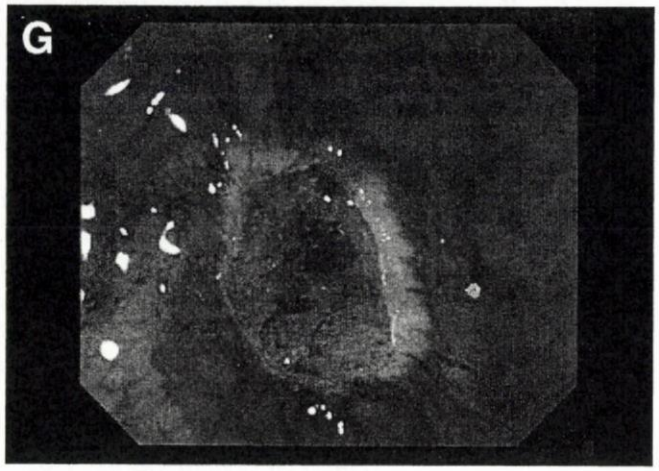

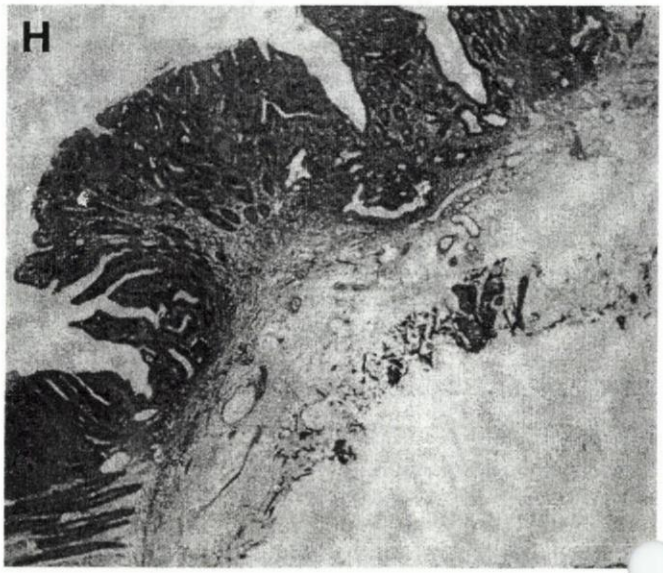

Answer to the Clinical Challenges and Images in GI Question: Image 3: Small Depressed Colon Cancer

The diagnosis was early colon cancer with slight submucosal (SM) invasion so the lesion was resected en bloc by endoscopic mucosal resection (EMR) using the injection-and-cut method (Figure *G*). NBI showed thick microvessels (Figure *E*) and crystal violet staining with magnification of the depressed area indicated a type V_I (non-invasive) pit pattern (Figure *F*). Subsequent histologic evaluation disclosed a well-differentiated adenocarcinoma with SM invasion <1000 μm (SM1; Figure *H*; original magnification, 40×).

In this case, the magnified endoscopic view with crystal violet staining revealed a small demarcated area with a slightly irregular type V_I (non-invasive) pit pattern[1] indicative of a carcinoma rather than an adenoma, despite its small size. The estimated depth was intramucosal (M) or SM1. SM1 lesions without lymphovascular invasion or poorly differentiated components have no risk of lymph node metastasis. The recent Paris endoscopic classification of superficial neoplastic lesions determined 1,000 μm to be the appropriate cutoff point between SM1 and deeper SM invasion (SM2) lesions. To determine whether endoscopic resection or surgery is the appropriate treatment, the nature of a lesion's pit pattern has been used to ascertain the depth of SM invasion.[2,3]

NBI is a new technology that uses 2 optical filters with wavelengths of 415 and 540 nm for sequential blue and green illumination of the videoendoscopic system. The 415 nm image channel analyzes the fine surface architecture of the mucosa and the superficial capillary network and the 540 nm image channel analyzes the collecting vessels in greater detail. In the final mixed image, the processor further enhances contrast by reassigning the color channels; superficial and deep details are superimposed in a single image, thereby improving the visibility of flat lesions and displaying subepithelial capillaries in brown and veins in the submucosa in cyan.[4] It is known that neovascularization by angiogenesis occurs in pathologic settings such as tumor growth. With NBI, increased capillary vessel density in neoplasms turns brown and makes the pit pattern evident without dye spraying.[5]

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REVIEW

Narrow-band imaging optical chromocolonoscopy: Advantages and limitations

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Abstract

Narrow-band imaging (NBI) is an innovative optical technology that modifies the center wavelength and bandwidth of an endoscope's light into narrow-band illumination of 415 ± 30 nm. NBI markedly improves capillary pattern contrast and is an *in vivo* method for visualizing microvessel morphological changes in superficial neoplastic lesions. The scientific basis for NBI is that short wavelength light falls within the hemoglobin absorption band, thereby facilitating clearer visualization of vascular structures. Several studies have reported advantages and limitations of NBI colonoscopy in the colorectum. One difficulty in evaluating results, however, has been non-standardization of NBI systems (Sequential and non-sequential). Utilization of NBI technology has been increasing worldwide, but accurate pit pattern analysis and sufficient skill in magnifying colonoscopy are basic fundamentals required for proficiency in NBI diagnosis of colorectal lesions. Modern optical technology without proper image interpretation wastes resources, confuses untrained endoscopists and delays inter-institutional validation studies. Training in the principles of "optical image-enhanced endoscopy" is needed to close the gap between technological advancements and their clinical usefulness. Currently available evidence indicates that NBI constitutes an effective and reliable alternative to chromocolonoscopy for *in vivo* visualization of vascular structures, but further study assessing reproducibility and effectiveness in the colorectum is ongoing at various medical centers.

Key words: Narrow-band imaging; Colonoscopy; Sequential system; Non-sequential system; Polyps; Chromoendoscopy

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INTRODUCTION

In 1971, Folkman proposed that all tumor growth was angiogenesis-dependent. This was the foundation for the development of angiogenetic research and helped to stimulate investigation that is now being pursued by scientists in many different fields worldwide[1]. New blood vessel creation favors a transition from hyperplasia to neoplasia (i.e., the passage from a state of cellular multiplication to a state of uncontrolled proliferation characteristic of tumor cells)[2].

An *in vivo* means for visualizing angiogenesis or microvessel morphological changes in superficial neoplasms would constitute a promising method for the diagnosis of early gastrointestinal tumors. Narrow-band imaging (NBI) is an innovative optical technology developed in Japan that modifies the center wavelength and bandwidth of an endoscope's light into a narrow-band illumination of 415 ± 30 nm. By utilizing this narrow spectrum, contrast in the capillary pattern of the superficial layer is markedly improved[3], thereby facilitating clearer visualization of vascular structures during gastrointestinal endoscopy[4].

The first clinical study of the NBI system for the diagnosis of gastrointestinal tumors was reported by Sano *et al*[5] in 2001. Their promising observations resulted in the first pilot colorectal study in which the NBI system demonstrated better vascular pattern

visualization than conventional colonoscopy in the diagnosis of colorectal polyps[6]. These early studies opened the way for subsequently using NBI in the diagnosis of pre-malignant and malignant lesions of the hypo-pharynx, esophagus and stomach[4,7,8].

This review focuses on the current advantages and limitations of using the NBI system in the diagnosis of colorectal lesions.

SCIENTIFIC BASIS FOR NBI

Video endoscopes use white light from a xenon source for illumination. In order to understand the reflectance spectrum of any tissue, both the scattering process and absorption must be taken into account. Based on the Monte Carlo simulation, several investigations into the mechanism of scattering from tissue structures have determined that the penetration depth of the light depends on the wavelength. The depth of penetration into the gastrointestinal tract mucosa is superficial for the blue band, intermediate for the green band and deep for the red band (penetration depth range: 0.15 to 0.30 mm). As a result, NBI systems use optical filters for green and blue sequential illumination and narrow the bandwidth of spectral transmittance[9,10] (Figure 1).

The scientific basis for the NBI system is that light with a short wavelength falls within the hemoglobin absorption band, so that blood vessels may be more clearly seen due to sufficient contrast[6].

IMAGE RECONSTRUCTION FROM REFLECTED LIGHT

Two different types of NBI systems are used to reconstruct images from the reflected light. The non-sequential system (Exera Ⅱ), also referred to as the "color chip system", uses a color charge coupled device (CCD) in which pixels are selectively assigned to specific wavelength ranges. The CCD captures the full range of the white light and transfers it in a single step to the processor in order to reconstruct natural color on the video monitor (Figure 2).

In contrast, the sequential system (Lucera Spectrum) uses a monochrome CCD in which pixels are not selectively attributed to specific colors, but transferred sequentially in the RGB bands to the processor. A rotating RGB interference filter is interposed after the white light source and the mucosa is illuminated alternately in each of the three RGB bands[11] (Figure 3).

Although the concept and basic design is the same for both the NBI sequential and non-sequential systems, a difference in color images exists due to differences in the color spectral characteristics of the RGB rotary filters used in the Lucera Spectrum and the color CCD used in the Exera Ⅱ. There is considerable potential for further development, however, by improving NBI technology in the non-sequential endoscopic video system.

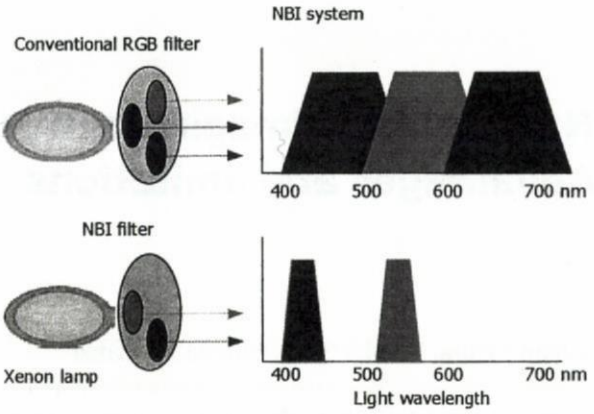

Figure 1 NBI system. Different from the conventional RGB filter, the NBI filter consists of two narrow bands (415 ± 30 nm and 540 ± 30 nm, respectively) that make it possible to observe clearly superficial vascular patterns for clinical evaluation.

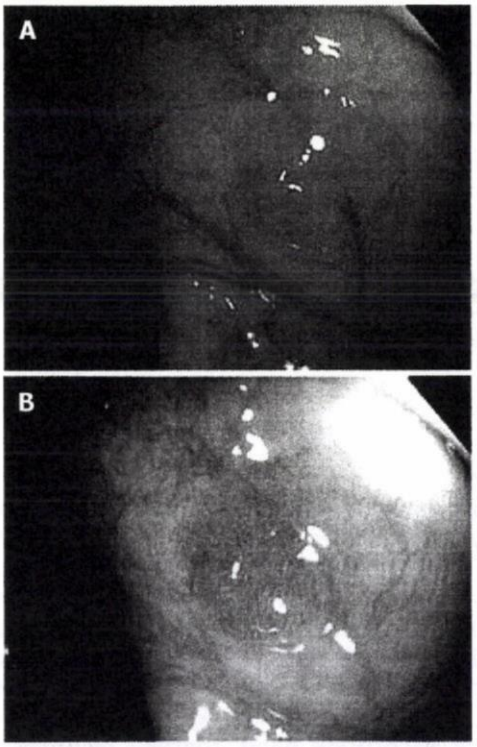

Figure 2 NBI colonoscopy image with non-sequential system. **A**: Conventional view of an Is polyp, 12 mm in diameter located in the sigmoid colon; **B**: NBI view clearly showing the superficial meshed vascular pattern on the polyp's surface indicating an adenomatous polyp.

ARE YIELDS OF SMALL AND FLAT ADENOMAS HIGHER WITH NBI?

An interesting Japanese study involving 48 patients in which conventional white light colonoscopy was first performed followed later by blind NBI colonoscopy on the same patients found that the total number of neoplastic lesions detected by NBI was significantly higher than the total number of neoplastic lesions detected using conventional colonoscopy ($P = 0.02$). Based on macroscopic appearance, location and tumor

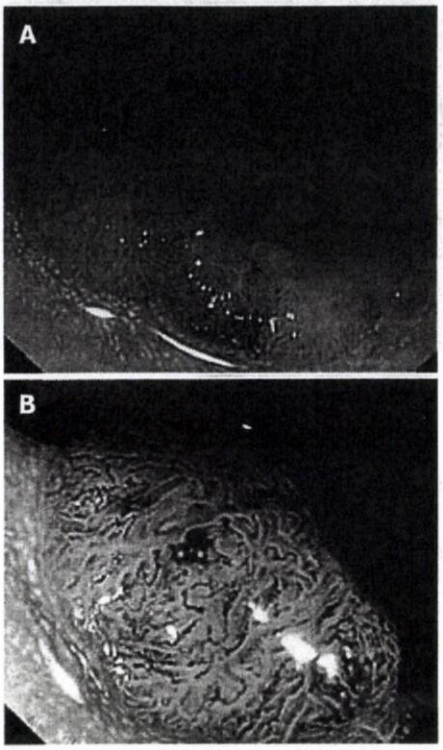

Figure 3 NBI colonoscopy image with sequential system. **A**: Conventional view of an II a polyp, 20 mm in diameter located in the rectum; **B**: Meshed capillary vessels are clearly seen using magnifying NBI as dark brown areas diagnosing an intramucosal cancer.

size, flat lesions < 5 mm located in the right colon in particular were more frequently diagnosed using NBI[12].

Although no Western study has as yet validated those Japanese results, a recent report indicated that adenomas were detected more frequently in the NBI group (23%) than in the control group (17%), but the difference was not statistically significant ($P = 0.129$)[13]. In contrast, it has also been recently reported that NBI did not result in better detection of ademomas. In that particular study, a colonoscopist with a known high detection rate using white light colonoscopy conducted patient examinations with high-definition colonoscopes using either white light or NBI[14].

The fact that differences still exist between Japan and Western countries demonstrates that prospective studies are needed to determine which of these early reports are valid.

NBI FOR NON-NEOPLASTIC AND NEOPLASTIC LESIONS

For lesions < 10 mm, it is generally accepted that hyperplastic polyps and other non-neoplastic colorectal lesions do not require endoscopic treatment because they are benign and have no malignant potential[15,16]. In contrast, adenomatous polyps should be removed to prevent progression of the adenoma-carcinoma sequence[17].

Magnified chromocolonoscopy (MCC) has been presented as the best means for *in vivo* selective management of colorectal polyps[18,19] and it is suggested that colorectal polyps should not be treated only on the basis of polyp size, but also with respect to the underlying histological characteristics observed during MCC[20]. The NBI system has been proposed for optical image-enhanced endoscopy because it features a simple one-touch button for changing from white light to NBI and does not require indigo carmine dye spraying.

An early study of an NBI prototype used for differentiating non-neoplastic from neoplastic lesions in 34 patients with 43 lesions reported better visualization of the mucosal vascular network and lesion compared to conventional endoscopy. Chromocolonoscopy and NBI both had a sensitivity of 100% and a specificity of 75%[6]. Thereafter, the effectiveness of conventional colonoscopy, chromoendoscopy and the NBI system in distinguishing between non-neoplastic and neoplastic colonic polyps was assessed in 78 patients with 110 lesions. No significant difference existed between the NBI system and chromoendoscopy, but the sensitivity, specificity and accuracy of conventional colonoscopy were significantly lower (82.9%, 80.0% and 81.8%, respectively) compared to both chromoendoscopy and the NBI system (95.7%, 87.5% and 92.7%, respectively)[21].

More recently, a classification of colorectal polyps based on the presence or absence of superficial meshed capillary vessels and their diameter, observed under NBI (CP type I - III) was proposed in Japan by Sano *et al*[22]. Although a promising and exciting alternative to differentiate the nature of colorectal polyps, Western prospective studies, however, are needed for its standardization worldwide.

NBI FOR INVASIVE AND NON-INVASIVE COLORECTAL CANCER

There is growing evidence to support the theory that lesions with submucosal (sm) invasion < 1000 μm (sm1) without lympho-vascular invasion or a poorly differentiated component do not involve lymph node metastases[23]. In Japan, analysis of the pit pattern types proposed by Kudo *et al*[24] has been proven effective in predicting the level of sm invasion. In practice, however, limitations have been reported using the V_I pit pattern to discriminate between mucosal (m), slight submucosal (sm1) and, deep submucosal (sm2) or deeper invasion[25]. The invasive pattern proposed by Fujii *et al*[26-28] (distorted and irregular crypts and a demarcated area) has also been reported to be effective in predicting sm2.

One promising area for NBI is in the accurate estimation of invasive depth for early colorectal cancers. Hirata *et al*[29] analyzed 148 colorectal lesions and recently reported a high degree of correspondence between pit pattern analysis by NBI and chromoendoscopy although the correspondence between MCC and NBI in evaluating the V_I pit pattern of 48 early carcinomas

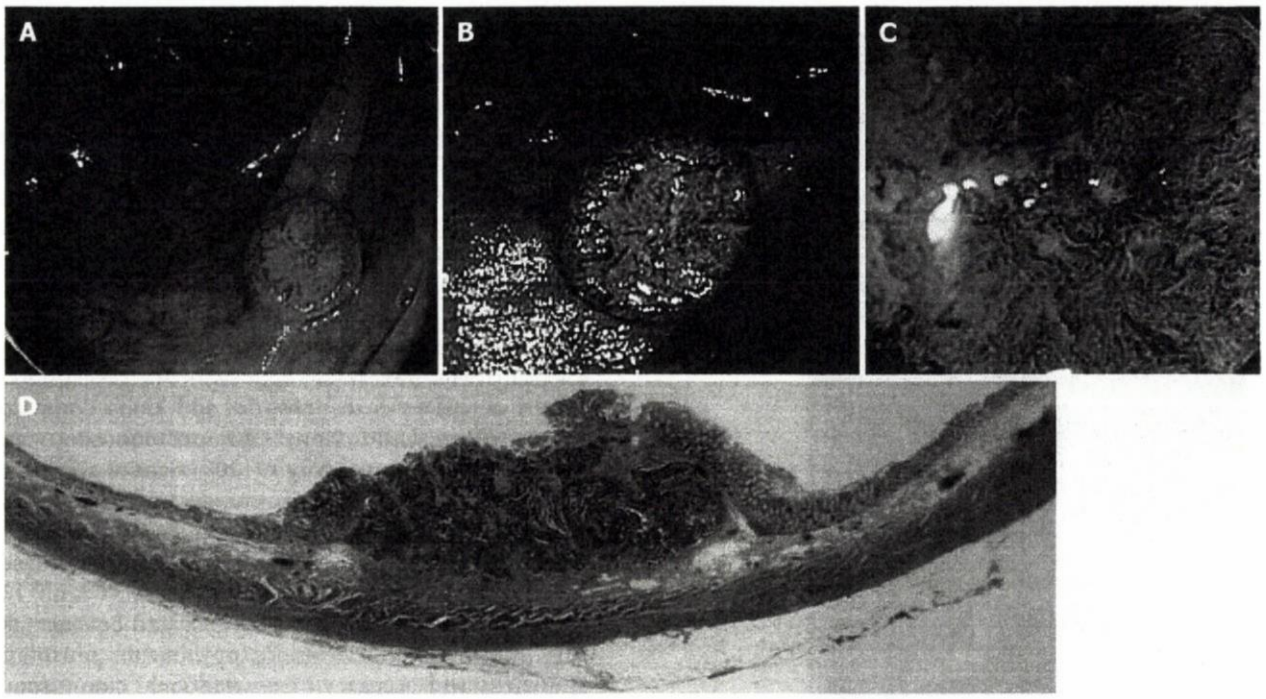

Figure 4 NBI image of colorectal cancer. **A**: Conventional view of an IIa + IIc lesion, 12 mm in size, located in the transverse colon; **B**: NBI view shows a well demarcated area and meshed capillary vessels clearly visible characterized by thick diameter, branching and curtail irregularity; **C**: Magnifying NBI view additionally shows the presence of a nearly avascular or loose microvascular area due to histological desmoplastic changes in the stromal tissue, suggesting deep submucosal invasion; **D**: Histopathological analysis revealed an adenocarcinoma invading deeply into the submucosa (2500 μm) with lymphovascular invasion.

was only 78%. Diagnosis using the type V pit pattern was possible by also evaluating various capillary features including vessel diameter, irregularity and the capillary network observed during NBI and not by relying solely on the pit pattern.

Two other promising studies on predicting the depth of invasion of early colorectal cancer by analyzing the microvascular architecture were published recently. Using NBI with magnification, Fukuzawa *et al*[30] observed several microvascular architecture characteristics in 61 early colorectal lesions (m-sm1: 37; sm2-3: 24). Univariate analysis showed that wide caliber, irregular caliber, tortuousity, irregularity, short length and non-dense arrangement were significantly more frequent in sm2-3 lesions compared to m-sm1 lesions ($P < 0.001$). Multivariate analysis, however, revealed that irregularity and non-dense arrangement were the remaining independent factors[30] (Figure 4). Horimatsu *et al*[31] analyzed the presence of "meshed brown capillary vessels" in 27 colorectal lesions (m-sm1: 12; sm2: 15) also using NBI colonoscopy with magnification. The overall diagnostic accuracy, sensitivity, and specificity of microvessel density and the lack of uniformity in microvessel diameters for distinguishing between sm1 and sm2 lesions was 82.4% (14/17), 93.3% (14/15) and 75.0% (9/12), respectively[31] (Figure 4).

DETECTION OF DYSPLASTIC AREAS IN ULCERATIVE COLITIS

Although patients with longstanding ulcerative colitis are at increased risk of developing colorectal cancer, endoscopic detection of early neoplasia is difficult because these lesions can be subtle and even macroscopically invisible at times. A laborious protocol has been proposed involving not only target biopsies from suspicious lesions, but also two to four random biopsies taken every 10 cm of the colon[32]. MCC has emerged as the best method currently available for identifying dysplastic lesions in an inflammatory bowel disease setting[33,34].

In terms of NBI research, the limitations of the first NBI prototype were recently shown in a prospective randomized crossover study of 42 patients with longstanding ulcerative colitis. In that study, the sensitivity of NBI for the detection of neoplasia was merely comparable to conventional colonoscopy although a larger number of suspicious lesions were found during NBI colonoscopy[35]. A more positive report on the effectiveness of a third generation NBI prototype plus magnification indicated that just as NBI reveals fine superficial blood vessels whose diameters and densities are increased in neoplastic lesions compared with normal mucosa, dysplastic lesions observed using NBI also have a darker capillary vascular pattern compared with normal mucosa[36].

WILL CONVENTIONAL CHROMOCOLONOSCOPY BE REPLACED BY NBI?

It is still too early to answer this question. In Japan,

chromocolonoscopy has demonstrated its effectiveness in the differentiation between adenomatous and hyperplastic polyps and is a promising method for distinguishing superficial from deep submucosal cancers, but it is regarded as an inconvenient and difficult procedure in Western countries[37]. Indigo carmine dye spraying is inexpensive and differs in practice from the NBI system in that it does not target superficial vascular patterns, but instead accentuates lesion contours and highlights the pit pattern of colonic crypts[25]. It is interesting to note that indigo carmine dye spraying is not recommended before an NBI examination because it might obscure blood vessel visualization.

In contrast, NBI even without magnification when using the non-sequential system provides accurate definition of vascular vessels throughout the entire colonic mucosa and more clearly defines the borders of a lesion without the necessity of using dye spraying. The recently developed NBI system requires an expensive new processor, however, so the cost-benefit issue requires further analysis[38]. In addition, the diagnostic accuracy of NBI is affected by the learning curve associated with this new methodology and extra time may be needed to perform the examination.

USELESS TECHNOLOGY IN UNQUALIFIED HANDS

The acquisition and use of NBI technology is increasing in many countries, but it should be emphasized that accurate analysis of the pit pattern types and familiarity with MCC are basic fundamentals necessary to become proficient in NBI diagnosis of colorectal lesions. Modern optical technology without proper image interpretation wastes valuable resources, can cause confusion for inadequately trained endoscopists and may result in the delay of inter-institutional validation studies. Training general endoscopists in the principles and applications of optical image-enhanced endoscopy as practiced in Japan (i.e., stereomicroscopy, conventional chromoendoscopy, magnifying endoscopy and pit pattern analysis)[20,24-26] in approved centers by qualified experts will be required to narrow and, hopefully, close the existing gap between the latest advancements in optical technology and their clinical usefulness.

CONCLUSION

Several studies have previously reported on the advantages and limitations of NBI optical image-enhanced colonoscopy in the diagnosis of colorectal diseases. One difficulty in evaluating the results, however, has been non-standardization of the NBI systems and prototypes used in the research. Despite this shortcoming, there seems to be considerable potential for further development by improving NBI technology in the non-sequential endoscopic video system by modifying the characteristics of the interference filters.

In practice, the latest technological advancements incorporated into third generation NBI prototypes appear to offer a clear advantage over conventional chromocolonoscopy. Additional validation studies are needed, however, to confirm the effectiveness of NBI for screening colonoscopy, identification of adenomatous polyps, determining depth of invasion of early colorectal cancers, evaluating free margins after endoscopic resection and detection of dysplastic lesion in an inflammatory bowel disease setting.

A number of other questions remain unsolved that deserve additional examinations including whether NBI is less time-consuming, its cost effectiveness, whether magnification is absolutely required and whether the NBI system should completely replace chromocolonoscopy. Further studies assessing these issues are ongoing at various medical centers worldwide.

At the present time, NBI constitutes an effective and reliable alternative to chromocolonoscopy for *in vivo* visualization of vascular structures. Due to widespread incorporation of NBI technology outside Japan, however, there is an increasing need to train general endoscopists in the basic principles and applications of advanced optical image-enhanced endoscopy.

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COMPUTER TOMOGRAPHY

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CT colonography: computer-aided detection of morphologically flat T1 colonic carcinoma

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Abstract The purpose was to evaluate the ability of computer-aided detection (CAD) software to detect morphologically flat early colonic carcinoma using CT colonography (CTC). Twenty-four stage T1 colonic carcinomas endoscopically classified as flat (width over twice height) were accrued from patients undergoing staging CTC. Tumor location was annotated by three experienced radiologists in consensus aided by the endosocpic report. CAD software was then applied at three settings of sphericity (0, 0.75, and 1). Computer prompts were categorized as either true positive (overlapping tumour boundary) or false positive. True positives were subclassified as focal or non focal. The 24 cancers were endoscopically classified as type IIa (n=11) and type IIa+IIc (n=13). Mean size (range) was 27 mm (7–70 mm). CAD detected 20 (83.3%), 17 (70.8%), and 13 (54.1%) of the 24 cancers at filter settings of 0, 0.75, and 1, respectively with 3, 4, and 8 missed cancers of type IIa, respectively. The mean total number of false-positive CAD marks per patient at each filter setting was 36.5, 21.1, and 9.5, respectively, excluding polyps. At all settings, >96.1% of CAD true positives were classified as focal. CAD may be effective for the detection of morphologically flat cancer, although minimally raised laterally spreading tumors remain problematic.

Keywords Colonography · Computed tomographic · Diagnosis · Computer-assisted · Colonic neoplasms

Introduction

CT colonography (CTC) is increasingly utilized as a relatively non-invasive method of colonic investigation in both patients with symptoms suggesting possible colorectal neoplasia and asymptomatic individuals undergoing colorectal cancer screening [1]. Meta-analysis data suggest the procedure is robust for detection of "clinically significant" neoplasia, including larger adenomatous polyps and established cancer [2, 3]. However, one area of concern is the ability of CTC to reliably detect morphologically flat lesions [4]. The histopathological definition of a flat lesion is one where the height is less than twice the thickness of the surrounding mucosa [5], although a more practical definition used by both endoscopists and radiologists is a lesion whose width is over twice its height [5]. Flat lesions may be slightly elevated above the mucosa, flush with the mucosa, or even depressed below the surrounding mucosal

surface, and are manifest on CTC as subtle areas of mural thickening [6–9]. Although there are some data suggesting CTC may depict these lesions [10], it is apparent that many are missed prospectively [6, 11, 12]. The clinical importance of flat lesions is debated, with some evidence they are no more significant than their polypoidal counterparts of similar size [13]. Undoubtedly a proportion of flat lesions are malignant [14], and failure to diagnose such lesions at CTC will often deny the patient potentially curative treatment.

Computer-aided detection (CAD) software systems are proving increasingly robust in detecting colonic neoplasia [15–17]. Because most CTC errors are perceptual [18–20], it seems likely CAD will play an increasingly important role in interpretation. The high clinical importance, but radiological subtlety of morphologically flat early colonic cancer make it an ideal target for CAD systems, but at the time of writing there is little if any literature on detection characteristics for such lesions. The purpose of our study was to evaluate the ability of computer-aided detection (CAD) software to detect morphologically flat early colonic carcinoma using CT colonography (CTC).

Materials and methods

Local ethical committee approval was obtained, and patients gave informed consent for the study.

Patient source

Patients were recruited from a single tertiary referral center. Patients with a known histological diagnosis of colorectal cancer (based on prior endoscopic biopsy) were referred to the center for treatment. As part of the pre-treatment workup, all patients were re-colonoscoped (to confirm the site of the tumour and to assess potential endoscopic respectability) by one of three experienced colonoscopists. Colonoscopy was immediately followed by same-day contrast-enhanced CT colonography (see below) for staging using the same bowel preparation (3 l of polyethylene glycol). Careful note of the endoscopic morphology of all diagnosed cancers was recorded by the colonoscopist using standard criteria (type 0 to 5) [5], together with the segmental location of the lesion. Maximal dimension was also documented (by assessment against adjacent open biopsy forceps). Those lesions classified by the endoscopist as superficial, i.e., depth of penetration no greater than the submucosa-type 0, were sub-classified as either polypoidal, i.e., protruding above the surrounding mucosa (type 0-I) or flat ("non-polypoidal")-i.e., slightly elevated (height less then twice width; type 0-II). Type 0-II tumors were then further sub-classified as type 0-IIa (minimally elevated), type 0-IIb (completely flat), or type 0-IIc (depressed) (Fig. 1). Lesions showing a mix of these features were classified as such [5], depending on the predominant component (Fig. 1). Type II-a and type II-b lesions were classified as "laterally spreading" if their estimated maximal dimension was greater than 20 mm [21–23]. As per usual clinical practice at the referral center, not all synchronous polyps were removed by the colonoscopist, especially if less than 6 mm in size. For the purpose of the study, the colonoscopist recorded the presence (maximum diameter and segmental location) of any unremoved synchronous colonic polyps.

Colonic distension prior to same day CTC was achieved using automated carbon-dioxide insufflation (Protocol, EZEM, NY) and performed on a 64-detector–row CT scanner (Aquilion, Toshiba Medical Systems) according to the following protocol: 120 kV, 200–400 mA with automatic exposure control, 64 rows × 0.5 mm collimation, helical pitch 53.0 (effective dose 18 mSv). The supine scan acquisition was acquired 50 s following intravenous contrast administration [150 ml of iohexol 350 (Omnipaque, Daiichi-Sankyo Pharmaceutical)]. There were at least 3 weeks (range 3 to 6 weeks) between the original biopsy of the lesion and CTC.

Patient selection

Between October 2005 and May 2006, a total of 165 patients were referred to the center and underwent same-day colonoscopy and CTC. The endoscopic report of all patients was reviewed by the study coordinator who retrieved the records of all patients in whom the endoscopic classification of the tumour was grade 0-II (i.e., superficial or flat morphology). Those lesions in which the ultimate

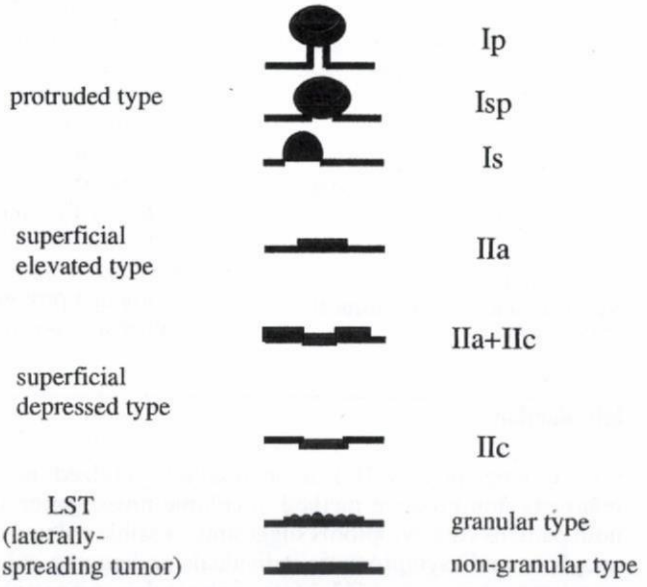

Fig. 1 Schematic representation of the various morphologies of superficial colorectal neoplasia

histopathological diagnosis was greater than T1 were excluded.

Dataset annotation

The CTC datasets of all patients with endoscopically flat T1 cancers were loaded onto a workstation equipped with CTC viewing software (Vitrea 3.9.01, Vital Images Minnetonka, MN) and reviewed in consensus by three radiologists experienced in CTC interpretation (over 200, 400, and 800 endoscopically validated cases, respectively), fully aware of the colonoscopic report. The radiologists located the cancer (and any unremoved polyps) and recorded the 2D axial image numbers for both supine and prone datasets (if applicable). Observers used segmental location (within one colonic segment of colonoscopy) and size (within 50%) to aid matching. Any uncertainty was resolved by face-to-face discussion between the observers.

A digital screen shot image of the tumour and any polyps was also taken to facilitate subsequent identification during CAD application (see below). Although the workstation used for initial dataset annotation had a CAD facility, this was not used by the radiologists so as not to bias the consensus-derived location of the cancer by prior knowledge of the position of any CAD prompts.

CAD application

After the ground truth dataset annotation was complete, one of the radiologists applied the CAD software (ColonCAD API 4.0, Medicsight plc) integrated into the Vitrea workstation to the datasets as described below.

Functionality and development of the commercially available CAD system used for the study have been described elsewhere [24, 25]. In brief, the software segments the colon from the CT dataset before applying a mathematical algorithm with the aim of detecting raised endoluminal objects, all of which are regarded as potential neoplasia. A sphericity filter is then applied that aims to facilitate discrimination between real polyps and false-positive prompts, due to haustral folds, for example, by analyzing every voxel on the candidate surface to determine whether or not it and its neighbors form part of the surface of a theoretical sphere. Detections whose sphericity is above a pre-determined threshold are prompted visually to the observer via small red dots superimposed over the region of interest on both 2D axial and 3D endoluminal views (Fig. 2) or by a yellow triangle when the polyp candidate is hidden behind a fold during 3D endoluminal analysis (Fig. 3). With the sphericity enhancement filter set at 1.0, only those voxels that potentially formed part of a perfect sphere were retained as prompts, and the others were dismissed as likely false positives. As the filter value reduces towards zero, voxels that may form part of an increasingly less perfect sphere are retained as prompts.

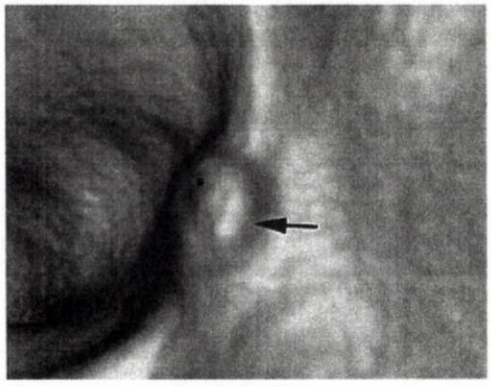

Fig. 2 3D endoluminal CT colonographic image demonstrating a CAD mark (red dot) on an 11-mm transverse colonic T1 cancer (arrow)

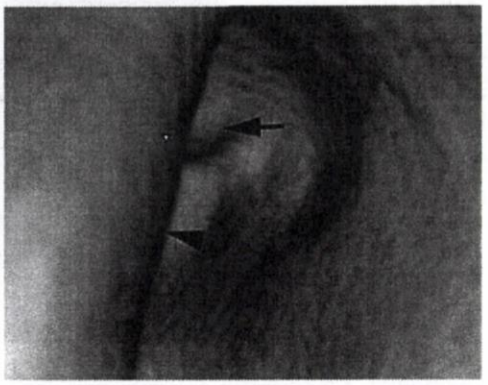

Fig. 3 3D endoluminal CT colonographic image demonstrating the same lesion (arrow) as Fig. 2 barely visible behind a haustral fold (arrowhead). CAD alerts the reader to the hidden lesion via a yellow triangle

In the CAD workstation iteration used for the present study, the user could influence the sphericity threshold for prompted polyps via slider bars with a scale between 0 (most sensitive) and 1 (least sensitive). The recommended default sphericity setting for the software was 0.75 [26].

No data from the origin of datasets used for the present study had been used to develop the CAD algorithm previously.

The observer applied the CAD at each of three sphericity settings (0, 0.75, and 1). At each setting the observer recorded whether the CAD has successfully detected the flat cancer present in each dataset [supine and prone (if

Fig. 4 Schematic representation of a focal (**a**) and non-focal (**b**) correct CAD mark (red circle). Black shape represents the tumor

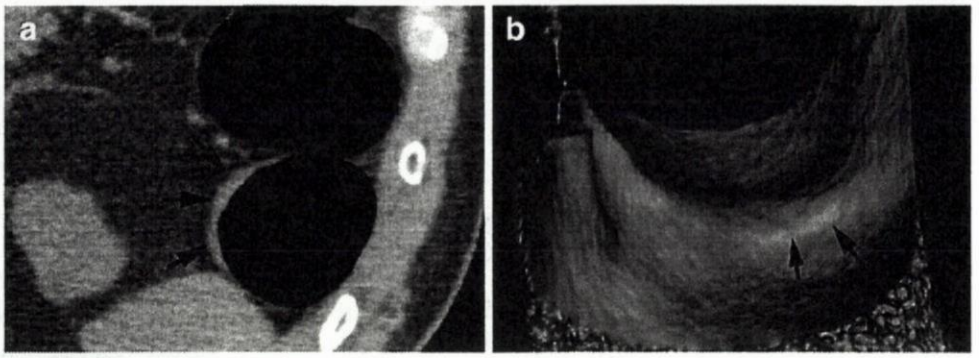

Fig. 5 **a** 2D axial CT colonographic image (a) shows a type 0-IIa cancer (arrows) as an area of subtle mural thickening. The lesion was not detected by CAD. **b** 3D endoluminal CT colonographic image showing the same lesion as 5A. The lesion (arrows) is barely visible

visible on both)]. A successful detection was defined when at least one CAD mark directly overlapped any part of the tumor outline previously determined when the ground truth was established. CAD was deemed to have successfully classified the patient if there was at least one correct CAD detection of cancer on either the supine or prone datasets, or on both. The observer further sub-classified each correct CAD detection as "focal" or "non focal" (Fig. 4). A focal detection was ascribed when the CAD mark was located over a recognizable focal tumor elevation or protuberance beyond the contour of the main lesion. A non-focal detection was defined as a CAD mark correctly located over the cancer, but overlying no recognizable focal elevation or protuberance beyond the contour of the main lesion. All other CAD detections (including "true" polyp detections for the purpose of this study) were considered false positives. The observer classified all the CAD false positive detections at each filter setting as follows: 1-bulbous fold (prominent fold in otherwise well-distend segment), 2-segmental under distension, 3-fecal residue/residual fluid, 4-normal colonic anatomy, e.g., ileocaecal valve, redundant mucosa, internal hemorrhoid, normal fold, 5-extracolonic, 6-benign polyp, and 7-unexplained.

Statistical analysis

Data were collated and descriptive statistics (notably sensitivity) were calculated for the CAD at each of the three sphericity settings used. Categorical differences in detection according to tumor morphology sub-classification were analyzed using Fischer's exact test.

Results

The final study cohort consisted of 24 patients (6 females, mean age 66 years, range 41 to 80 years). The final endoscopic classification of the 24 tumors was 0-IIa (n=11) and IIa+IIc (n=13). All 0-IIa tumors measured over 20 mm and were thus classified as lateral spreading.

Four tumors were located in the rectum, six in the sigmoid, four in the descending, six the transverse, three in the ascending colon, and one in the cecum. The mean size was 25 mm (range 7 to 60 mm). Of the 24 tumors, 3 were visible on the supine dataset only, 1 on the prone dataset only, and 20 on both supine and prone datasets.

CAD detection

Sensitivity for tumor detection increased as sphericity threshold decreased (from 54.1% at a sphericity of 1 to 83.3% at a sphericity of 0). Sensitivity for type IIa tumors was in general less than for type IIa+IIc, notably at a sphericity setting of 0 (p=0.03) (Fig. 5; Tables 1 and 2).

Each tumour detected by CAD had on average more than two correct CAD marks per scan position (other than at

Table 1 CAD detection of tumors according to scan position and sphericity setting

Tumor classification	Sphericity 0				Sphericity 0.75				Sphericity 1			
	Detection (%)*	Detected			Detection (%)*	Detected			Detection (%)*	Detected		
		Supine only	Prone only	Supine and prone		Supine only	Prone only	Supine and prone		Supine only	Prone only	Supine and prone
0-IIa (n=11)	8 (72.7)	2	2	4	7 (63.6)	3	1	3	3 (27.3)	0	0	3
0-IIa+IIc (n=13)	12 (92.3)	3	3	6	10 (76.9)	4	1	5	10 (76.9)	4	2	4
Total (n=24)	20 (83.3)	5	5	10	17 (70.8)	7	2	8	13 (54.1)	4	2	7

*Per patient

Table 2 Mean number and type of CAD detections per cancer according to sphericity

Mean true-positive CAD detections per cancer						
	Sphericity 0		Sphericity 0.75		Sphericity 1	
	N=20 cancers detected		N=17 cancers detected		N=13 cancers detected	
	Supine	Prone	Supine	Prone	Supine	Prone
Focal (%)	2.14 (97.7)	2.32 (96.2)	2.37 (97.9)	2.26 (97.8)	2.13 (100)	1.57 (100)
Non-focal (%)	0.05 (2.3)	0.09 (3.7)	0.05 (2.1)	0.05 (2.2)	0.0	0.0
Total	2.19	2.41	2.42	2.31	2.13	1.57

sphericity of 1 in the prone orientation) (Table 2; Fig. 6). The overwhelming majority of correct CAD detections were classified as focal (at least 96.2%), with a very small minority being non focal (Table 2; Fig. 7).

False positives

False positives decreased with increasing sphericity. On average there were 19.3 (range 1–46), 11.6 (range 1 to 38), and 5.9 (range 0 to 21) false positives at sphericity settings of 0.75, and 1, respectively, for supine data. On average there were 21.3 (range 1 to 58), 12.9 (range 0 to 39), and 6.4 (range 0 to 15) false positives at sphericity settings of 0, 75, and 100, respectively, for prone data. The majority of false positives were related to normal colonic anatomy, although an increasing proportion (over 20% at sphericty setting of 0) were due to correct detections of small benign polyps. Excluding polyp detections, the mean number of CAD false positives was per patient was 36.5, 21.1, and 9.5 at sphericity settings of 0, 0.75, and 1, respectively (Table 3).

Discussion

It is widely accepted that the majority of colorectal cancers arise from benign polypoidal precursors [27]. However, there is an increasing recognition that non-polypoidal (i.e., "flat") adenomas also may progress to invasive cancer. Although originally believed to be particularly prevalent in Japanese patients, it is now clear that flat adenomas are found throughout the world. For example, a recent study found flat or depressed colorectal neoplasia in 22.7% of North Americans [28], with similar data from Europe [29]. Although the overall incidence of invasive carcinoma in non-polypoidal lesions is in the order of 2% [14, 28], recent reports suggest up to 20% of early cancers (the prime target for any screening test) may have this morphology [14]. Furthermore, non-polypoidal flat cancers are smaller than polypoidal tumours of the same stage. Given this, strategies to increase detection of non-polypoidal neoplasia, such as use of dye spray, are increasingly adopted in endoscopic screening programs. The ability of CTC to detect such lesions will undoubtedly be subject to increasing scrutiny.

The CTC appearance of non-polypoidal colorectal neoplasia (shallow plaque-like areas of mural thickening) is well described [6, 9]. Anecdotally, although flat lesions are generally believed "invisible" at CTC, the small amount of available literature concerning their depiction is more encouraging. Using a dataset containing 22 non-polypoidal lesions and 3 readers, Fidler et al. reported a prospective sensitivity of between just 15% and 65% [6]. However, double reading resulted in 100% flat adenoma detection, and 19 of the 22 lesions were visible at least in retrospect. A recent report by the ESGAR CTC study group investigators found that most of the large polyps missed by expert observers were non polypoidal, emphasizing that their detection is difficult [12]. However, almost all lesions were visible in retrospect and most were detected by at least one reader. Moreover, in the present study all 24 tumors

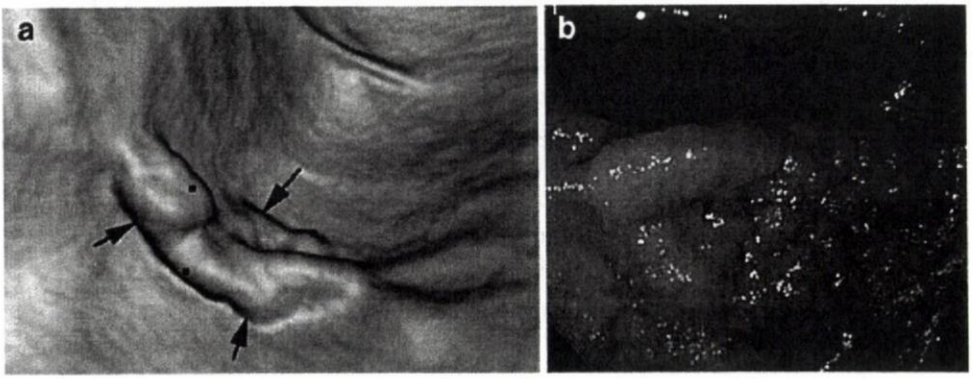

Fig. 6 **a** 3D endolumonal images show a transverse colon type 0-IIa cancer with three correct CAD marks (red dots). **b** Colonoscopic image of the lesion in Fig. 6a

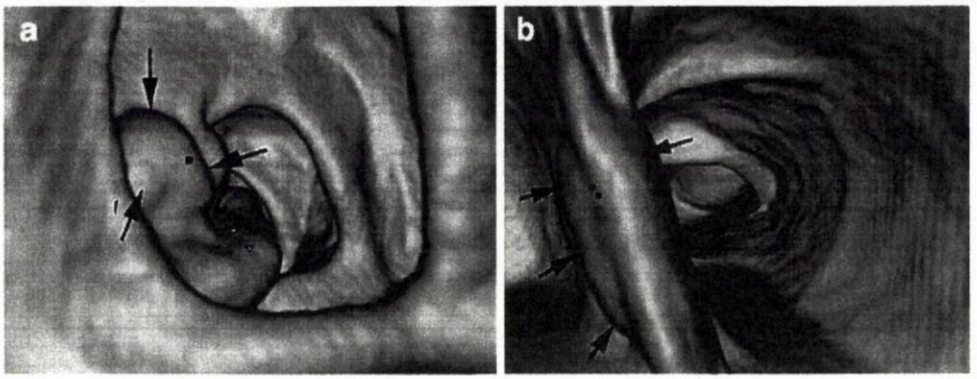

Fig. 7 **a** 3D endoluminal CT colonographic image showing a CAD-detected type 0-IIa+IIc T1 ascending colonic carcinoma (arrows). The CAD detection (red dot) was classified as "focal" as located on a recognizable focal elevation. Yellow triangles represent further correct CAD marks on the hidden side of the lesion. **b** 3D endoluminal CT colonographic image shows a CAD-detected type IIa transverse colonic carcinoma (arrows). The two correct CAD marks were classified as non focal

were identifiable in retrospect by 3 unblinded experienced radiologists. Although in his series, Pickhardt et al. prospectively achieved high sensitivity for "flat colorectal lesions" [10], most data to date suggests non-polypoidal neoplasia, while visible on CTC, is often missed prospectively because of perceptual error [6, 9, 11].

Computer-aided detection software has proved successful in scenarios where radiologist must pick up subtle abnormalities that appear infrequently, notably in screening mammography. Non-polypoidal neoplasia is therefore potentially an ideal target for colon CAD software. Our study used a single vendor CAD system, developed ostensibly for detection of raised polyps [25]. Importantly, the present study employed an external validation paradigm [30]-no datasets from the hospital donating the cancers had been used previously to develop the CAD software. We specifically selected early cancers rather than non-malignant flat lesions since the former have unquestionable clinical significance, and it is important they are detected by CTC.

Overall CAD sensitivity was clinically acceptable with 71% detection at the manufacturer's currently recommended default operating point for the CAD, rising to 83% at a sphericity setting of 0. As would be expected, although sensitivity increased as sphercity was reduced, this occurred at the expense of increased false-positive detections (i.e., decreased specificity). Most false-positive detections were due to normal colonic anatomy, and previous work has suggested such prompts are easily dismissed by most experienced radiologists [24]. Although fewer CAD false positives are desirable, it is still unclear at what threshold the benefit of CAD diminishes significantly. It could be argued, for example, that a CAD generating 25 prompts, one of which correctly identifies a subtle flat cancer originally missed by a radiologist, is more useful than an algorithm with fewer false positives, but that fails to detect the cancer. Indeed, recent data suggest that current CAD systems may be relatively poor at detecting cancer as opposed to polyps [16]. In the case of flat cancers, improved detection algorithms may inevitably engender decreased specificity.

Table 3 Grading and distribution of CAD false positives (n=24 datasets) according the sphericity setting (supine and prone datasets combined)

Cause of CAD FP (grade)	Sphericity 0 (%)	Sphericity 0.75 (%)	Sphericity 1 (%)
Bulbous fold*	22 (2.3)	6 (1.0)	1 (0.3)
Segmental under distension	27 (2.8)	47 (8.1)	26 (9.1)
Fecal residue/residual fluid	85 (8.9)	23 (4.0)	15 (5.2)
Normal colonic anatomy**	658 (69.1)	386 (67.8)	162 (56.4)
Extracolonic	83 (8.7)	43 (7.4)	24 (8.4)
Non-malignant polyp	75 (7.8)	72 (12.5)	59 (20.6)
Unexplained	2 (0.2)	1 (0.17)	0 (0)
Total	952	578	287

*Bulbous fold (prominent fold in otherwise well-distended segment)
**E.g., ileocaecal valve, redundant mucosa, internal hemorrhoid, normal fold

Interestingly, the vast majority of CAD detections were related to a "focal" protuberance on the cancer. Also, detection of the lateral spreading type 0-IIa lesions (minimally raised) was overall inferior to type 0-IIa+IIc lesions, possibly because the CAD detects a focal "protuberance" at the junction of the main lesion and the central depression. Colon CAD systems rely on differences in geometric shape between raised colonic polyps and surrounding colonic wall and haustral folds. As recently reviewed by Yoshida and Dachman [31], various computational models have been proposed to take advantage of the shape difference, including sphere fitting [32], volumetric shape index [33], surface curvature with rule-based filter [34], surface normal overlap [35], and more recently Haussian matrix [36]. False-positive detections, for example, due to haustral folds, then are often reduced by various techniques, including gradient concentration [17] or application of a edge displacement field [37]. Recent publications have confirmed the increasingly robust detection characteristics of colon CAD systems for detecting polypoidal neoplasia [15], but it remains unclear whether such systems will reliably detect non-polypoidal malignancy. While some workers have successfully proposed algorithms based on fuzzy merging and wall thickness analysis to detect colonic masses (i.e., large cancers) [38], again the ability of such systems to detect subtle raised lesion remains unknown. It is reassuring, however, that even endoscopically confirmed non-polypoidal lesions often possess focal raised areas that may be targeted successfully by CAD. Indeed, on average the CAD in the current study placed at least two marks on each cancer detected. It is clear, however, that some "smooth" type 0-IIa lateral spreading tumors will prove difficult to detect reliably and will likely need new algorithms, possibly based on mural thickening.

Our study does have limitations. Although we included all non-polypoidal T1 tumors in our inclusion criteria, only two endoscopic sub-classification types were available (0-IIa and 0-IIa+IIc). However, it is not surprising we did not have any type II-b lesions in our cohort since such morphology is exceedingly rare [14]. The endoscopists in the present study defined a non-polypoidal lesion as one where the height is less than half the width. Others have defined such lesions as having a height less than 2.5 mm (the width of closed biopsy forceps). However, the definition we used is adopted by the working group created specifically to consider the definitions of flat neoplasia in Western endoscopic practice [5, 39]. We used a single CAD algorithm and, as discussed above, it is uncertain whether similar results would be obtained using different vendors. Finally, we did not incorporate a radiologist observer into our analysis, choosing to determine the "stand-alone" performance of the software, as have many others. The stand-alone detection characteristics of CAD for flat cancers have not been determined previously, and, based on our data, studies incorporating human readers are now appropriate.

In conclusion, the CAD system tested is relatively effective for detection of morphological non-polypoidal cancer, although some minimally raised lateral spreading tumors remain problematic.

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Medicsight plc, London, supplied the CAD software for this study.

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$P = 0.6$), respectively. There was no statistically significant difference between the groups ($P = 1.0$). A Wilcoxon signed-rank test was used for within-group analysis, and a Wilcoxon rank-sum test was used for between-group analysis. One patient who underwent direct injection had returned to the baseline pain level at week 1, and one patient who underwent indirect injection had a 2-point worsening of pain level at week 1. The difficulties in accurately assessing the pain levels and pain medication usage over the long term (due to death from underlying pancreatic cancer, withdrawal from the postprocedure telephone questionnaire protocol due to patient transfer to hospice, patient loss to follow-up, etc.) led to an early closure of the study.

Although limited, the data presented above represent the first prospective, randomized trial of intraneuronal *versus* perineuronal injection of the celiac ganglia. This study adds weight to the concept that the celiac plexus can be quickly and reliably identified via EUS, and that direct injection of agents into the celiac ganglion is safe, easy to perform, and well tolerated by patients. Larger prospective trials with long-term follow-up, both in pancreatic cancer and chronic pancreatitis, are needed to further evaluate this concept.

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Cautionary Note on Using Rectosigmoid Biopsies to Diagnose Graft-Versus-Host Disease: Necessity of Ruling Out Cytomegalovirus Colitis

TO THE EDITOR: Ross *et al.* reported that the rectosigmoid is the best site for diagnosing gastrointestinal (GI) graft-versus-host disease (GVHD) (1) using endoscopic biopsies. While we completely agree with the authors' conclusions, we would like to comment about the necessity of conducting a total colonoscopic examination in order to rule out cytomegalovirus (CMV) colitis.

CMV disease is a serious complication after allogeneic hematopoietic stem cell transplantation as well as GVHD (2). Most reports have indicated that the right colon and ileocecum are the most common sites of CMV colitis (3), but others have reported diffuse colorectal involvement (4) with only a few reports concerning CMV colitis limited to the rectosigmoid colon. It is our opinion that most cases of CMV colitis would have been missed if only the rectosigmoid colon had been examined and biopsies taken from that single location.

Patients with GVHD carry a high risk of CMV disease and most patients with CMV colitis overlap GVHD (5). If a patient with both GI GVHD and CMV colitis were diagnosed as having only GVHD, the patient would be exposed to a contraindicative steroid therapy that would probably worsen the CMV disease. CMV antigenemia, of course, could compensate for the diagnostic limitation of a rectosigmoid biopsy; however, the clinical significance of CMV antigenemia remains unclear in diagnosing GI CMV disease (5). In order to definitely rule out CMV colitis, it would be necessary to endoscopically examine the entire colorectum including the terminal ileum in diagnosing GI GVHD even if biopsy was limited to the rectosigmoid.

Since there was no mention in the Ross article (1) as to whether or not total colonoscopic examinations were performed, we would appreciate the authors commenting on this subject.

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Bleeding Colonic Ulcers Due to Invasive Mold Infection

TO THE EDITOR: A 65-yr-old nondiabetic man was admitted with fever and mental status changes. He was diagnosed with high-grade methicillin-sensitive *Staphylococcus aureus* bacteremia complicated by mitral valve endocarditis and septic arthritis involving multiple joints. His past medical history was significant for bilateral total knee arthroplasties and coronary artery disease. He was treated with oxacillin therapy. He underwent multiple joint washouts for septic arthritis. On day 15, he underwent a porcine mitral valve replacement with one-vessel coronary artery bypass grafting. He was recovering uneventfully until day 19 when he developed hematochezia. Colonoscopy revealed blood clots and multiple large discrete ulcers in the cecum and ascending colon (Fig. 1). No endoscopic intervention was performed due to absence of active bleeding. Esophagogastroduodenoscopy (EGD) revealed a diminutive distal esophageal superficial ulcer related to nasogastric tube trauma. He received 6 units of packed red blood cells over the following 48 h. A repeat EGD and colonoscopy revealed identical findings. On day 22, he underwent a right hemi-colectomy with ileostomy for refractory lower gastrointestinal (GI) bleeding. Pathology revealed numerous ischemic ulcers in the cecum, ascending and transverse colon (Fig. 2). Histology demonstrated abundant nonseptated fungal hyphae with 90° branching consistent with mucor. Some septated hyphae were present and a second fungus such as *Aspergillus* spp. could not be ruled out (Fig. 3). While immunohistochemistry using an aspergillus antibody was negative, serum Galactomannan level was elevated at 1.0 (normal <0.5). Foci in the bowel showed transmural destruction of the bowel wall with dense fibrosis suggesting a chronic ischemic event (Fig. 4). Fungal cultures were not obtained from the pathology specimen. Fungal blood cultures were negative. He was not receiving corticosteroids and was not neutropenic. The invasive mold infection prompted an extensive search for an underlying malignancy or immunocompromised state. Flow cytometry, peripheral blood smear, histopathology of the surgical specimen, prostate surface antigen, HIV, quantative immunoglobin levels and computed tomography scans of head, chest, abdomen and pelvis were all unremarkable. He was treated with intravenous caspofungin and lipid formulation of amphotericin B for several weeks

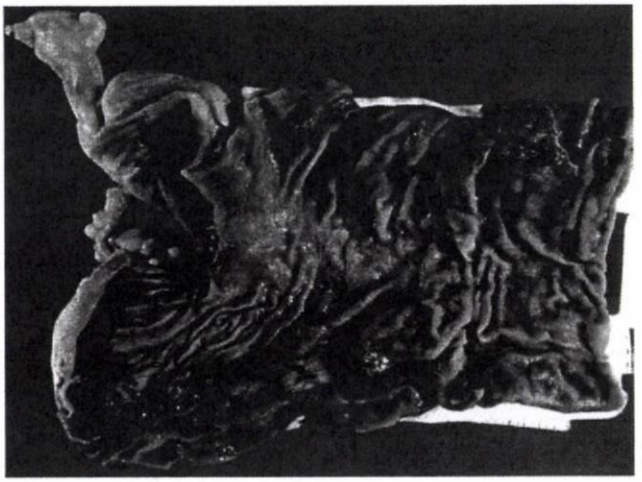

Figure 2. Surgical colonic specimen showing discrete ulcers (arrows).

Figure 1. Colonoscopic image of cecum showing ulcers.

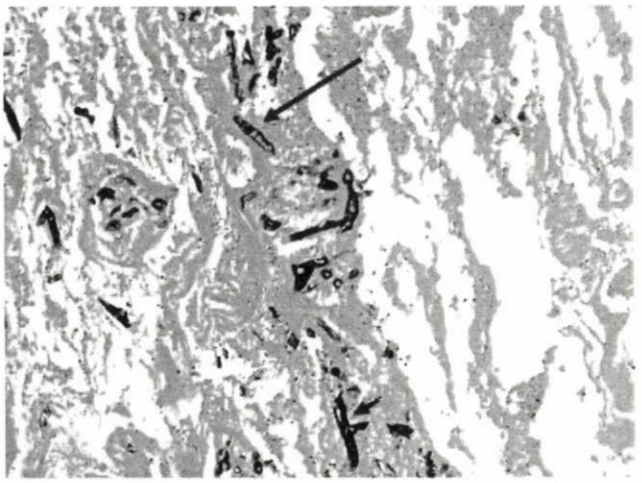

Figure 3. Septated hyphae (long arrow) and nonseptated hyphae with 90 degree branching (short arrow) identified in the surgical colonic specimen.

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ORIGINAL ARTICLE

Local recurrence after endoscopic resection of colorectal tumors

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Abstract
Background and aims Local recurrence frequently occurs after endoscopic resection of large colorectal tumors. However, appropriate intervals for surveillance colonoscopy to assess local recurrence after endoscopic resection have not been clarified. The aim of the present study was to determine local recurrence rates following en-bloc and piecemeal endoscopic resection and establish appropriate surveillance colonoscopy intervals based on retrospective analysis of local recurrences.
Materials and methods A total of 461 patients with 572≥ 10-mm lesions underwent endoscopic resection and follow-up. We retrospectively compared local recurrence rates on lesion size, macroscopic type, and histological type after en-bloc resection (440 lesions) and piecemeal resection (132 lesions). Cumulative local recurrence rates were analyzed using the Kaplan–Meier method.
Results Local recurrence occurred for 34 lesions (5.9%). Local recurrence rates for the en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132), respectively ($P<$ 0.001). The difference between the two groups was distinct in terms of lesion size, macroscopic type, and histological type. Of the 34 local recurrences, 32 were treated endoscopically and two cases required additional surgery. The 6-, 12-, and 24-month cumulative local recurrence rate of the en-bloc group was 0.24%, 0.49%, and 0.81%. Then the 6-, 12-, and 24-month cumulative local recurrence rate for the piecemeal group was 18.4%, 23.1%, and 30.7%.
Conclusion Local recurrence occurred more frequently after piecemeal resection than en-bloc resection. However, almost all cases of local recurrences could be cured by additional endoscopic resection, so piecemeal resection can be acceptable treatment.

Keywords Colorectal tumors · Colonoscopy · Neoplasm recurrence · Follow-up studies

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Introduction

Endoscopic resection is used to treat early colorectal tumors around the world. However, the high frequency of local recurrence after piecemeal resection for large colorectal tumors is a serious problem [1–6]. Based on national polyp study [7], the appropriate interval for surveillance colonoscopy after endoscopic resection of adenomatous polyps is 3 years. However, the appropriate intervals after incomplete endoscopic resection has not yet been clarified. In the present study, we retrospectively analyzed the local recurrence frequency after en-bloc and piecemeal endoscopic resection for colorectal neoplasms ≥10 mm in size in large number of follow-up cases. We also analyzed clinicopathologic features and treatment of local recurrences. Our goal was to establish appropriate surveillance colonoscopy programs after endoscopic resection for colorectal tumors based on our retrospective analysis of local recurrence.

Table 1 The clinicopathologic characteristics

	En-bloc (n=440)	Piecemeal (n=132)
Follow-up (months)	22 (1–57)	18 (1–54)
Size (mean, mm)	13.9 (10–40)	23.3 (10–45)
Location (Rb/Ra/Rs/S/D/T/A/C)	23/23/32/140/39/73/81/29	12/4/8/20/6/25/29/28
Macroscopic type		
Protruding	324	26
Flat elevated	114	100
Depressed	2	6
Pathological type		
Adenoma	181	35
M-ca	253	88
SM-ca	5	8
Unevaluated	1	1

Rb lower rectum, *Ra* upper rectum, *Rs*: rect-sigmoid colon, *S* sigmoid colon, *D* descending colon, *T* transverse colon, *A* ascending colon, *C* cecum, *M-ca* intramucosal carcinoma, *SM-ca* submucosal invasive carcinoma

Materials and methods

A total of 461 patients (311 men, 150 women), with 572≥10-mm lesions underwent endoscopic resection and were followed up endoscopically between January 1998 and March 2002 at the National Cancer Center Hospital (Tokyo, Japan). Patients that required additional surgical treatment immediately after endoscopic resection and in whom follow-up colonoscopy could not be performed were excluded from the study. Clinical and pathological records were retrospectively analyzed. The mean patient age was 63.8 years (range 19–89). Of 572 lesions, 440 (76.9%) were removed en-bloc and 132 (23.1%) were removed by piecemeal. The clinicopathologic characteristics of the en-bloc and piecemeal groups are shown in Table 1. There was no difference in the follow-up period for the groups. For the piecemeal group, the mean size of the lesion was 23.3 mm. For the en-bloc group, the mean size of the lesion was 13.9 mm. The rates of rectal lesions were about 20% in both groups. In the piecemeal group, the dominant macroscopic type was flat-elevated. In the en-bloc group, the dominant macroscopic was protruded. We compared the local recurrence rates in the two groups by lesion size, macroscopic type, and histological type. Furthermore, we analyzed the clinicopathologic features and treatments of cases with local recurrence. All patients provided informed consent prior to endoscopic resection.

Endoscopic technique

Good bowel preparation is essential for detection and detailed observation of lesions. We used 2 L of polyethylene glycol electrocyte solution on the day of examination. We used conventional or magnifying video colonoscopies (CF200I, CF-Q240I, CF-200Z, CF-Q240ZI, PCF-230, PCF-Q240ZI; Olympus Optical, Tokyo, Japan). Scopolamine butyl bromide was administered intravenously unless contraindicated. The initial dose was 10 mg and was increased as required. If necessary, the conscious sedation was maintained with intravenous boluses of midazolam or pethidine. We routinely used chromoendoscopy with 0.2% indigo carmine dye to accentuate the lesion contours [8]. This procedure was useful for determining the area of endoscopic resection and detecting local recurrence at the site of resection. Furthermore, we used a magnifying endoscope with 0.2% indigo carmine or 0.05% crystal violet to estimate the depth of invasion in the target lesion [8] and to detect the residual tumor immediately after

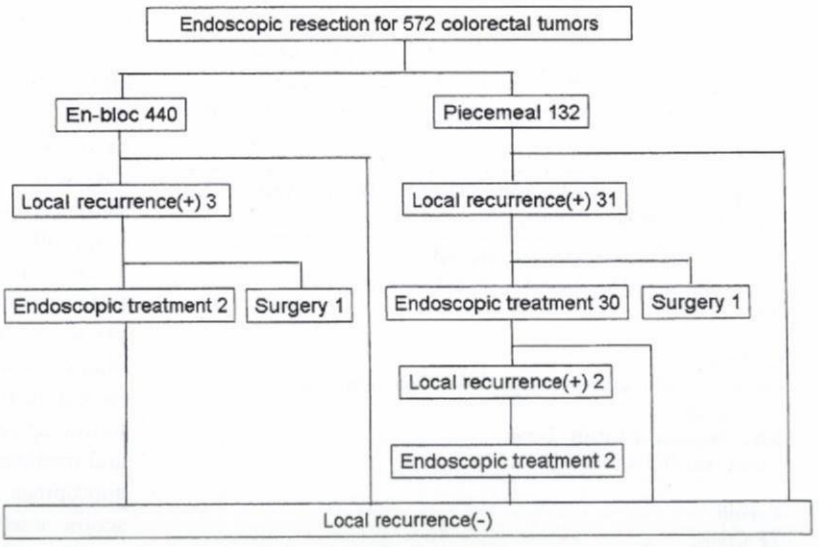

Fig. 1 A chart of 572 colorectal tumors followed up after endoscopic resection

endoscopic resection. Macroscopically, at the margins, lesions can be classified into three major groups: protruding type including sessile (Is), semi-pedunclated (Isp), pedunclated (Ip); flat-elevated type including IIa, IIa+IIc, and Is+IIa; and depressed type including IIc. The indication for endoscopic resection is lesion invasion depth limited to the mucosa and shallow submucosa. After the visible lesion was completely removed, 0.2% indigo carmine was sprayed over the area and the area was magnified. Residual tumor was removed with hot biopsy forceps. We performed all endoscopic treatments in a single session.

Histological examination

All tissue was retrieved for histological evaluation. Removed specimens were fixed in 10% formalin for 24 h and embedded in paraffin wax. Serial sections (3 μm) were stained with hematoxylin and eosin. Two or more pathologists specializing in gastroenterology made histological diagnoses including histological type, invasion depth, vessel invasion, and surgical margin. In the present study, histological type was classified into three groups: adenomas, mucosal carcinomas (M-ca), and submucosal carcinomas (SM-ca).

A principle of additional surgical treatment

Patients that were (1) diagnosed with deep SM-ca >1,000 μm, (2) positive for vessel invasions, (3) positive for poorly differentiated adenocarcinoma at the sites of invasion, and (4) positive for vertical margins were judged to require additional surgical treatment with resection of regional lymph nodes. Cases that were judged to have positive or indistinct for lateral margins were followed up endoscopically.

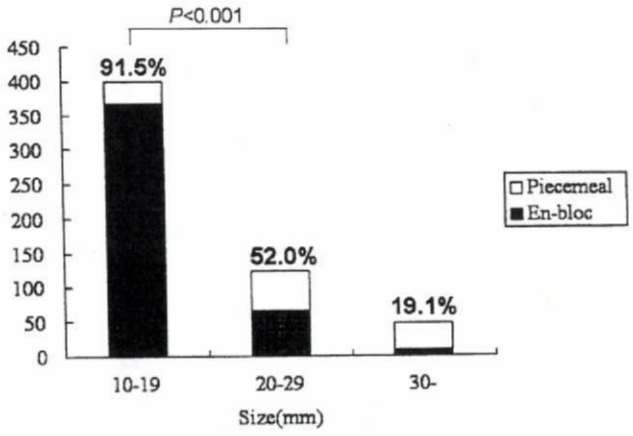

Fig. 2 En-bloc resection rates by lesion size

Table 2 Local recurrence rates by the lesion size

Size (mm)	10–19	20–29	30+	Total
En-bloc	0.8%* (3/366)	0%* (0/65)	0% (0/9)	0.7% (3/440)
Piecemeal	14.7% (5/34)	21.7% (13/60)	34.2% (13/38)	23.5% (31/132)
Total	2.0% (8/400)	10.4% (13/125)	27.7% (13/47)	5.9% (34/572)

*$P<0.001$

Statistical analysis

Local recurrence rates were compared with a chi-square test. Cumulative local recurrence rates were analyzed with the Kaplan–Meier method. Comparison of local recurrence rates were analyzed with log rank test. All statistical analysis was performed with Stat Mate Ver.3 for Windows (ATMS Tokyo, Japan). Calculated P values <0.05 were considered statistically significant.

Results

Local recurrence occurred in 34 lesions (5.9%) of 572 lesions. The local recurrence rates in en-bloc and piecemeal groups was 0.7% (3/440) and 23.5% (31/132, chi-square, $P<0.001$; Fig. 1). The en-bloc resection rates of lesions (Fig. 2) decreased in proportion to increase in size (chi-square; $P<0.001$). The local recurrence rates by lesion size are shown in Table 2. Based on lesion size, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group (10–19 and 20–29 mm, chi-square, $P<0.001$). Based on macroscopic type, local recurrence rates of the en-bloc group were significantly lower than those in the piecemeal for protruding and flat-elevated types (chi-square, $P<0.001$; Table 3). Based on histological type, local recurrence rates of the en-bloc group were significantly lower than those of the piecemeal group for adenoma and M-ca (chi-square, $P<0.001$; Table 4).

Table 3 Local recurrence rates by macroscopic type

Type	Protruding	Flat elevated	Depressed	Total
En-bloc	0%* (0/324)	2.6%* (3/114)	0% (0/2)	0.7% (3/440)
Piecemeal	19.2% (5/26)	24.0% (24/100)	33.3% (2/6)	23.5% (31/132)
Total	1.4% (5/350)	12.6% (27/214)	25.0% (2/8)	5.9% (34/572)

*$P<0.001$