Methods

Patients

A total of 127 consecutive patients with 130 lesions endoscopically diagnosed as NBI CP type IIIA /IIIB who underwent endoscopic or surgical resection at the National Cancer Center East Hospital (NCCEH) from October 2005 to October 2007 were analyzed. The protocol was approved by the medical ethics committee of our hospital, and written informed consents for diagnosis and treatment were obtained from all patients prior to the procedures. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Cases judged as NBI CP III but with familial adenomatous polyposis (FAP), and inflammatory bowel disease (IBD) were excluded from the study. CP type III lesions with an obvious appearance of advanced cancer were also excluded.

Colonoscopy procedure using the RGB sequential illumination based NBI system

Bowel preparation consisted of 2 to 3L of polyethylene glycol solution in the morning before the procedure, as previously reported [15]. Hyoscine methobromide (10-20 mg IV) was administered if there were no contraindications, and light sedation with diazepam (3-5 mg IV) was used in selected subjects. All procedures were performed up to the cecum using high-definition colonoscopy (CF-H260AZI [with a magnifying power of 75 at maximum]; Olympus, Optical Co., Ltd., Tokyo, Japan) with NBI magnification. A videoendoscope system (EVIS LUCERA SPECTRUM; Olympus, Optical Co., Ltd., Tokyo, Japan) and a digital image filing system (nexus sif; Fujifilm, Tokyo, Japan) was used. In NBI mode using this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm Optional enhancement setting was set at enhancement mode A5 and color mode 3. Lesions were classified macroscopically based on the Paris classification of superficial gastrointestinal lesions [2]. Next, lesions were observed in NBI and each CP were evaluated by magnifying NBI view in real time. For larger lesions, the highest quality NBI image from the macroscopically worst area (e.g. large nodule, depression and reddened area) was evaluated.
In lesions identified as CP type IIIA, snare polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD) were performed. In lesions identified as CP type IIIB, surgical or endoscopic resection was performed.

Capillary pattern classification

Following conventional white light observation all cancer lesions were evaluated by magnifying NBI. Based on the surface characteristics of the meshed capillaries, CP type III were defined as demonstrating irregular and unarranged pattern in a mesh-like microvascular architecture and exhibiting at least one of the following: irregular size, complicated branching, disrupted irregular winding when compared to the regular small caliber capillaries observed in adenomatous polyps (CP type II) [Figure 1] [9, 11, 14].

Moreover, CP type III lesions were further classified into two groups: types IIIA or IIIB.

Capillary pattern type IIIA

CP type III lesions clearly show visible microvascular architecture and high microvessel density with lack of uniformity, blind ending, branching and curtailed irregularly. [Figure 2A].

Capillary pattern type IIIB

CP type III lesions show a clear distinction between normal/cancerous mucosa on the surface (demarcated area) and the presence of a nearly avascular or loose microvascular area. [Figure 2B]

Histological examination

All resected specimens were retrieved and immediately fixed in 10% buffered formalin solution and examined histologically using hematoxylin and eosin staining. Histopathological diagnosis was determined according to the Vienna classification [16]. Non-pedunculated lesions with a vertical invasion length of less than 1000μm in the submucosal layer were classified as pSM1, and those with invasion of more than 1000μm were classified as pSM2-3 [2]. Pedunculated lesions were categorized according to Haggitt's classification [17]. Pedunculated lesions with head invasion were classified as pSM1, and those with stalk invasion were classified as pSM2-3.

Image evaluation

In an independent sub-study, inter- and intraobserver variabilities of the NBI CP type III for estimating the depth of early colorectal cancer were assessed by three colonoscopists experienced in NBI (YS, TM, HI). All 130 lesions were evaluated. The best magnifying NBI image of each lesion was selected. All selected images were arranged randomly for pattern assessment by the three readers who were blinded to the histological diagnosis of the lesions. All readers diagnosed the image of one pattern one day, and diagnosed another pattern one week later. The obtained data was not used for evaluating diagnostic accuracy of the lesions.

Clinical data evaluation

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CP type III for estimating the depth of invasion of early colorectal cancer was calculated according to the pathological report. Inter and intraobserver variabilities were calculated using kappa statistics.

Results

Clinicopathologic features of colorectal lesions

A total of 130 early colorectal lesions in 127 patients were analyzed. The clinicopathological data is shown in Table 1. According to the macroscopic types, there were 85 (65.4%) flat elevated and depressed lesions and 45 (34.6%) polypoid and protruded lesions. The mean lesion size was 17 mm (range 5-80 mm). There were 81 (62.3%) lesions located in the left colon and rectum and 49 (37.7%) lesions located in the right and transverse colon. Histologically, there were 15 adenomas, 66 pM, 49 submucosal cancers (pSM): 14 pSM1 and 33 pSM2-3. Among lesions diagnosed as CP IIIA 86 out of 91 (94.5%) were adenomas, pM, or pSM1; while among lesions diagnosed as CP IIIB 28 out of 39 (72%) were pSM2-3.

Diagnostic accuracy, NPV and PPV of CP type IIIA and type IIIB

Sensitivity, specificity and diagnostic accuracy of the CP type IIIA / IIIB for differentiating pM or pSM1 (<1000 μm) from pSM2-3 (≥1000 μm) were 84.8%, 88.7% and 87.7%, respectively. The accuracy of CP type IIIA (NPV) was 94.5% (86/91), and that for lesions of CP type IIIB (PPV) was 71.8% (29/39) [Table 2].

Image evaluation

The calculated interobserver variability of HI-YS, HI-TM, and YS-TM was $\kappa = 0.68, 0.67,$ and 0.72, respectively. Intraobserver agreement of HI, YS, and TM was $\kappa = 0.79, 0.76, 0.75,$ respectively (Table 3).

Discussion

We previously demonstrated that NBI with magnification is a simple and reliable method to differentiate non-adenomatous from adenomatous colorectal polyps less than 10 mm (sensibility 96%, specificity 92, overall accuracy 95) [13] and, low grade adenomatous polyps from high grade adenomas or early colorectal neoplasms (Sensitivity 90%, specificity 97, overall accuracy 95) [14].

Based on the clinical observation and detailed characterization of lesions based on changes in the pattern and size of microvessels using magnifying NBI, we have described three different types of CP: CP type I (non-neoplastic lesion), CP type II (adenomatous lesion) and CP type III (cancerous lesion) [9]. The initial studies on CP type III lesions showed that within this group, there were lesions invading the intramucosal or the superficial submucosal layer, which require endoscopic treatment and lesions invading deeply into the submucosal layer, which require surgical treatment. These two subgroups could be differentiated from each based upon their respective CP patterns [17,18]. Concurrent to this study, we performed a pilot study using magnifying NBI to predict the depth of invasion of early colorectal lesions at the National Cancer Center Hospital, Tokyo. From the results of this investigation the following factors were found significantly more frequently in pSM2-3 lesions compared to pM-pSM1 lesions ($P<0.001$): wide caliber, irregular caliber, tortuousity, irregularity, short length and non-dense arrangement. Multivariate analysis, however, revealed that irregularity and non-dense arrangement remained as independent factors [19]. These results supported the reliability of our classification. Consequently, we evaluated the efficacy of subdividing CP type III lesions into two groups (CP type IIIA / Type IIIB) and demonstrated that this may provide an effective in vivo method to predict the depth of invasion of colorectal neoplasms.

In this study, the overall diagnostic accuracy of the CP type IIIA classification to differentiate pM or pSM1 from pSM2-3 (87.7%) was quite similar to results obtained by magnifying chromocolonoscopy (87%) [20]. On the other hand, the sensitivity of using CP IIIA/IIIB to differentiate pM/pSM1 from pSM2-3 lesions (84%) was quite similar when compared to that obtained by the non-invasive/invasive pattern using MCC (85%) [21]. The specificities however, differed markedly (88% and 99%) in these two studies. Possible reasons for these differences are the inclusion of more than 3000 thousand adenomatous lesions in the study and due to the learning curve for estimating depth using NBI in early colorectal neoplasms.

When the NBI results were analyzed, it was found that 5 out of 91 (5.5%) lesions judged as CP type IIIA were ultimately classified as pSM2-3 in the pathological report. On the other hand, 11 out of 39 (28.2%) lesions diagnosed as CP IIIB were demonstrated to be pM or pSM1 according to the pathological report. Therefore the 71.8% positive predictive value (PPV) of CP was lower than the 86.5% PPV associated with using the pit pattern classification [21]. However diagnosis using pit pattern classification is time consuming due to the need to spray indigo carmine and crystal violet. An advantage of NBI is the

ability to diagnose lesions without using any dye solution. Fundamentally, it is suggested that the lesion showing CP type IIIA is recommended for endoscopic treatment. In contrast, when a lesion is classified as CP type IIIB it is then necessary to perform Kudo's pit pattern observation using dye method or EUS assessment. Consequently, accurate pit pattern analysis and sufficient skills in magnifying colonoscopy are basic fundamentals required for accurate NBI diagnosis of depth of invasion in colorectal lesions [22].

In the sub-study, the rate of diagnostic agreement among the three observers was not excellent but good without variability (according to inter and intraobserver agreement rates). Some difficulties may relate to the study design in which the assessment was undertaken using only one image per lesion making the judgment difficult. Huang et al. reported a mean kappa value for inter and intraobserver agreement rate using pit pattern analysis of 0.716 and 0.810, respectively [23]. Considering that analysis of pit pattern has been performed for many years, the inter and intraobserver agreement rates associated with NBI reported in this study may indicate acceptable results. However, further multicenter research with endoscopists of different abilities and interobserver and intraobserver variability studies are necessary to validate these results.

The primary limitation of this study was that the NBI CP appearance was judged by a single endoscopist well experienced in magnifying NBI colonoscopy. Another point worth mentioning is that endoscopic judgment of the interobserver and intraobserver studies was carried out by experienced examiners. This means that the effectiveness of classifying CP by NBI deserves further validation studies including less experienced endoscopists.

Conclusions

This study has demonstrated that the CP (Type IIIA/Type IIIB) evaluated by magnifying NBI may be an effective in vivo alternative method to predict the depth of invasion of colorectal neoplasms without the application of any dye solution. However, additional comparative research with MCC may be necessary to validate the results of this study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The study was planned by HI, TM, FE, YS, TU, K-IF, KK, YS participated in the design and coordination of the study. OA and TF analyzed a pathologic finding. HI collected the clinical data and wrote the manuscript. HI, TM and YS performed the statistical analyses. All authors have read and approved the final the manuscript.

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Figures

Figure1 - Capillary pattern classification

Figure2 - Capillary pattern type IIIA, IIIB (magnifying NBI image at full max 75 times)
A : Capillary pattern type IIIA
B : Capillary pattern type IIIB

Tables

Table 1 - Clinicopathological features of CP III lesions

No. of patients/lesions	**127/130**
Sex (Male/Female)	**81/46**
Mean age (y [range])	**65.3 [41-86]**
Macroscopic types	
Flat, depressed	**85**
Sessile, protruded	**45**
Mean size of lesions (mm [range])	**17.0 [5-80]**
Locations	
Right colon	**49**
Left colon, rectum	**81**
Histopathology	
Adenoma	**15**
pM*, pSM-superficial (pSM1)**	**82**
pSM-deep(pSM2-3)#	**33**

*** intramucosal cancer, ** SM superficial invasion (<1000μm), # SM deep invasion (≥1000μm)**

Table 2 - Sensitivity, specificity and diagnostic accuracy of the CP Type III

	Histological diagnosis	
	M*, SM-superficial (SM1)**	**SM-deep(SM2-3)#**
CP type IIIA	**86**	**5**
CP type IIIB	**11**	**28**

Sensitivity: 84.8%, Specificity: 88.7%, Accuracy: 87.7%,
NPV (negative predictive value): 94.5%, PPV (positive predictive value): 71.8%

*** intramucosal cancer, ** SM superficial invasion (<1000μm), # SM deep invasion (≥1000μm)**

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**

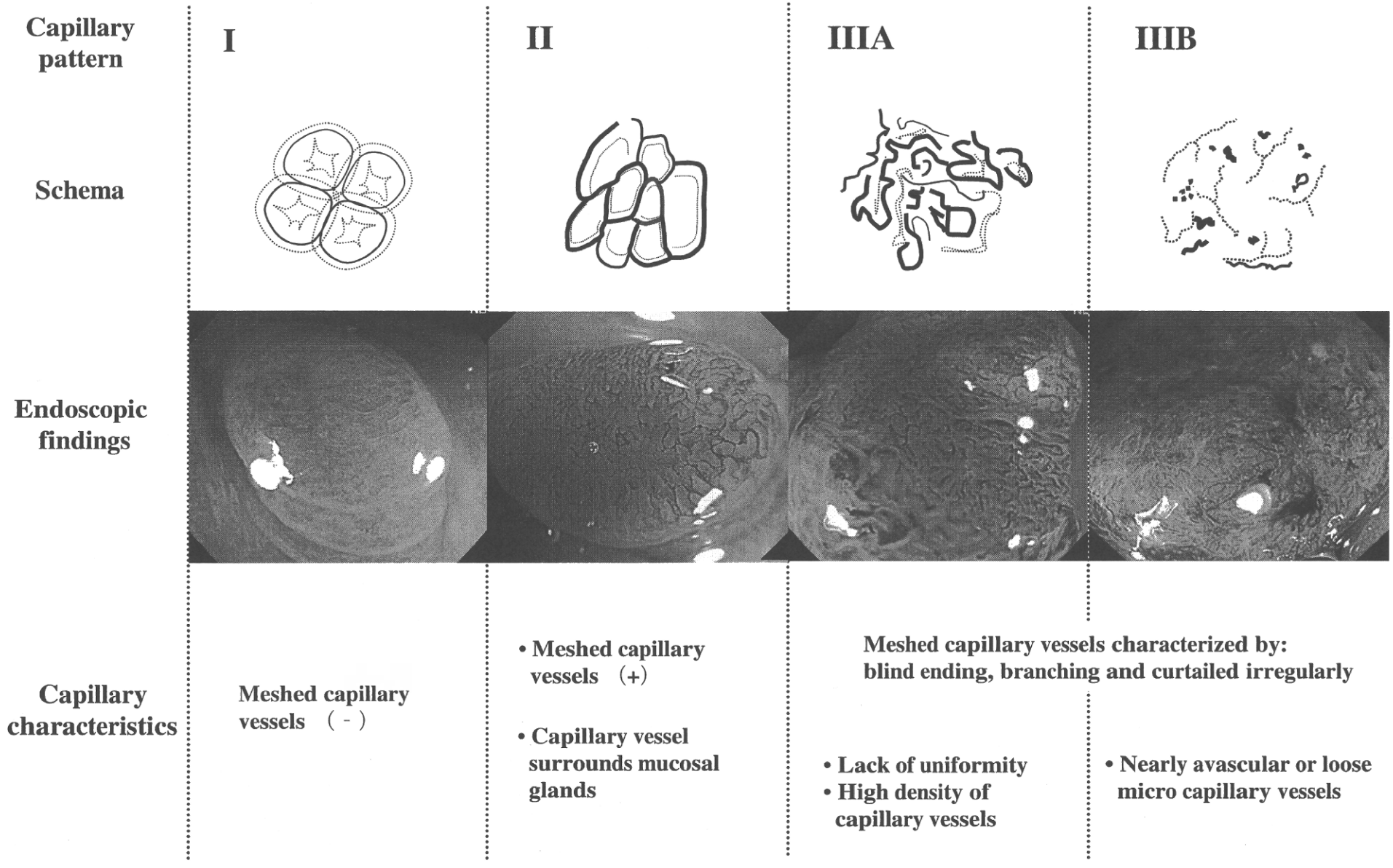
Capillary pattern
I
II
IIIA
IIIB
Schema
Endoscopic findings
Capillary characteristics
Meshed capillary vessels (-)
• Meshed capillary vessels (+)
• Capillary vessel surrounds mucosal glands
Meshed capillary vessels characterized by: blind ending, branching and curtailed irregularly
• Lack of uniformity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

Figure 1

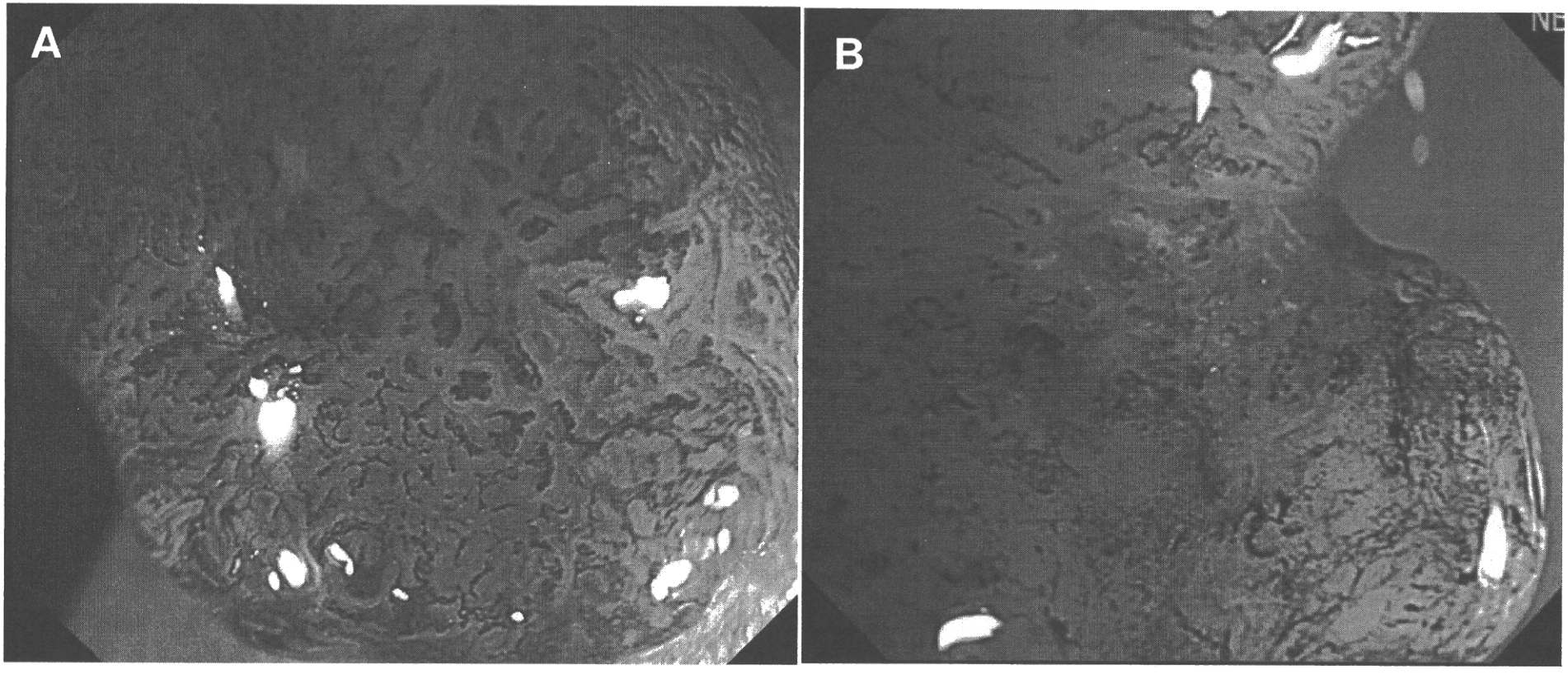

Figure 2

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INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

IMPACT OF NARROW-BAND IMAGING IN SCREENING COLONOSCOPY

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Narrow band-imaging (NBI) enhances mucosal visualization of the vascular network and surface structure and helps to increase the visibility of neoplasia by improving contrast. Studies on the detectability of colorectal neoplastic lesions using NBI have primarily been reported in Western countries, but the published opinions and conclusions remain controversial at the present time. Our earlier prospective pilot study demonstrated that NBI colonoscopy significantly improved detection of flat lesions, which are more likely to be missed, particularly on the right side of the colon. It is especially important that even examiners performing routine screening colonoscopies become sufficiently familiar with flat and depressed lesions and then take full advantage of the endoscopic systems and specific image enhancement functions currently available for improved detection of flat and diminutive lesions. Adequate bowel preparation is another important consideration.

Key words: detection, colonoscopy, narrow-band imaging (NBI), screening.

INTRODUCTION

Colonoscopy is the preferred screening method for colorectal cancer, but the number of missed colon polyps can be considerable. Back-to-back colonoscopies have found that the undetected rate for adenomatous polyps is approximately 25%[1,2] and even adenomas greater than 1 cm have been missed on occasion. Several techniques including chromoendoscopy,[3] cap-fitted colonoscopy,[4] retroflexion of the colonoscope[5] and wide-angle colonoscopy[6] have been used to improve the polyp detection rate and the newly developed Third Eye Retroscope system is expected to further increase overall detection.[7]

Narrow band-imaging (NBI) is based on modifying the bandwidth transmittance of spectral features using various optical filters to enhance visualization of the mucosal vascular network and surface structure.[8,9] This relatively new endoscopic technology has recently become available worldwide for use in the detection of colorectal neoplastic lesions, so greater attention is now being paid to whether NBI can be effective in adenoma detection.

This review focuses on the present status of the role of NBI, taking into account various other screening modalities, this promising technology's future prospects and the need for its further refinement.

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NARROW-BAND IMAGING

The center wavelengths of the dedicated trichromatic optical filters are shifted to shorter wavelengths of 500 nm, 445 nm and 415 nm with each having a bandwidth of 30 nm.[9] The NBI system is a relatively simple device in which two filters, a standard filter and an NBI filter, are built into one light source. NBI provides unique views especially of the mucosal vascular network and surface structure and helps in the visualization of neoplasia by improving contrast. One of the system's advantages is that the conventional view can be switched instantaneously to the NBI view and vice versa by pressing a single electronic button on the control handle of the colonoscope. NBI could potentially improve both polyp detection and differentiation of neoplastic from non-neoplastic polyps thereby serving a dual purpose in screening colonoscopy.

NBI in differentiating neoplastic from non-neoplastic colorectal polyps

Machida, Sano and their colleagues first reported that the NBI system improved endoscopic visualization without the need for any dye solution (high-contrast endoscopy).[10] In addition, their research examined the usefulness of NBI with magnification for the differential diagnosis of neoplastic from non-neoplastic lesions and determined that diagnostic accuracy using NBI was higher than that of conventional colonoscopy (93.4% *vs* 79.1%) and equal to that of chromoendoscopy using indigo-carmine dye spraying. Subsequently, the effectiveness of NBI in the differential diagnosis of colorectal polyps has clearly been demonstrated in several prospective studies[11–13] indicative of a growing consensus on the subject.

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NBI for improving colorectal adenoma detection

Results from the first American randomized study on detectability using NBI were quite negative,[14] but a subsequent British comparative study on NBI was more positive particularly with respect to the detection of flat lesions.[15] Table 1 shows the results of our prospective pilot study.[16] Compared to conventional colonoscopy, the total number of adenomas detected by NBI was significantly higher. Based on the macroscopic type, flat lesions were detected significantly more often with NBI than with conventional colonoscopy. In terms of location, lesions on the right side of the colon were identified with NBI significantly more often compared to conventional colonoscopy. A number of NBI reports published primarily in Western countries, including the studies mentioned above, are characterized as being either positive or negative in Table 2,[17-21] but the opinions and conclusions are still controversial.

RECOMMENDATIONS

Comparing NBI systems and lack of reported information on function settings

In our review of the published reports on the detectability of colorectal adenomas using NBI, we noticed that two different Olympus (Tokyo, Japan) endoscopic video systems, either the sequential LUCERA series or the simultaneous EXERA-II series (also known as the 'color chip system') were used in all of the studies as both Olympus systems are now in service in different parts of the world. Nearly all of the positive studies used the LUCERA system while all of the negative studies relied on the EXERA-II system. Accordingly, the LUCERA system may be preferable to the EXERA-II system for polyp detection. Unfortunately, the specific NBI system image enhancement settings (i.e. surface structure and adaptive index of hemoglobin [IHb] color enhancement settings) were not indicated in any of the other reports so a truly accurate comparative analysis is even more problematic.

Table 1. Comparison of detected adenomas – total number, lesion size, macroscopic type and location

		CC	NBI	*P*-Value
Total number of detected adenomas		58	72	0.04
Lesion Size	<5 mm	48	57	0.15
	5–9 mm	58	68	0.06
	≥10 mm	10	9	0.61
Macroscopic type	Flat	58	72	0.04
	Polypoid	58	62	0.45
Location	Right Colon	72	87	0.02
	Left Colon	31	36	0.45
	Rectum	13	11	>0.99

CC, conventional colonoscopy; NBI, narrow-band imaging.

Table 2. Clinical outcomes of studies comparing adenoma detectability using narrow-band imaging and conventional colonoscopy

	Negative Studies	Olympus Endoscopic Video System
Rex DK, *et al.*[14]	2007, USA	EXERA-II
Kaltenbach T, *et al.*[17]	2008, USA	EXERA-II
Alder A, *et al.*[18]	2009, Germany	EXERA-II
Paggi S, *et al.*[19]	2009, Italy	EXERA-II
	Positive Studies	**Olympus Endoscopic Video System**
East JE, *et al.*[15]	2008, UK	LUCERA
Rastogi, *et al.*[20]	2008, USA	EXERA-II
Inoue, *et al.*[21]	2008, Japan	LUCERA
Our Study[16]	2008, Japan	LUCERA

Appropriate system function settings and other important considerations

We believe that appropriate NBI system function settings are essential in order to properly assess the detectability of adenomas using NBI.[22] Use of both enhancement functions previously mentioned markedly improves the contrast of NBI system images. The surface structure enhancement function includes six different image settings that provide increased definition of mucosal and microcirculatory structure. The adaptive IHb color enhancement function with its three separate level settings automatically calculates the average hemoglobin concentration in formulating the NBI view of the surrounding tissue in combination with the enhanced image features. The A-5 image setting of the surface structure enhancement function together with the level 3 adaptive IHb color enhancement setting seem to be the most suitable for detection of colorectal adenomas based on our experience.

Selection of an appropriate colonoscope is another important consideration. A high-definition colonoscope should be used for polyp detection, but a standard definition colonoscope is unsuitable for such a purpose (Fig. 1). In contrast, use of a high-definition colonoscope is not necessary for the differential diagnosis of polyps with magnification. In addition, the importance of adequate bowel preparation is even more pronounced with NBI compared to conventional colonoscopy. Lastly, it is increasingly important that screening colonoscopy examiners be sufficiently familiar with flat and depressed lesions in order to ensure a thorough colorectal screening examination.

NBI FUTURE PROSPECTS AND REFINEMENTS

A multicenter randomized controlled trial utilizing appropriate NBI system settings is currently being conducted in Japan to evaluate the efficacy of screening and surveillance colonoscopies. More precise NBI system settings for screening colonoscopy could increase the detection rate for flat adenomatous lesions and reduce variations in diagnostic performance. Finally, we recommend further refinement of the NBI system itself with practical improvements such as a more powerful light source to extend the NBI view in the colon and better enhancement of lesion margins, which would be most helpful in the detection of adenomas.

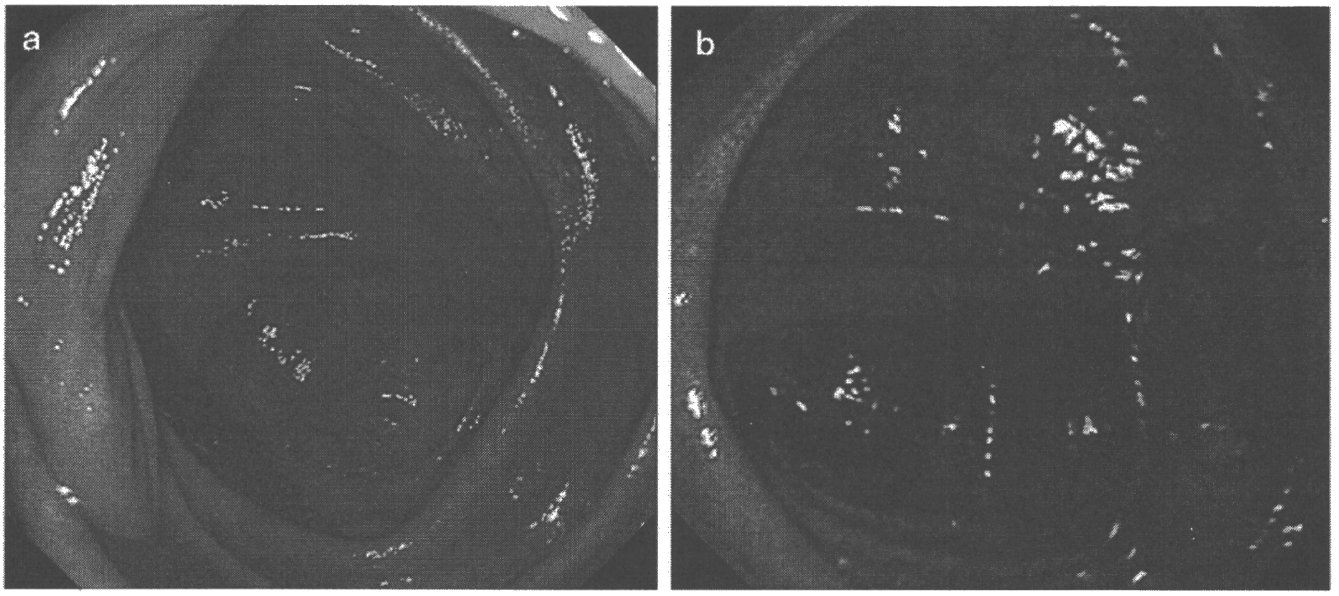

Fig. 1. Comparison of narrow-band images from different colonoscopes. (A) High-definition colonoscopy view with CF-H260AZI (Olympus, Tokyo, Japan). (B) Standard-definition colonoscopy view with PCF-240ZI (Olympus).

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Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy

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Key words
colon cancer, colorectal cancer, depth diagnosis, magnifying endoscopy, submucosal cancer.

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Abbreviations:
CRC, colorectal cancer; EMR, endoscopic mucosal resection; s.m., submucosal; s.m.-s., submucosal slight; s.m.-d., submucosal deep; LST-G, laterally spreading tumor granular type.

Abstract

Background and Aims: Early colorectal cancer (CRC) with submucosal deep (s.m.-d.) invasion should not be treated with endoscopic mucosal resection due to the higher incidence of lymph-node metastasis. It is, therefore, clinically important to accurately diagnose s.m.-d. lesions before treatment.

Methods: We analyzed the endoscopic features, including pit patterns, of early CRC with s.m.-d. invasion observed using magnifying colonoscopy. We retrospectively investigated 379 cases of early CRC. Lesions were divided into three macroscopic subtypes (pedunculated type, sessile type and superficial type) based on endoscopic findings. Eight endoscopic factors were evaluated retrospectively for association with s.m. invasion and then compared to histopathological findings.

Results: The superficial type had a significantly higher frequency of s.m.-d. invasion (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], P-value < 0.05, respectively, for pedunculated and sessile types). Based on multivariate analysis, an independent risk factor for s.m.-d. invasion was the existence of an invasive pit pattern in sessile and superficial types (odds ratios of 52.74 and 209.67, respectively). Fullness was also an independent risk factor for s.m.-d. invasion in the superficial type (odds ratio = 9.25). There were no independent risk factors for s.m.-d. invasion in the pedunculated type.

Conclusion: High magnification pit pattern diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial types although it was not as helpful with the pedunculated type.

Introduction

The incidence of colorectal cancer (CRC) has recently been increasing in Japan. Early CRC that consist of intramucosal cancers or submucosal (s.m.) cancers that only superficially invade the s.m. layer (s.m.-s.) can be removed by endoscopic mucosal resection (EMR).[1] Endoscopic treatment for early CRC is considered appropriate when the following conditions have been satisfied: a lesion is determined histopathologically to be well differentiated; invasion of the s.m. layer is < 1000 μm (s.m.-s.); and the lesion is negative for both lymphovascular invasion and sprouting.[2] Early CRC with s.m. deep (s.m.-d.) invasion should not be treated with EMR due to an increased risk of lymph-node (LN) metastasis, which has been reported to range from 6.9% to 22.2%.[2] Consequently, it is clinically important to accurately diagnose the depth of invasion before treatment.

A role for magnifying endoscopy in the colon has previously been indicated for the diagnosis of flat and depressed lesions, identification of dysplasia in ulcerative colitis, discrimination among polyp types and assessing the completeness of EMR.[3-5] Pit pattern classification for colonic lesions has also been well documented in the past. We have already reported that pit pattern analysis using magnification colonoscopy was useful in the diagnosis of invasive depth in early CRC, particularly flat and depressed lesions.[6-9] No studies have been reported as yet, however, that focused on the diagnosis of s.m. invasion in pedunculated and sessile type lesions.

The aim of this study was to analyze the endoscopic features (including pit patterns) of early CRC with s.m.-d. invasion from a large number of early CRC including pedunculated and sessile types using magnifying colonoscopy in order to determine the appropriate therapeutic strategy.

Methods

A total of 844 early CRC were resected endoscopically or surgically at the National Cancer Center Hospital in Tokyo between October 1998 and September 2005. In this series, 687 lesions were removed by endoscopic resection and 157 underwent surgical treatment. All lesions were examined using magnifying colonoscopy before treatment. Among them, 232 tumors were positive for s.m. invasion (612 intramucosal cancer lesions, 52 s.m.-s. lesions

and 180 s.m.-d. lesions). We also investigated the 256 consecutive intramucosal early CRC that were resected between January 2004 and September 2005 as our control group (EMR, 253 lesions; and surgery, three lesions) to help ascertain and evaluate differences between intramucosal and s.m. invasive cancers. From this total of 488 early colorectal lesions, 68 (13.9%) were excluded because the quality of their magnifying colonoscopy pictures was too poor for an accurate assessment either because of mucous or the pictures were out of focus leaving 420 (86.1%) lesions with suitable pictures for s.m. invasion diagnostic purposes. In addition, granular type laterally spreading tumors (LST-G) consist of several different shapes. For example, some LST-G have a flat elevated component surrounding a large nodule. It is therefore difficult to categorize such lesions as being either the protruded or flat type.[10,11] Accordingly, 41 LST-G were excluded from this study. Eventually, a total of 379 lesions were analyzed retrospectively (179 intramucosal lesions, 40 s.m.-s. lesions and 160 s.m.-d. lesions). These lesions were then divided into three subtypes according to the Paris classification: pedunculated type (type 0-Ip), sessile type (type 0-Is) and superficial type, which included slightly elevated (0-IIa), completely flat (0-IIb) and slightly depressed lesions without ulcer (0-IIc).[13]

Endoscopic examination

In our medical facility, all colonoscopies are performed with magnification. When a lesion was detected by conventional endoscopic examination, surface mucin was washed away with lukewarm water containing pronase (Pronase MS, Kaken Pharmaceutical, Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion in order to enhance its surface detail. High magnification colonoscopes (CF-240ZI, PCF-240ZI and CF-200Z, Olympus Optical, Tokyo, Japan) were also used in this study. When a high magnification observation with indigo-carmine dye was not enough to determine the surface structure (pit pattern analysis), staining was added with 0.05% crystal violet.[14] The additional time usually needed to complete the magnification observation was less than 10 min including 30 s to one minute to wash the lesion, one minute for crystal violet staining and one to five minutes for the actual observation.

The depth of tumor invasion was classified as intramucosal, s.m.-s. (invasion < 1000 μm from the muscularis mucosa) and s.m.-d. (invasion ≥ 1000 μm from the muscularis mucosa). In order to elucidate the possible association between s.m.-d. invasion and various endoscopic findings, we selected eight endoscopic factors related to s.m. deep invasion from previously published literature[10–12] and then those eight endoscopic factors were investigated retrospectively.

1 Tumor Size—receiver operating characteristic (ROC) curves were used to determine the relationship between tumor size cut-offs and diagnostic accuracy. Based on these ROC curves, we chose tumor size cut-offs for pedunculated (20 mm), sessile (15 mm) and superficial (10 mm) tumors. The size for en bloc resected specimens was estimated by histopathological examination and for piecemeal resected specimens by reviewing endoscopic photographs.
2 Loss of Lobulation—with or without a loss of lobulation (Fig. 1).

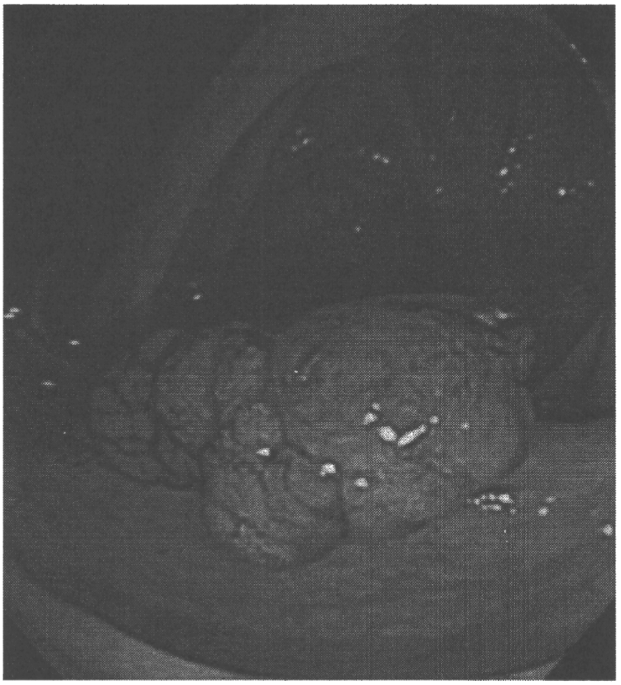

Figure 1 Loss of lobulation.

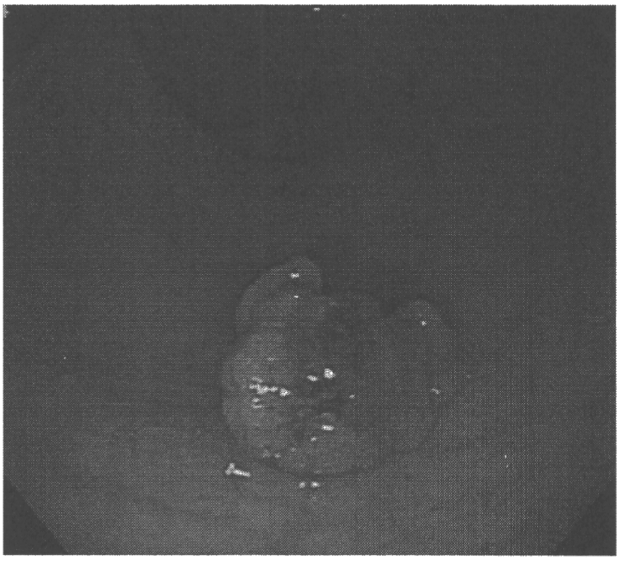

Figure 2 Excavation.

3 Excavation—a crumbled, damaged area of the tumor that prevents observation of the surface structure (Fig. 2).
4 Demarcated Depressed Area—with or without such a demarcation (Fig. 3).
5 Stalk Swelling—a thickened and expanded stalk (Fig. 4).
6 Fullness—a bursting appearance due to expansive growth of the tumor (Fig. 5).
7 Fold Convergency—a fold convergency towards the tumor (Fig. 6).

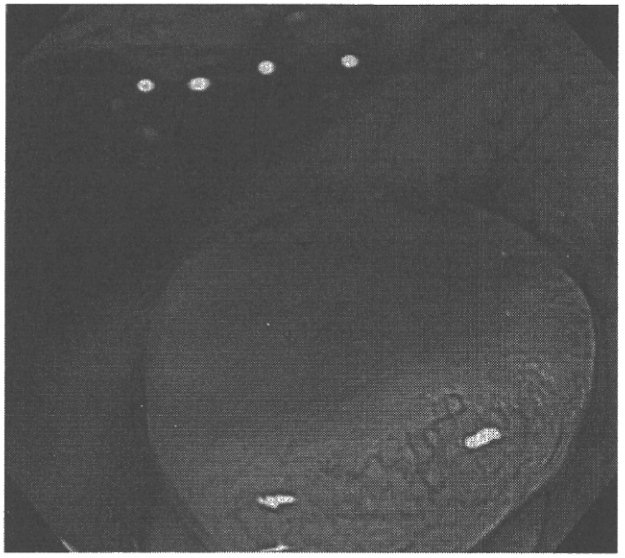

Figure 3 Demarcated depressed area.

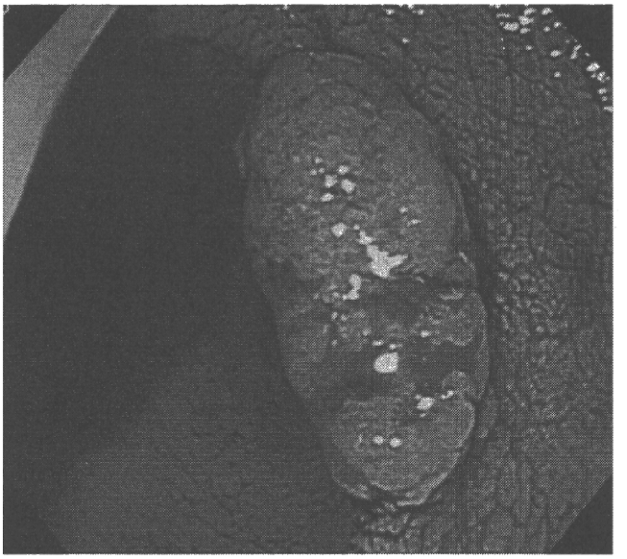

Figure 5 Fullness.

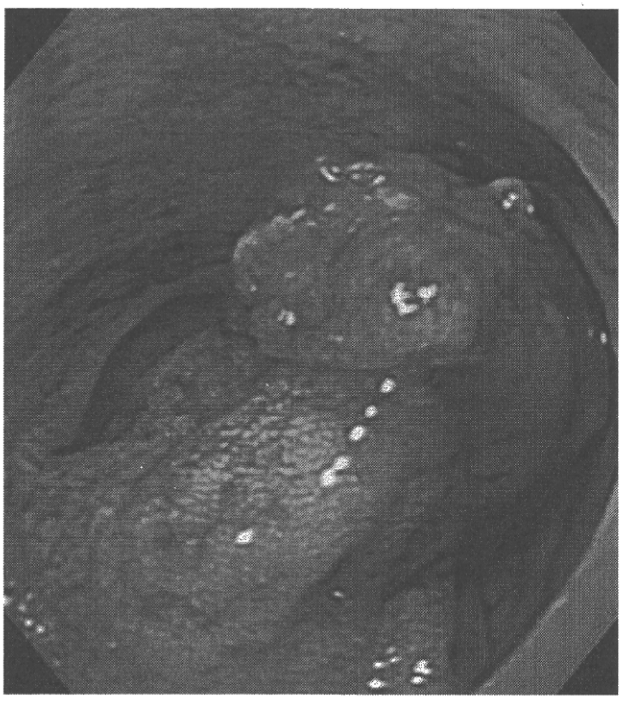

Figure 4 Stalk swelling.

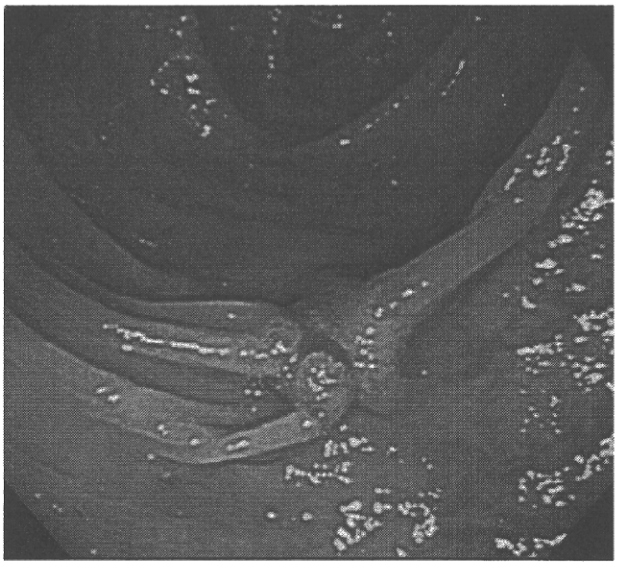

Figure 6 Fold convergency.

8 Pit Pattern—'Invasive pattern' or 'Non-invasive pattern' with the 'Invasive pattern' characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting s.m.-d. invasion $\geq 1000\ \mu m$ while the 'Non-invasive pattern' did not have those two findings that suggested intramucosal neoplasia or s.m.-s. invasion $< 1000\ \mu m$ (Fig. 7a,b).[2,3,15]

Different endoscopic factors were assessed for each type. 'Stalk Swelling' was assessed for only the pedunculated type; 'Loss of Lobulation' and 'Excavation' were assessed for the pedunculated and sessile types; 'Fullness' and 'Fold Convergency' were assessed for the superficial type; and 'Size', 'Demarcated Depressed Area' and 'Pit Pattern' were assessed for all three types.

All endoscopic factors were determined retrospectively by three highly experienced endoscopists (H. I., Y. S. and T. M.) each of whom had previously performed over 1000 colonoscopies each year for more than five years. Final determination of endoscopic findings was decided by agreement of at least two of the three endoscopists. The relationships between the various endoscopic factors and the extent of s.m.-d. invasion were analyzed histopathologically in those lesions with s.m.-d. invasion.