal dissection.

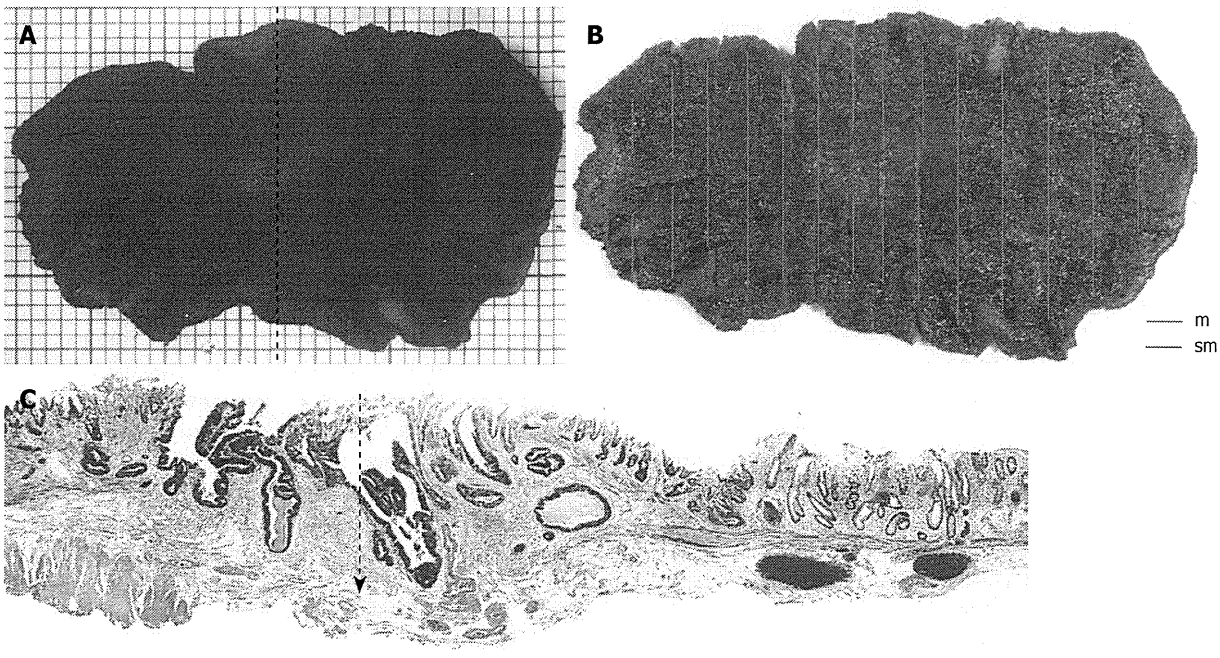

Figure 3 Stereomicroscopic view and histological images. A: Stereomicroscopic view; B: Red lines indicate submucosal penetration of the tumor; C: Histological diagnosis at dotted line in A was a well-differentiated adenocarcinoma and depth of invasion was sm (1300 mm) shown with the arrow. Invasion depth diagnosis using NBI with magnification was correct, based on findings of non-dense vessels and negative vessel regularity, but pit pattern diagnosis of this lesion was inaccurate.

nifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. There have been few studies to assess invasion depth in cancerous lesions from microvascular architecture. However, the NBI system enabled observation of

Table 3 Assessment of the carcinomatous invasion depth based on microvascular architecture

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Vessel density	33/43	68/69	0.97 (0.85-0.99)	0.87 (0.78-0.94)	90.2
Non-dense	0.77 (0.61-0.88)	0.99 (0.92-0.99)			
Vessel regularity	38/43	61/69	0.83 (0.69-0.92)	0.92 (0.83-0.97)	88.4
Negative	0.88 (0.75-0.96)	0.88 (0.78-0.95)			
Caliber regularity	42/43	25/69	0.49 (0.38-0.60)	0.96 (0.80-0.99)	59.8
Negative	0.98 (0.88-0.99)	0.36 (0.25-0.49)			
Vessel length	37/43	49/69	0.65 (0.51-0.77)	0.89 (0.78-0.96)	76.8
Short	0.86 (0.84-0.99)	0.71 (0.59-0.81)			
Meandering	41/43	20/69	0.46 (0.35-0.56)	0.91 (0.71-0.99)	54.5
Positive	0.95 (0.84-0.99)	0.29 (0.19-0.41)			
Caliber	41/43	7/69	0.40 (0.30-0.50)	0.78 (0.40-0.97)	42.9
Wide	0.95 (0.84-0.99)	0.10 (0.04-0.20)			

PPV: Positive predictive value; NPV: Negative predictive value.

Table 4 Assessment of the carcinomatous invasion depth: comparison between microvascular architecture & pit pattern analysis

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Non-dense vessel density	38/43	60/69	0.81 (0.67-0.91)	0.92 (0.83-0.97)	87.5
and/or negative vessel regularity	0.88 (0.75-0.96)	0.87 (0.77-0.94)			
Non-dense vessel density	35/43	69/69	1.00 (0.90-1.00)	0.90 (0.81-0.95)	92.9
and negative vessel regularity	0.81 (0.67-0.92)	1.00 (0.95-1.00)			
Pit pattern	37/43	68/69	0.97 (0.86-0.99)	0.92 (0.83-0.97)	93.8
(Invasive pattern)	0.86 (0.72-0.95)	0.99 (0.92-0.99)			

microvascular architecture of the tumor surface in the GI tract. In a similar fashion, we used NBI with magnification to investigate whether or not quantitative ECC invasion depth diagnosis was possible based on analysis of capillary vessel patterns instead of pit patterns. Based on our results, it appeared that non-dense vessel density and negative vessel regularity, as observed by NBI with magnification, could be diagnostic indicators of sm-d invasion, as effectively as pit pattern analysis.

Regular hexagonal or honeycomb-like capillary patterns are formed around the crypts of normal colorectal mucosa. In contrast, it has been reported that these capillaries are larger in tumor adenomas, whereas vascular disruption, caliber irregularity and dense vessels have been observed in severe atypical cases[37]. In addition, vascular changes do not generally occur in non-neoplastic lesions such as hyperplastic polyps, with the exception of inflammatory polyps[38]. The NBI technique provides clearer observation of microvascular architectural characteristics, therefore, it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy[21-30], and pit pattern diagnosis has likewise been explored using NBI[21,24,27,28]. Previous studies have shown that the accuracy of pit pattern diagnosis of invasion depth by magnification endoscopy was 98.8%[8], whereas such diagnostic accuracy in this study was 93.8%.

The area surrounding crypts in the superficial layer of the mucosa is covered with capillaries and has previously been recognized as a pit using the NBI technique. Machida *et al*[21] have reported that NBI pit pattern diagnosis is significantly more useful ($P < 0.001$) than conventional observation, but inferior to chromoendoscopy ($P < 0.05$). Hirata *et al*[24] have reported that overall diagnostic consistency in pit patterns between magnification NBI and dye-spraying observations was 84%, but even higher for types Ⅱ, Ⅲ, Ⅳ and V_N pit patterns, although somewhat lower at 78%, for the type V_I pit pattern. In addition, Tischendorf *et al*[27] have reported that there is no significant difference in the PPV for neoplastic lesions as determined by pit pattern and vascular findings using NBI. There was a discrepancy, however, between two endoscopists in their NBI pit pattern diagnosis of types Ⅲ-Ⅴ neoplastic lesions[27]. This may have been because the actual pit structure was not observed using the NBI technique, unlike the results from the contrast and staining methods; or, it could have been caused by the NBI pit pattern diagnosis of types Ⅲ-Ⅴ lesions, which are considered particularly important in determining the most suitable method of treatment, not having been performed accurately.

More recently, Katagiri *et al*[30] have reported that capillary patterns observed by NBI with magnification are highly accurate in distinguishing between low-grade and high-grade dysplasia/invasive cancer, and thus could be used to predict the histopathological features of colorectal neoplasia. In addition, Hirata *et al*[25] have reported vascular findings of significant sm-d invasion based on their NBI observation of thick blood vessels with irregularity on the surface of tumors. This differs somewhat from the results of our investigation, but the difference could be caused by a number of factors, such as variations in our respective definitions of vascular findings, and the macroscopic types of lesions involved in the two studies.

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. Patient symptoms including abdominal discomfort and peristalsis are more likely to appear in longer duration colonoscopy examinations, which may render detailed observation more problematic. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shorting examination times and reducing the burden on patients and endoscopists alike. A mucous attachment on the endoscope can also interfere with diagnosis, and washing the surface of a lesion with pronase solution takes additional time during pit pattern diagnosis by magnification colonoscopy with IC dye spraying or crystal violet staining. Hirata *et al*[24] have further reported that NBI observation results in more accurate pit pattern diagnosis than dye spraying observation in cases with mucous attachment.

Our study suffered from some limitations. First, the NBI assessments were made on still images by three endoscopists, whereas the pit pattern diagnosis was done in real time after initial inspection with NBI, which could account for some further bias. Second, the different NBI features of the microvasculature are not independent: the endoscopist is not blinded to one feature if he scores the other. In addition, lesions that were diagnosed histologically as cancer had a diameter of at least 10 mm, thus lesions < 10 mm in diameter were not assessed in this study. Accordingly, future prospective studies will require that relevant data be accumulated and analyzed on a more objective basis.

In conclusion, the results of this study indicated that two microvascular architectural characteristics, non-dense vessel density and negative vessel regularity, observed using NBI with magnification during colonoscopy examinations could be reliable indicators of ECC sm-d invasion.

ACKNOWLEDGMENTS

The authors wish to thank Christopher Dix for his assistance in helping to edit this manuscript.

COMMENTS

Background

The intra-papillary capillary loops can be seen in the normal esophageal mucosa by magnifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. Narrow-band imaging (NBI) enables detailed observation of microvascular architecture of the tumor surface.

Research frontiers

NBI provides clearer observation of microvascular architectural characteristics, and it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy. However, there have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases. This study clarifies the efficiency of NBI with magnification colonoscopy for invasion depth diagnosis of early colorectal cancer (ECC).

Innovations and breakthroughs

Some studies have already reported the clinical usefulness of pit pattern diagnosis using magnifying chromoendoscopy for predicting the depth of invasion of ECC. The authors' results indicate that NBI with magnification findings were comparable to pit pattern diagnosis results.

Applications

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shortening examination times and reducing the burden on patients and endoscopists alike.

Peer review

The authors present a trial analyzing the impact of NBI colonoscopy on assessing the invasion depth in ECC. Overall, 112 patients were included; additionally pit pattern analysis was performed in 64 patients. The study investigated interesting questions.

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S- Editor Wang YR **L- Editor** Kerr C **E- Editor** Lin YP

Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program

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Background: Previous reports assessing diagnostic skill using narrow-band imaging (NBI) and pit pattern analysis for colorectal polyps involved only highly experienced endoscopists.

Objective: To evaluate diagnostic skills of less-experienced endoscopists (LEE group) for differentiation of diminutive colorectal polyps by using NBI and pit pattern analysis with and without magnification after an expanded training program.

Design: Prospective study.

Patients: This study involved 32 patients with 44 colorectal polyps (27 adenomas and 17 hyperplastic polyps) of ≤5 mm that were identified and analyzed by using conventional colonoscopy as well as non-magnification and magnification NBI and chromoendoscopy followed by endoscopic removal for histopathological analysis.

Intervention: Before a training course, 220 endoscopic images were distributed in randomized order to residents with no prior endoscopy experience (NEE group) and to the LEE group, who had performed colonoscopies for more than 5 years but had never used NBI. The 220 images were also distributed to highly experienced endoscopists (HEE group) who had routinely used NBI for more than 5 years. The images were distributed to the NEE and LEE groups again after a training class. Magnification NBI and chromoendoscopy images were assessed by using the Sano and Kudo classification systems, respectively.

Main Outcome Measurements: Diagnostic accuracy and interobserver agreement for each endoscopic modality in each group.

Results: Diagnostic accuracy was significantly higher, and kappa (κ) values improved in the LEE group for NBI with high magnification after expanded training. Diagnostic accuracy and κ values when using high-magnification NBI were highest among endoscopic techniques for the LEE group after such training and the HEE group (accuracy 90% vs 93%; κ = 0.79 vs 0.85, respectively).

Limitations: Study involved only polyps of ≤5 mm.

Conclusion: Using high-magnification NBI increased the differential diagnostic skill of the LEE group after expanded training so that it was equivalent to that of the HEE group. (Gastrointest Endosc 2010;72:127-35.)

Abbreviations: CC, conventional colonoscopy; CE-H, high-magnification chromoendoscopy; CE-L, low-magnification chromoendoscopy; HEE, highly experienced endoscopist; LEE, less-experienced endoscopist; NBI, narrow-band imaging; NBI-H, high-magnification narrow-band imaging; NBI-L, low-magnification narrow-band imaging; NEE, no-experience endoscopist; SSA, sessile serrated adenoma.

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

0016-5107/$36.00
doi:10.1016/j.gie.2010.01.054

Received August 10, 2009. Accepted January 25, 2010.

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It is widely accepted that adenomatous polyps are precursors of colorectal cancer, and performing polypectomies on such lesions can reduce the risk of subsequent colorectal cancer by up to 80% for a period that may exceed 10 years.[1] In addition, adenomas are a major factor in guidelines that have been developed for recommended colonoscopy surveillance intervals after polypectomies because they are a powerful predictor for future colorectal cancer risk.[1-3] Small colorectal adenomas as well as advanced adenomas[4] are precursors of colorectal cancer, and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[5]

Endoscopic differentiation of small adenomas from non-adenomatous polyps is important because endoscopists should avoid performing any unnecessary procedure, including polypectomies, that can cause related complications such as bleeding and perforation.[6,7] The diagnostic accuracy of conventional colonoscopy for such colorectal polyps, however, has previously been reported to be unsatisfactory.[8,9] In contrast, chromoendoscopy with indigocarmine dye spraying has been shown to be an effective procedure for detecting and evaluating colorectal polyps[10-15] despite having several disadvantages, including a longer procedure time and the additional cost for dye spraying.

Narrow-band imaging (NBI) is an innovative optical technology providing a unique image that emphasizes the morphological and structural character of lesions as well as their surface capillary patterns.[16-25] It has been reported that this modality is a new non-dye tool for differentiating neoplastic from non-neoplastic polyps, with a diagnostic accuracy including pit pattern analysis equivalent to that of chromoendoscopy.[17-21] Such reports have been based on studies involving only highly experienced endoscopists, however, with few published articles concerned with the learning curve for NBI being dependent on an individual endoscopist's experience and ability. The aim of this study was to determine, therefore, whether expanded training in the effective use of NBI and pit pattern analysis with and without magnification would improve the diagnostic skill of less-experienced endoscopists in the differentiation of diminutive colorectal polyps.

Take-home Message

- Expanded interactive training in effective use of narrow-band imaging both with and without magnification as well as pit pattern analysis improved diagnostic accuracy and interobserver agreement of less-experienced colonoscopists in differentiating diminutive colorectal polyps. Using narrow-band imaging with high magnification increased the differential diagnostic skill of less-experienced colonoscopists who underwent such training to a level equivalent to that of highly experienced colonoscopists.

METHODS

Patients

Patients scheduled for a total colonoscopy at Okayama University Hospital and Sumitomo Besshi Hospital between September and October 2008 were invited to participate in this study. Informed consent was obtained from all patients before their examinations. Patients with inflammatory bowel disease, familial adenomatous polyposis, an international normalized ratio greater than 2.0, or a platelet count less than 50,000/mm^3 were excluded from this study.

Colonoscopy and polyp assessment protocol

Bowel preparation consisted of patients drinking 2 to 3 liters of polyethylene glycol solution in the morning before their procedures.[13] Total colonoscopies were prospectively performed by using a video endoscopic system (EVIS, Lucera Spectrum; Olympus Co, Tokyo, Japan) with CF-H260AZI or PCF-Q240ZI magnification colonoscopes (Olympus) by two highly experienced endoscopists (R.H., T.U.), each of whom had previously performed over 1000 colonoscopies annually.

When a lesion was detected by conventional colonoscopy examination, surface mucus was washed away with lukewarm water, and endoscopic images were taken in the following order: conventional colonoscopy (CC), low-magnification NBI (NBI-L), high-magnification NBI (NBI-H), low-magnification chromoendoscopy (CE-L) and high-magnification chromoendoscopy (CE-H). A standard optical filter was used for both CC and chromoendoscopy, with chromoendoscopic images taken after 0.2% indigocarmine dye was sprayed on the lesion surface. The enhanced surface structure function of the video image processor at the level A5 setting was used in taking all endoscopic images.[23] Location, size, and macroscopic type of each lesion were recorded, with size measured by using open forceps. Lesions were classified macroscopically based on the criteria of the Paris classification of superficial GI lesions.[26] A biopsy, polypectomy, or EMR was then performed, and the resulting specimen was analyzed histopathologically.

Image evaluator categories

A total of 12 doctors with different levels of endoscopic experience were asked to independently evaluate endoscopic images. The doctors were separated into 3 groups: 4 residents with no prior endoscopy experience (NEE group); 4 less experienced endoscopists each of whom had performed colonoscopies for more than 5 years but had never used NBI (LEE group); and 4 highly experienced endoscopists each of whom had routinely used magnification colonoscopy with NBI for more than 5 years (HEE group).

Assessment of endoscopic images

The best quality endoscopic images were selected for each modality and stored digitally in JPEG format. All images were distributed in randomized order to each group of evaluators. For the NEE and LEE groups, the same images were distributed in randomized order once before and once after those group members participated in an intensive, 1-hour, interactive training program on white-light endoscopy, NBI, and chromoendoscopy. The program included information on the Sano NBI classification[20,21] and the Kudo pit pattern classification[27,28] and used an atlas of endoscopic images of polyps produced by an independent group of highly experienced endoscopists. Although they were completely unaware of the histopathological results, every participant correctly diagnosed polyps as either neoplasms or non-neoplasms by using (1) chromoendoscopy based on the Kudo pit pattern classification, with types III (including IIIL and IIIs), IV, and V (including VI and VN) considered to be neoplasms and types I and II regarded as non-neoplasms;[27,28] (2) NBI-L that revealed a brownish area determined to be neoplastic; and (3) NBI-H with the Sano classification of meshed capillary vessel pattern, in which types II and III were considered neoplastic and type I, without meshed capillaries, was non-neoplastic (Figs. 1 and 2).[20-21] Patient information such as age, sex, and clinical diagnosis was not disclosed to any of the evaluators, and discussions were not permitted among the doctors individually or in groups.

Statistical analysis

The diagnostic accuracy of each endoscopic modality was assessed in reference to histopathological results. Estimates of diagnostic accuracy were calculated based on the average diagnostic accuracy for each group of doctors as well as for each diagnostic modality. The upper and lower 95% confidence interval (CI) limits were calculated by using a normal model that consisted of symmetric CIs, with limits at a distance from the estimate equal to the product of 1.96 times the standard error. Interobserver agreement in diagnosing colorectal lesions in each group and by each modality was determined by calculation of the kappa statistic (κ) and its 95% CI by using the Fleiss method. Diagnostic accuracies before training and after training in the NEE and LEE groups were compared with the McNemar test. As for differences in diagnostic accuracies after training among the NEE, LEE, and HEE groups, those findings were analyzed by using the Fisher exact test. Multiple statistical testing of outcome data was conducted in this study, therefore, a Bonferroni correction was applied, and differences with a P value of $< .025$ were considered significant as the correction. A κ value of <0.4 was regarded as poor agreement, 0.41 to 0.60 fair agreement, 0.61 to 0.80 good agreement, and >0.80 excellent agreement. Statistical analyses were conducted by using version 7.0 of the JMP statistical software package (SAS Institute, Cary, NC) and a Microsoft Excel 2007 spreadsheet (Microsoft, Renton, Wash).

RESULTS

Clinicopathological features of colorectal lesions

Seventy-two consecutive patients were enrolled in this study for prospective endoscopic evaluation. A total of 44 lesions of ≤5 mm were identified and analyzed in 32 patients (Table 1). Mean (± standard deviation [SD]) patient age was 61.2 ± 12.3 years, and the male/female ratio was 2.2:1. Bowel preparation was considered adequate in all examinations, and complete colonoscopy was performed to the cecum in every case. There were no complications during any procedure. Of the 44 lesions, 37 were macroscopically classified as type 0-Is, 6 as type 0-IIa, and 1 as type 0-IIc. Mean (± SD) lesion size was 3.4 ± 1.1 mm. As for location, 22 polyps (50%) were found in the right colon (cecum, ascending, and transverse colon), 14 (32%) in the left colon (descending and sigmoid colon), and 8 (18%) in the rectum. Histopathological assessments included 27 adenomas (61%) and 17 hyperplasic polyps (39%). A total of 220 images of the 44 lesions were collected as each lesion was photographed during CC, NBI-L, NBI-H, CE-L, and CE-H.

Diagnostic accuracy of NBI and pit pattern analysis

Table 2 indicates diagnostic accuracy for each endoscopic modality. In the NEE group, diagnostic accuracies using CC, NBI-L, and NBI-H significantly improved after the training program (CC, $P < .001$; NBI-L, $P = .006$; and NBI-H, $P < .001$), but the NEE group's diagnostic accuracies were still significantly lower in all modalities except CC compared with the HEE group (CC, $P = .049$; NBI-L, $P = .0023$; NBI-H, $P < .001$; CE-L, $P < .001$; and CE-H, $P < .001$). Diagnostic accuracies in the LEE group for NBI-L, NBI-H, and CE-H also improved significantly after the training program ($P = .001$, $P < .001$, and $P = .001$, respectively). In contrast with the NEE group's results, however, subsequent diagnostic accuracies of the LEE group were not significantly different from diagnostic accuracies of the HEE group with respect to the CC, NBI-L, NBI-H, CE-L, and CE-H modalities ($P = 1.0$, $P = .60$, $P = .57$, $P = .031$, and $P = .48$, respectively).

Assessment of interobserver agreement based on endoscopic experience

Interobserver agreements in the HEE group for NBI-H were >0.80 representing excellent agreement and >0.60 for NBI-L, CE-L, and CE-H, representing good agreement (κ value CC, 0.5; NBI-L, 0.62; NBI-H, 0.85; CE-L, 0.69; CE-H

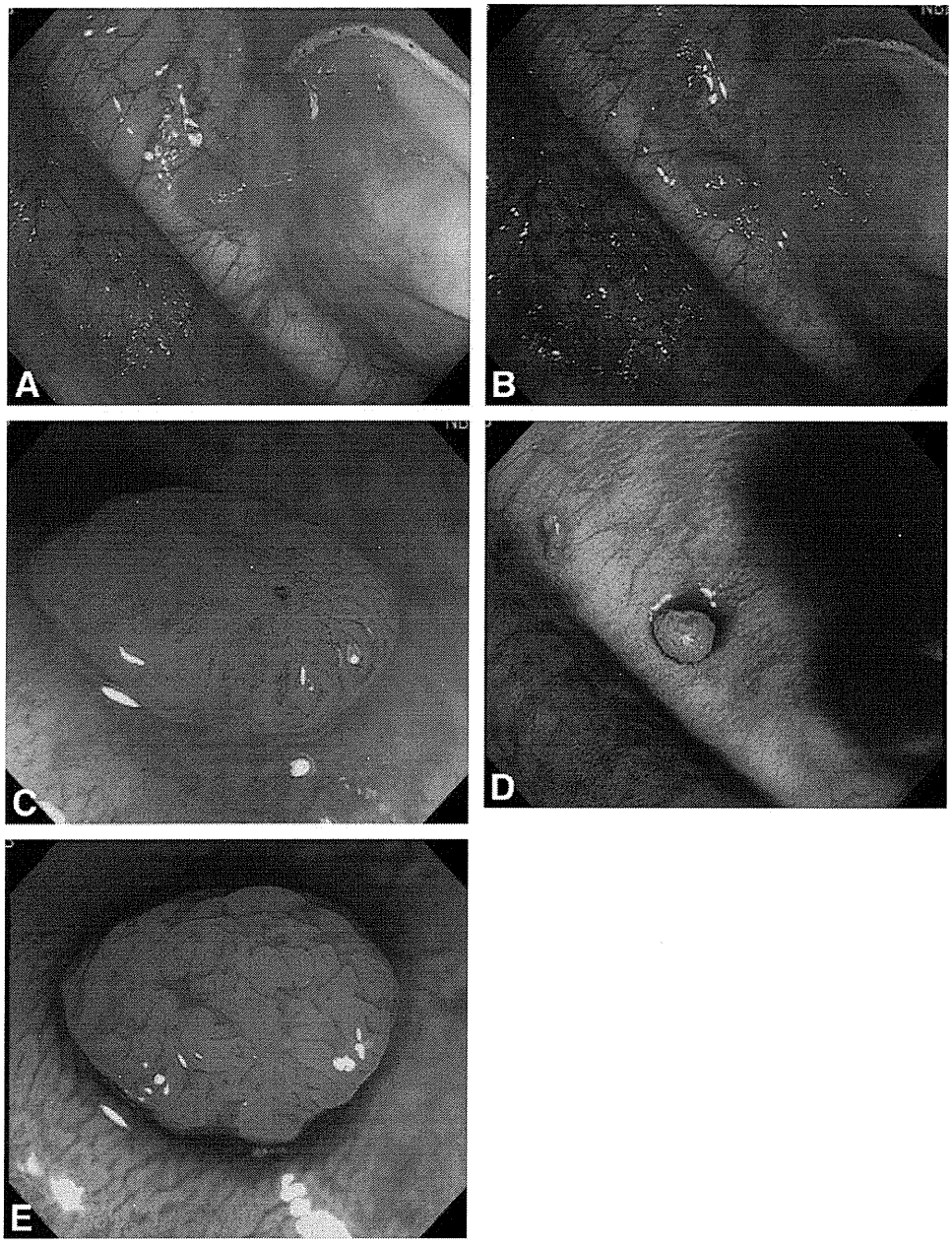

Figure 1. Examples of colorectal neoplastic polyps viewed by different endoscopic modalities in this study. **A,** Conventional colonoscopy view. **B,** Low-magnification NBI showed a brownish area. **C,** High-magnification NBI revealed meshed capillary vessels indicative of Sano classification type II. **D,** Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated margins and surface structure. **E,** High-magnification chromoendoscopy clearly indicated Kudo classification type IIIL. *NBI,* narrow-band imaging.

0.7). Meanwhile, κ values for NBI-H in the LEE group improved to "good agreement" after the training program, whereas the κ values for NBI-L, CE-L, and CE-H in the LEE group improved to "fair agreement" after the training program (κ value before vs after training: NBI-H, 0.46 vs 0.79; NBI-L, 0.31 vs 0.54; CE-L, 0.32 vs 0.44; and CE-H, 0.33 vs 0.59). In contrast, however, none of the κ values for any of the modalities in the NEE group improved beyond "poor agreement" after the training program (CC, -0.068 vs 0.24; NBI-L, 0.059 vs 0.25; NBI-H, 0.16 vs 0.39; CE-L, 0.28 vs 0.23; and CE-H, 0.12 vs 0.18) (Fig. 3).

When we compared diagnostic accuracy for each modality in the NEE group after the training program, the LEE group after the training program, and the HEE group, NBI-H had the highest accuracy rate among all 3 groups (Table 2). Similarly, the κ value for NBI-H was significantly higher in the NEE group after the training program, the LEE group after the training program, and the HEE group

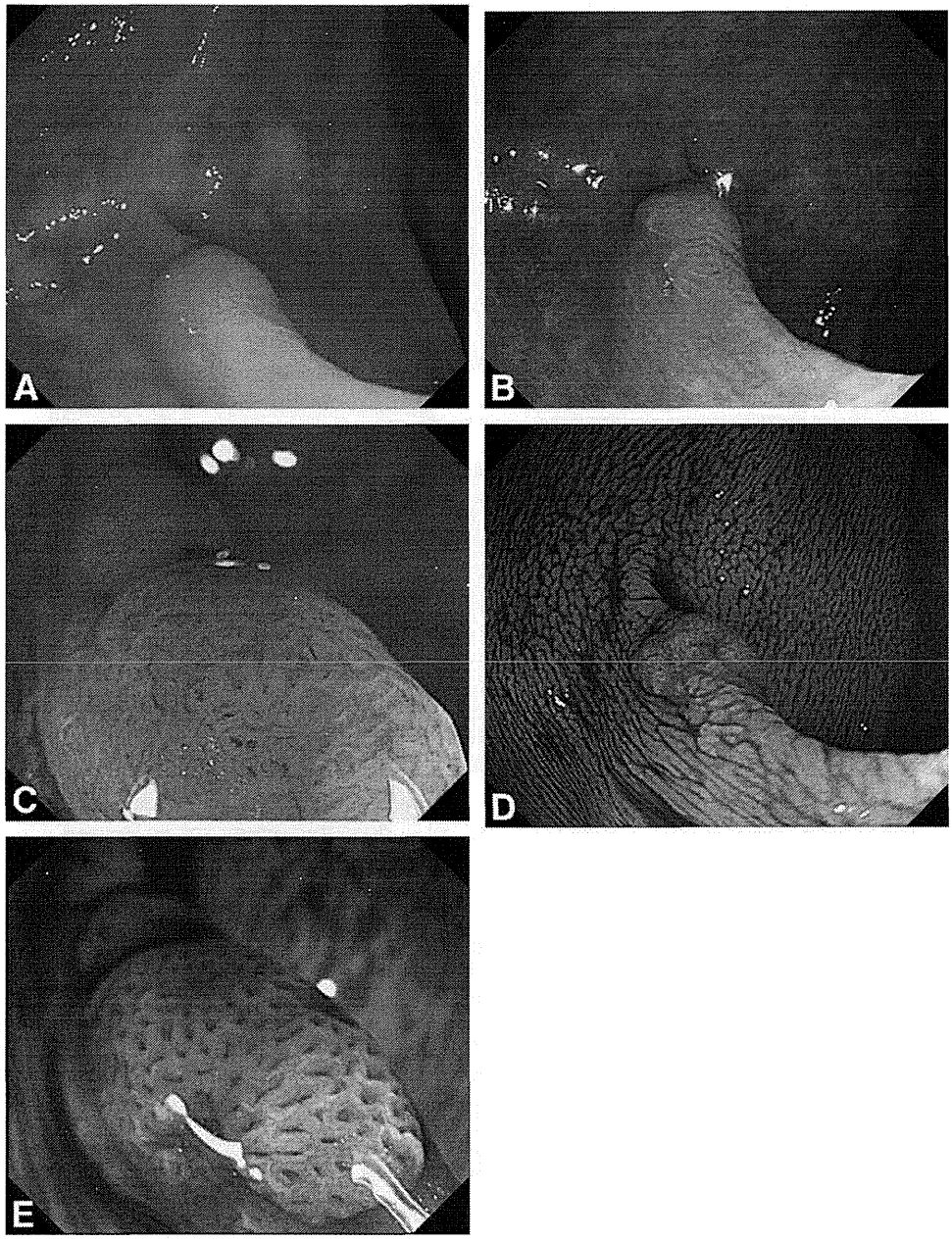

Figure 2. Examples of colorectal non-neoplastic polyps viewed by different endoscopic modalities in this study. **A,** Conventional colonoscopy view. **B,** Low-magnification NBI showed a non-brownish area. **C,** High-magnification NBI in which meshed capillary vessels were not visible or only faintly visible, indicative of Sano classification type I. **D,** Low-magnification chromoendoscopy using 0.2% indigo-carmine dye spraying clearly revealed demarcated margins and surface structure. **E,** High-magnification chromoendoscopy clearly indicated Kudo classification type II. *NBI,* narrow-band imaging.

compared with the other endoscopic diagnostic modalities (Fig. 3).

DISCUSSION

Endoscopic diagnostic tools and technology are expected to be accurate and provide reliably reproducible agreement as well as be easy to use, readily available, and relatively inexpensive, but sufficient skill on the part of the endoscopist is still required for proper diagnosis. Our prospective study demonstrated significant improvement in the LEE group in diagnostic accuracy when using NBI and CE after undergoing limited but intensive training. The improved diagnostic accuracy of the LEE group was equivalent to that of the HEE group in terms of differential diagnosis using NBI-L, NBI-H, and CE-H. In addition, both higher diagnostic accuracy (>80%) and good interobserver agreement (κ value >0.6) for diminutive colorectal

TABLE 1. Patient characteristics and histopathological features of lesions

Patients (n = 32)	
Sex, male/female	22/10
Age, years, mean (± SD)	61.2 (12.3)
Lesions (n = 44)	
Macroscopic type	
0-Is	37
0-IIa	6
0-IIc	1
Size, mm, mean (± SD)	3.4 (1.1)
Location (right*/left†/rectum)	22/14/8
Histopathology	
Tubular adenoma	27
Hyperplastic polyp	17

SD, Standard deviation.
*Right: cecum, ascending colon, and transverse colon.
†Left: descending colon and sigmoid colon.

polyps were achieved by the LEE group when using NBI-H after the training program.

The fact that the diagnostic accuracy and κ value of NBI-H were the highest among all the endoscopic techniques analyzed in this study for both the NEE and LEE groups after the expanded training program as well as for the HEE group leads us to suggest that NBI-H is more accurate and provides a higher level of reproducible agreement than the other diagnostic tools in differentiating diminutive neoplastic from non-neoplastic colorectal polyps. Chiu et al[29] earlier validated that diagnostic accuracy of NBI-H was equivalent to that of CE-H. Their study reported that diagnostic accuracies for two experienced endoscopists ranged from 91% to 92% using CE-H and from 87% to 90% using NBI-H. In our study, the diagnostic accuracy of the HEE group was 85% (95% CI, 79%-89%) using CE-H and 93% (95% CI, 88%-96%) with NBI-H, although the difference between the accuracy of the two modalities was not significant. Earlier reports analyzing the diagnostic accuracy rate based on polyp size indicated that differentiation using CE-H was more difficult with diminutive colorectal polyps of <6 mm in size.[6-7]

Our results indicated that it was possible to significantly improve the diagnostic skill for differentiating diminutive colorectal polyps by using NBI-L, NBI-H, CE-L, and CE-H in the LEE group following the limited but intensive 1-hour interactive training program. We believe that, of the various endoscopic modalities, the use of NBI-H by the LEE group subsequently became both statistically equivalent to that of the HEE group in terms of diagnostic accuracy and closest to reaching "excellent agreement" compared with the other modalities in terms of κ value for two possible reasons. The first concerns the smaller size of the polyps examined in this study, because diagnostic accuracy of diminutive colorectal polyps by using CE-H has been reported to be lower than for polyps of >5 mm.[6-9] It is conceivable that differentiation of diminutive colorectal polyps could have been similarly affected, somehow reducing the diagnostic accuracy of CE-H while not affecting the diagnostic accuracy of NBI-H by the LEE group. Secondly, the possibility exists that members of the LEE group were able to recognize whether or not there were meshed capillary vessels on the surface of the mucosa easier than they could identify the pit patterns of diminutive colorectal polyps.

In the Rogart et al[30] report on the NBI learning curve, diagnostic accuracy by using NBI-L significantly improved as the experience level of endoscopists increased, with the diagnosis of approximately 130 lesions necessary for basic competency. Their findings indicated that educational sessions conducted before the assessment of lesions in combination with continual feedback regarding the accuracy of endoscopic diagnoses compared with histopathological results every 2 weeks for half a year were important factors in achieving a satisfactory learning curve. It has also been reported that use of the Kudo pit pattern classification required a longer learning curve, with experience from diagnosing at least 200 lesions needed to become competent.[6,7,31] In contrast, our study demonstrated that an expanded 1-hour intensive interactive training program conducted by a highly experienced endoscopist enabled the LEE group members in particular to accelerate their learning curve. In addition, the Sano classification with NBI-H appears to have had a shorter learning curve compared with using NBI-L or the Kudo pit pattern classification in the diagnostic differentiation of diminutive colorectal polyps.

Besides having a higher differential diagnosis accuracy and being easier to improve the necessary diagnostic skill for accurately differentiating diminutive colorectal polyps, NBI has other clinical advantages. First, the conventional endoscopic view can be switched almost instantaneously to the NBI view by pressing a single button on the control handle of the colonoscope, and, second, NBI does not require any dye or staining solution to detect and differentiate neoplastic lesions from non-neoplastic lesions.

In recent years, advancements in the quality of endoscopic images available from high-definition endoscopy and chromoendoscopy have considerably enhanced polyp detection. Although the risk of neoplasia in diminutive polyps is <50%, and the risk of high-grade dysplasia is <2%,[7,32,33] diminutive colorectal neoplasms as well as advanced neoplasms are among the precursors of colorectal cancer, and multiple genetic alterations have been implicated in the adenoma-carcinoma sequence.[4] It also has been reported that lesions of ≤5

TABLE 2. Effectiveness of training program on diagnostic accuracy

Modality	NEE group Before-training accuracy (95% CI)	NEE group After-training accuracy (95% CI)	NEE group *P* value*	LEE group Before-training accuracy (95% CI)	LEE group After-training accuracy (95% CI)	LEE group *P* value*	HEE group Accuracy (95% CI)	HEE group *P* value†
CC	0.43 (0.35-0.50)	0.64 (0.57-0.71)	< .001	0.72 (0.65-0.78)	0.74 (0.67-0.80)	NS	0.74 (0.68-0.80)	NS
NBI-L	0.53 (0.46-0.61)	0.66 (0.59-0.73)	.006	0.65 (0.58-0.72)	0.78 (0.72-0.84)	= .001	0.81 (0.75-0.87)	NS
NBI-H	0.63 (0.56-0.70)	0.74 (0.68-0.80)	< .001	0.73 (0.66-0.79)	0.90 (0.85-0.94)	< .001	0.93 (0.88-0.96)	NS
CE-L	0.68 (0.60-0.74)	0.67 (0.60-0.74)	NS	0.68 (0.60-0.74)	0.76 (0.69-0.82)	NS	0.85 (0.79-0.90)	NS
CE-H	0.63 (0.56-0.70)	0.66 (0.59-0.73)	NS	0.67 (0.60-0.74)	0.81 (0.75-0.87)	= .001	0.85 (0.79-0.89)	NS

NEE, No endoscopy experience; *LEE,* less experienced endoscopist; *HEE,* highly experienced endoscopist; *CI,* confidence interval; *CC,* conventional colonoscopy; *NS,* not significant; *NBI-L,* low-magnification narrow-band imaging; *NBI-H,* high-magnification narrow-band imaging; *CE-L,* low-magnification chromoendoscopy; *CE-H,* high-magnification chromoendoscopy.

**P* values determined by McNemar test comparing before and after training.

†*P* values determined by Fisher exact test comparing LEE after training and HEE.

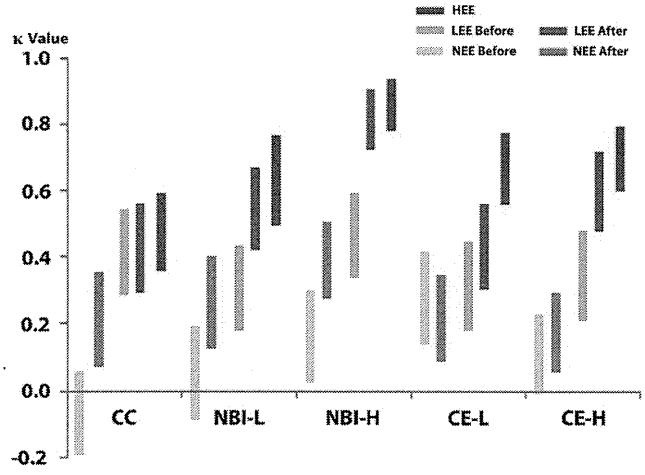

Figure 3. Comparison of 95% confidence interval of κ value for each endoscopic diagnostic modality according to endoscopy experience. Each bar represents the range of 95% confidence interval of the κ value. *HEE,* highly experienced endoscopist group; *LEE,* less experienced endoscopist group; *Before,* before participation in an intensive 1-hour interactive training program; *After,* after participation in an intensive 1-hour interactive training program; *NEE,* no endoscopy experience group; *CC,* conventional colonoscopy; *NBI-L,* low-magnification narrow-band imaging; *NBI-H,* high-magnification narrow-band imaging; *CE-L,* low-magnification chromoendoscopy; *CE-H,* high-magnification chromoendoscopy.

mm make up more than 80% of the colorectal polyps subjected to histopathological assessment.[33] Besides the primary consideration of reducing the risk of future colorectal cancer, the endoscopic differentiation of diminutive neoplastic polyps from non-neoplastic polyps is essential because endoscopists should avoid performing unnecessary procedures, including polypectomies on non-neoplastic polyps, and this also will reduce substantially the number of colorectal polyps requiring histopathological assessment.

There has been considerable interest recently in sessile serrated adenoma (SSA) and serrated adenoma (SA) polyps that also have been associated increasingly with an apparent increased risk of malignant transformation.[34] SSAs endoscopically appear as hyperplastic polyps, but there have not been any published reports as yet applying the Kudo pit pattern analysis to such SSA polyps. In the general population, the prevalence of SSAs has been estimated to range from only 1% to 7% of all polyps, and it further has been shown that most such SSA polyps can exceed 10 mm in size,[35] but we did not detect any SSAs or serrated adenomas in this study. Although it was recently reported that SSAs could be differentiated from hyperplastic polyps by combining NBI and autofluorescence imaging, the report in question had several limitations including the total number of SSAs being relatively small and the lack of any comparison between those two modalities and pit pattern analysis.[36] In addition, the actual prevalence of SSAs is difficult to assess because pathologists have been unable to reach a consensus on the diagnosis of either hyperplastic polyps or SSAs.[37,38] Further studies will be required, therefore, to clarify the endoscopic features and conduct histopathological and molecular-based analyses of SSAs and serrated adenomas.

The primary limitation of our study is that it involved only a small number of polyps. The power of the trial compared to the observed difference was lower because the observed difference was smaller than in the alternative hypothesis used in planning this study. The sample size that was set, however, was not much different from the sample size used in similar studies. Another limitation is that this study was conducted by using endoscopic images. During a "real-time" evaluation, an endoscopist can usually view a detected lesion by using multiple angles and light modalities at variable distances, but we digitally stored all the endoscopic images taken during each exam-

ination, selected the best image from each of the 5 endoscopic observation modalities, and then randomized the distribution order of the images for diagnosis. This process was intended to decrease the likelihood of observational bias and strengthen the reliability of our results, because separate findings based on NBI images and chromoendoscopic images might otherwise have been influenced by the other and made objective evaluation of the individual diagnostic modalities difficult. A third limitation was the relatively short interval between the intensive training program and the follow-up reviews by the NEE and LEE groups. The participants in both groups reviewed all the images for the second time within 24 hours of the training program so as to avoid any possible bias resulting from a feedback learning effect such as self-training. It has previously been reported that feedback received during the development of a diagnostic skill is effective.[39]

In conclusion, NBI, particularly high-magnification NBI, was shown to be a promising tool for diagnostic differentiation of diminutive colorectal neoplastic polyps from non-neoplastic polyps. Expanded training of the LEE group members improved their overall diagnostic ability so that it was equivalent in certain key respects to that of the participating HEE group.

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