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## Recent Advances in Diagnostic Endoscopy for Colorectal Neoplasm

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### 1. Introduction

Colorectal cancer is one of the most common causes of cancer-related death in the western world (Jemal et al., 2009). Most non-hereditary colorectal cancers arise from benign adenomas (Morison et al., 1974). It has been reported that removal of adenomatous polyps reduces the risk of subsequent colorectal cancer by as much as 80% (Winawer et al., 1993). Therefore, detection and removal of colorectal adenomas, as well as of cancer in the early stages, is utmost importance in improving the prognosis of patients with colorectal cancer. Although colonoscopy is one of the most reliable methods for diagnosis of colorectal neoplasms, conventional colonoscopy could be improved by addressing some of its shortcomings.

In this article, the new and promising technologies that comprise image-enhanced endoscopy (IEE) are reviewed, and a new colonoscopic strategy that incorporates some of these techniques is proposed.

### 2. Detection of colorectal neoplasms using colonoscopy

It is generally known that conventional colonoscopy fails to detect some colorectal neoplasms (Rex, et al., 1997) and that such failure may lead to interval cancers between successive colonoscopies. To date, many attempts have been made to improve screening and surveillance colonoscopy. Mounting a transparent hood (TH) on the tip of the colonoscope helps in the detection of colorectal neoplasms by pressing and flattening the colonic folds, thus improving the endoscopic view (Hewett & Rex, 2010). On the other hand IEE, including the total colonic dye-spray method, narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE) and autofluorescence imaging (AFI) offers the possibility of increasing the detection rate of colorectal neoplasms by increasing the visibility of colorectal neoplasms.

Although the reasons for overlooking colorectal neoplasms are unknown, there are two major possibilities (Fig. 1). One is that the overlooked lesions are small and hidden behind colonic folds. Endoscopists should check possible blind spots by using 'mechanical' devices which allow them to look behind colonic folds. The other possible reason is that the overlooked lesions are flat and similar in color to the surrounding mucosa, which makes

them difficult to recognize using conventional white light endoscopy. Some type of 'optical' image enhancing device should be used for detection of this type of lesion. Therefore, endoscopists should utilize both 'mechanical' and 'optical' devices to minimize the overlooking of colorectal neoplasms.

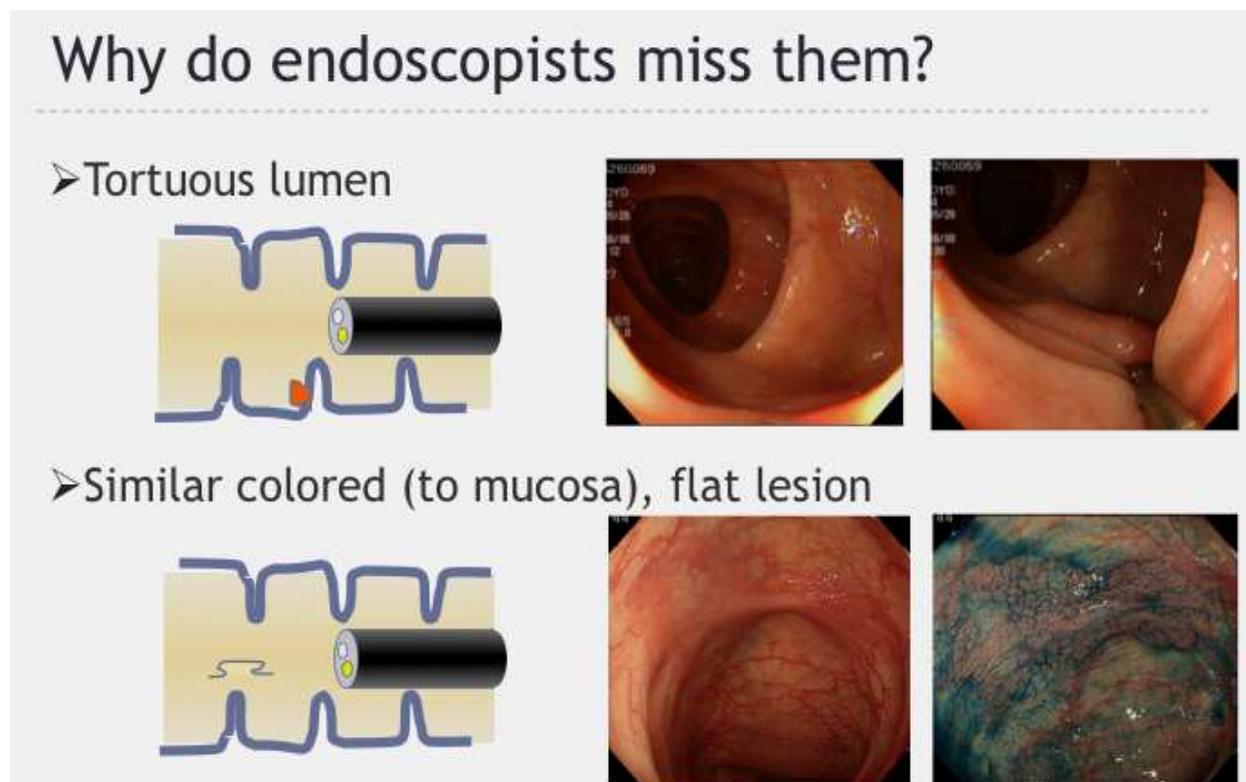


Fig. 1. Possible reasons for overlooking colorectal lesions. A tortuous lumen with colonic folds can result in the overlooking of small lesion behind the folds. Flat lesions of a similar color to the surrounding mucosa can also be easily overlooked

### 2.1 Mechanical methods for minimizing the overlooking of colorectal neoplasm

Some mechanical methods for minimizing the overlooking of colorectal neoplasms have been proposed. One of them is the Third Eye Retroscope, which is passed through the working channel of a standard colonoscope and provides retrograde visualization of the colon (Triadafilopoulos, et al., 2007). In a multicenter randomized controlled trial, it resulted in the diagnosis of about 50% additional adenomas (Leufkens, et al., 2011). The other is the Aer-O-Scope, which provides simultaneous 360° viewing of the mucosal surface of the colon. The use of this device was reported in a preliminary pilot feasibility study (Vucelic, et al., 2006). Although both are promising devices that allow direct visualization of the back of colonic folds, they require an additional endoscope or endoscopic system and are much too complicated technically. Therefore, they have not become standard methods for screening colonoscopy.

Cap-fitted colonoscopy uses a TH affixed to the colonoscope tip (Fig. 2). It flattens the colorectal folds and improves mucosal exposure. The method is very simple and requires only a TH, which costs about \$20. The efficacy of THs has been reported previously (Matsushita et al., 1998). They performed tandem colonoscopy on 24 patients and proved

that the TH reduced the miss rate for polyps from 15% to 0%. In their randomized tandem colonoscopy study, Hewett & Rex also reported that cap-fitted colonoscopy reduced the miss rates for all adenomas, and specifically for small adenomas (Hewett & Rex, 2010).

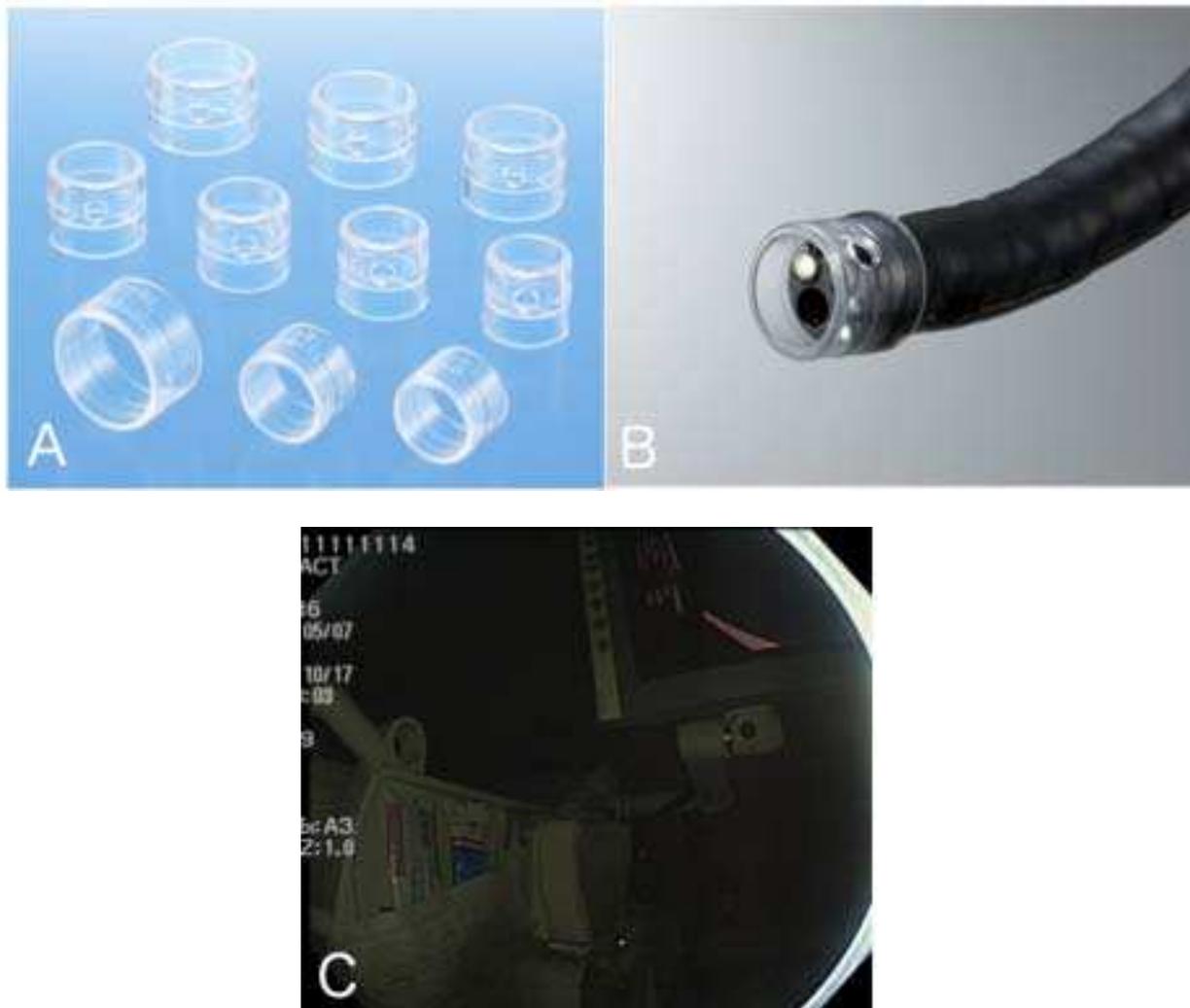


Fig. 2. (A) Transparent hood (TH, D-201 series; Olympus Medical Systems, Tokyo, Japan). (B) The TH attached to the tip of the colonoscope. (C) The endoscopic view of the cap-fitted colonoscope. The tip of TH is seen on the right edge of the endoscopic view

## 2.2 Optical methods for minimizing the overlooking of colorectal neoplasms

Image-enhanced endoscopy is expected to be better at detecting adenomas than conventional white light imaging (WLI). There are two types of IEE: dye-based and equipment-based (Kaltenbach, et al., 2008). In dye-based IEE, absorptive or contrast dye is used to enhance the features of the lesion. The typical absorptive dye for colonoscopy is crystal violet and the typical contrast dye indigo carmine. Indigo carmine, which can provide enhancement of the details of lesions by highlighting subtle changes in mucosal topography, is usually used to minimize the overlooking of colorectal neoplasms. On the other hand, there are a number of categories of equipment-based IEE. These include optical method such as NBI, electronic methods such as FICE, and optical-digital methods such as AFI.

Brooker et al. reported that total colonic dye-spray increases the detection of diminutive adenomas (Brooker et al., 2002). In their trial, they detected 89 diminutive adenomas using total dye-spray colonoscopy and 37 using conventional colonoscopy. Certainly, total colonic dye-spray might improve the adenoma detection rate, but it has not become a standard method for screening because it is much too complicated and time consuming for clinical use. Only methods that are simple and quick are likely to become widely adopted for screening colonoscopy.

Narrow band imaging is a type of equipment-based IEE that uses short-wavelength light (Fig. 3). NBI provides a unique image which emphasizes the capillary pattern as well as the surface pattern. Colorectal adenomas are shown as brownish areas by NBI and are significantly better visualized by NBI than by WLI. NBI is expected to result in better detection of colorectal adenomas and better distinction between neoplasms and non-neoplastic lesions. Recently, although several investigators in western countries have been trying to demonstrate its ability to detect colorectal adenomas, most randomized trials have reported negative results (Adler et al., 2008, 2009). On the other hand, Japanese investigators have reported positive results in their articles (Inoue et al., 2008; Uraoka et al., 2008). Therefore, the efficacy of NBI for detection of colorectal adenoma is still contentious and further investigation is needed.

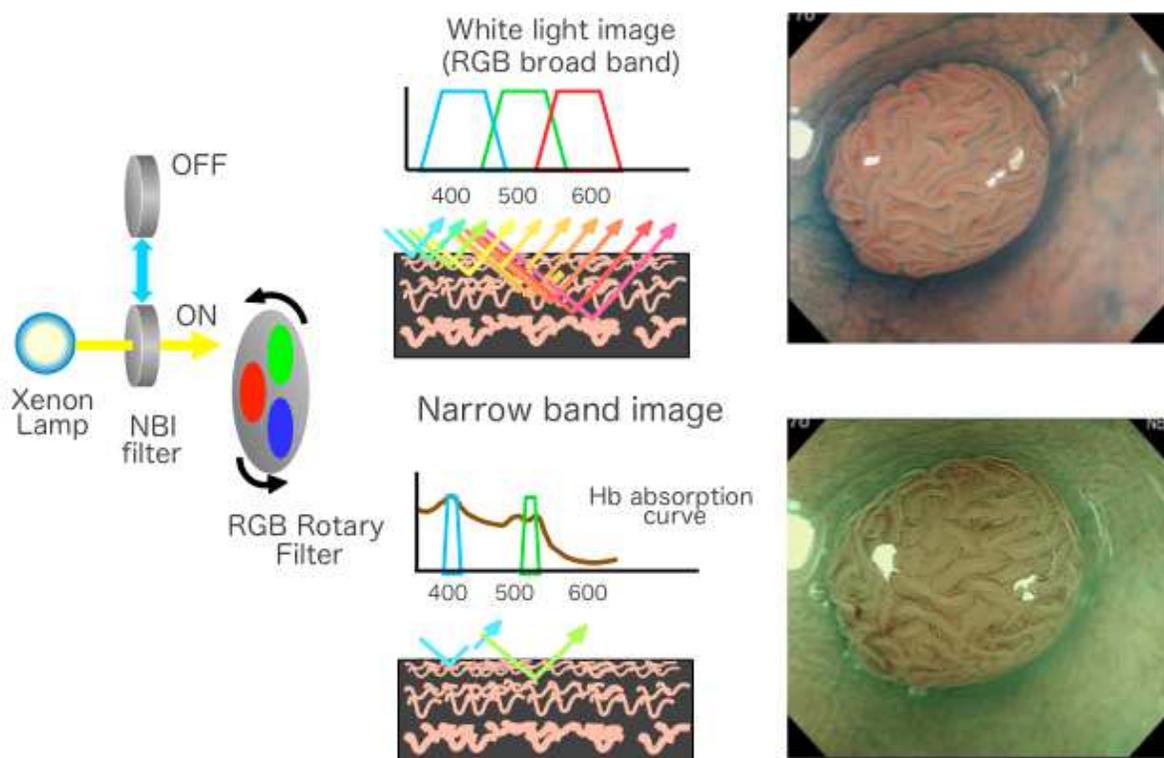


Fig. 3. The mechanism of narrow band imaging (NBI). The NBI system is based on modification of spectral features with each optical filter narrowing a bandwidth of spectral transmittance. (RGB; Red, Green, Blue)

Flexible spectral imaging color enhancement modifies spectral transmittance arithmetically by using a computing processor; therefore, it does not require optical filters. Furthermore, because of its variable setting functions (up to 10), the operator has flexibility in selection of

the most suitable wavelengths for each examination. Although some randomized controlled trials have been conducted (Aminalai et al., 2010 Chung et al., 2010), no one has yet demonstrated improvement in adenoma miss or detection rates compared with WLI.

Autofluorescence imaging is an endoscopic technique for visualizing with reflected autofluorescence, which is emitted from an endogenous fluorophore by exposing it to short wavelength excitation light (Fig. 4). The latest model of AFI system can switch between observation modes in a few seconds. Because colonic adenomas are shown as distinct purple areas in the surrounding green mucosa using AFI, this technique is expected to improve the detection rate of colonic tumors during screening colonoscopy, especially in regard to flat lesions, which are difficult to detect using WLI (Fig. 5). Matsuda et al. reported that AFI is better than WLI at detecting polyps in the right-sided colon. The miss rate for all polyps with AFI (30%) was significantly less than that with WLI (49%,  $P=0.01$ ) (Matsuda et al., 2008).

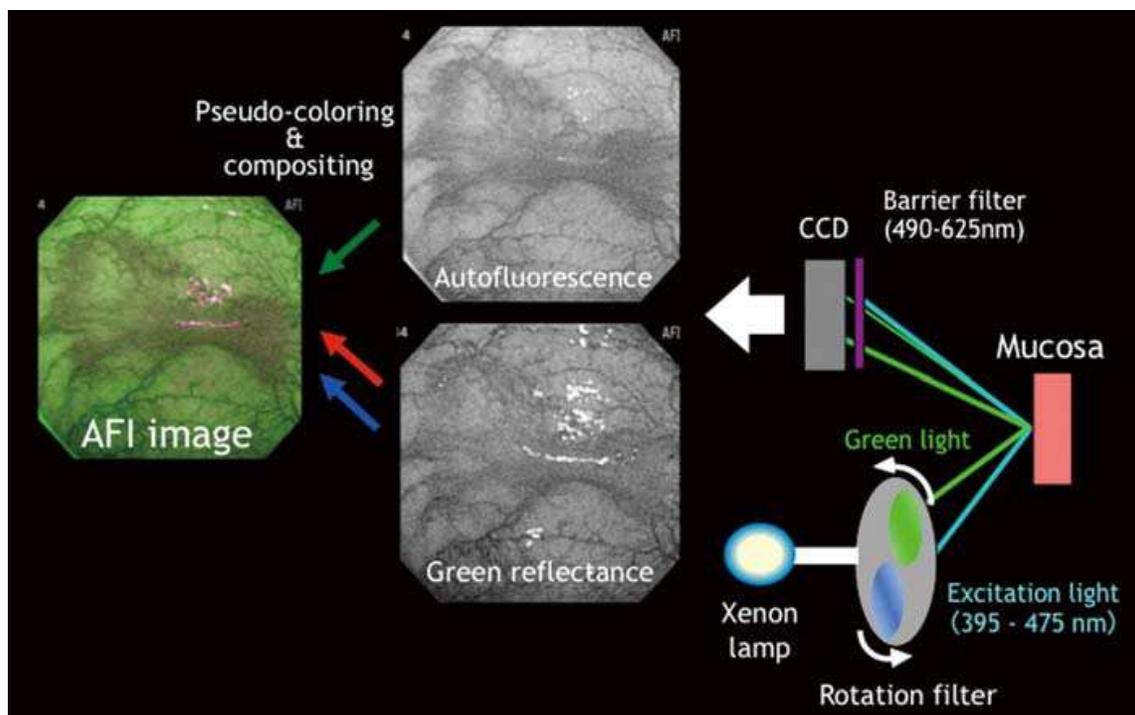


Fig. 4. The mechanism of autofluorescence imaging (AFI). AFI images are produced by illuminating the mucosa by light that has passed through a rotation filter. The image processor artificially colors the autofluorescence images green, and the green reflection images red and blue, then composite images are displayed on the video screen

### 2.3 Combination of mechanical and optical methods for minimizing the overlooking of colorectal neoplasms

To determine whether a combination of the different complementary mechanisms of AFI and a TH would be better at detecting colorectal neoplasms than conventional WLI without a TH, a prospective, randomized controlled trial was conducted.

In this trial, both patients undergoing colonoscopy for investigation of a positive screening fecal occult blood testing (FOBT) and those who had been referred for surveillance colonoscopy after endoscopic resection of colorectal neoplasms were enrolled. A  $2 \times 2$  factorial design was adopted to investigate the impact of simultaneous AFI and a TH. The

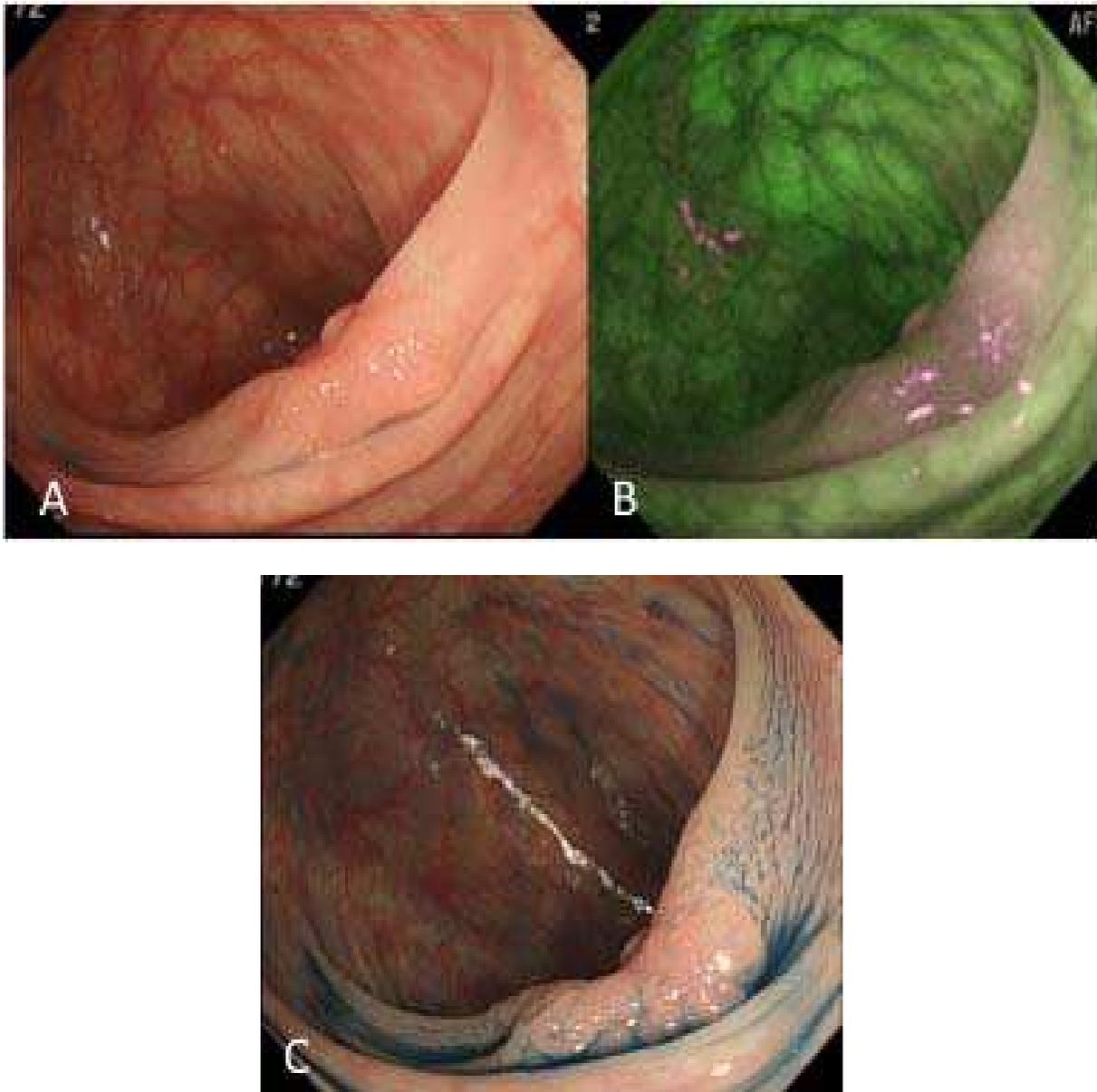


Fig. 5. Images of colonic tumor using autofluorescence imaging (AFI). (A) Conventional endoscopic image of colon cancer in the transverse colon. The lesion is flat and similar in color to the surrounding mucosa. (B) AFI image of the lesion. The lesion shows as a distinct purple area surrounded by green mucosa. (C) Chromo-endoscopic image of the lesion. The features of the lesion are enhanced by indigo carmine

participants were assigned randomly to the following four groups: (1) WLI: colonoscopy using WLI without a TH; (2) WLI + TH: colonoscopy using WLI with a TH; (3) AFI: colonoscopy using AFI without a TH; and (4) AFI + TH: colonoscopy using AFI with a TH (Fig. 6). All patients gave written informed consent to participate in this study and the study protocol was approved by the Research Ethics Committee of our center.

Between 4 November, 2008, and 11 November, 2009, 923 patients who had a positive FOBT or who had been referred for surveillance colonoscopy were scheduled to undergo colonoscopy in our endoscopy unit. Three hundred and sixty-two patients were excluded from enrolment for the following reasons: (1) a history of colectomy or major abdominal

surgery; (2) symptoms suspicious of colorectal stenosis or cancer; (3) inflammatory bowel disease, familial polyposis or known colorectal cancer; (4) severe organ failure, non-correctable coagulopathy, or receiving anticoagulant therapy; or (5) when the colonoscopist judged that the patient was unable to comprehend and give true consent to the process of random allocation. This left 561 patients to be randomly assigned to the different groups. One thousand one hundred and five lesions were detected in 380 patients. Specimens were not obtained from 13 lesions, thus histological diagnosis was available for 1092 lesions. Eight hundred and seventy-five lesions were diagnosed as neoplasms and 217 as non-neoplastic. There were 383 (69%) patients in whom lesions were detected and 329 (59%) with neoplasms.

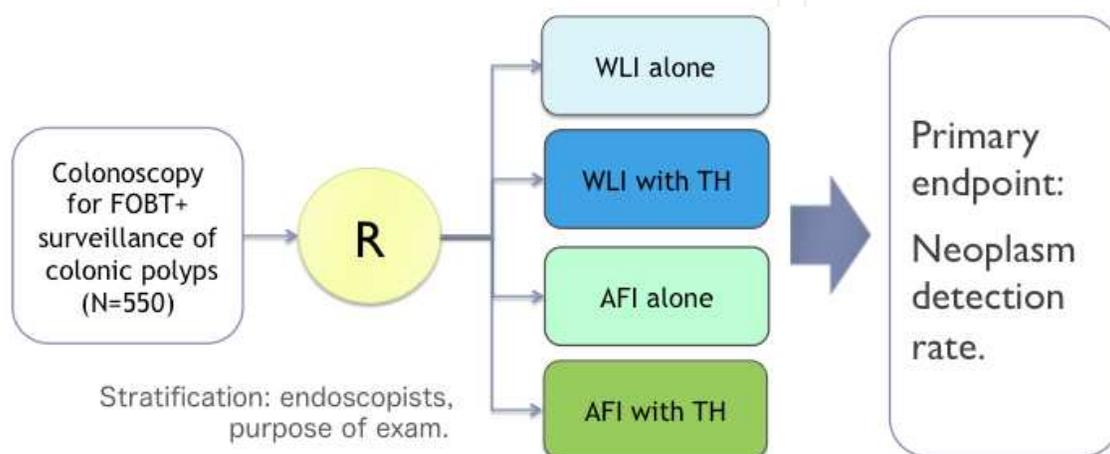


Fig. 6. Study design of a 2 × 2 factorial designed randomized controlled trial for investigation the impact of autofluorescence imaging and a transparent hood. (R; randomization.)

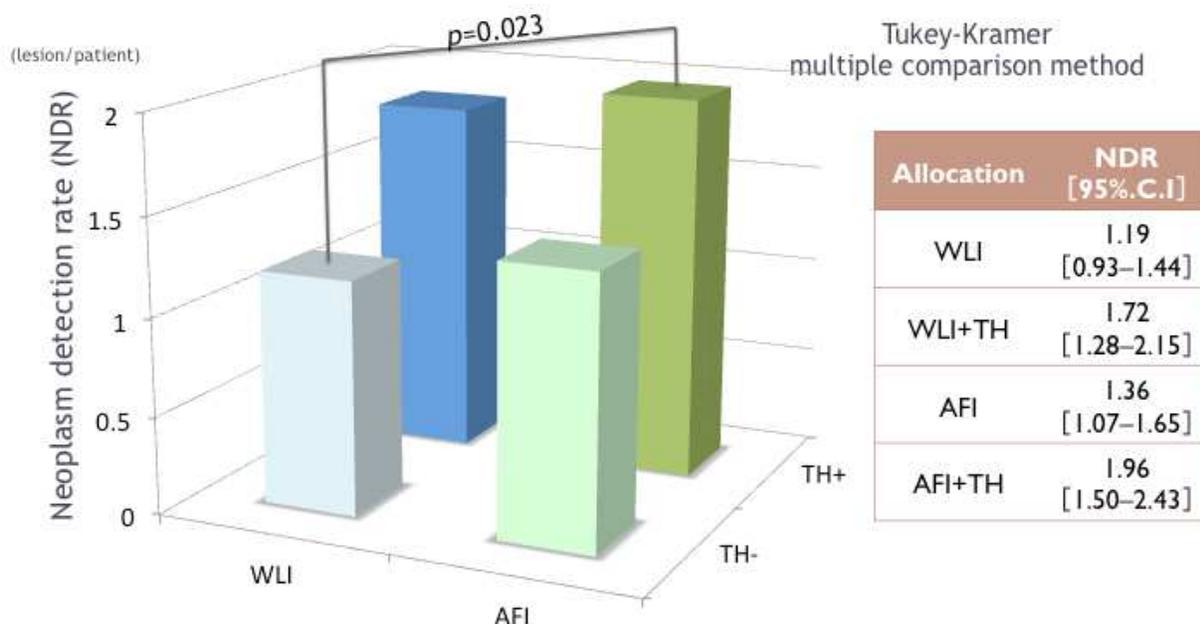


Fig. 7. Primary endpoint of the randomized controlled trial. Neoplastic lesion detection rate in the AFI + TH group was significantly higher than in the WLI group. (AFI; Autofluorescence imaging, TH; transparent hood, WLI; white light imaging)

The primary endpoint, neoplasm detection rate (number of detected neoplasms per patient [95% CI]) in the AFI + TH group was significantly higher than in the WLI alone group (1.96 [1.50–2.43] vs 1.19 [0.93–1.44],  $P = 0.023$  [Tukey-Kramer multiple comparison method]). AFI with a TH detected more neoplasms than did conventional colonoscopy (Fig. 7). Subgroup analysis revealed that mounting a TH resulted in a higher detection rate for polypoid neoplasms than did not mounting a TH, and that AFI observation resulted in a higher detection rate for flat neoplasms than did WLI observation. It was concluded that a combination of the different complementary mechanisms of AFI and a TH would be efficacious in the detection of colorectal neoplasms.

### 3. New problems caused by accurate colonoscopy and the key to a solution to these problems

It has here been reported that a combination of AFI and a TH detects more colorectal neoplasms than does conventional WLI colonoscopy, however most of the lesions detected in the trial were small, low-grade adenomas. Although detection and resection of colorectal adenomas is an efficacious and basic strategy for prevention of colorectal cancer, such an accurate diagnostic method for detection of colorectal neoplasms increases the cost, time and labor required for formal histopathological diagnosis of the resected small indolent neoplasms. Because it results in a high yield of colorectal neoplasms, more accurate colonoscopy can, in itself, cause a new problem.

The 'DISCARD' (Detect InSpect ChAracterize Resect and Discard) policy (Ignjatovic et al., 2009), which is supported by 'optical diagnosis' using NBI without magnification, can lead to substantial savings in cost, time and labor for formal histopathology, making it a really impressive proposal. In the 'DISCARD' trial, it was reported that the capability to correctly diagnose polyps during screening colonoscopy (optical diagnosis) allows recto-sigmoid hyperplastic polyps to be left *in situ* and small adenomas to be resected and discarded without the need for formal histopathology. This policy could be key to a solution to the new problems created by the high yields of the new colonoscopic techniques.

However, small polypoid invasive cancer, though uncommon, does actually exist. The present authors have detected an 8 mm polypoid carcinoma that had invaded the submucosa in the sigmoid colon (Fig. 8). It looked like a small adenoma in the sigmoid colon.

We suppose that NBI without magnification cannot distinguish a small polypoid invasive cancer from a small indolent adenoma because their shapes are so similar. Although invasive cancer requires colectomy with lymph node dissection after estimation of the possibility of lymph node metastasis, such lesions may be discarded without formal histopathology under the 'DISCARD' policy. Furthermore, NBI without magnification does not allow assessment of the degree of dysplasia. In the United States, the interval between surveillance colonoscopies is determined according not only to the number of detected adenomas and their size, but also to the degree of dysplasia and the presence of villous components. Therefore, the 'DISCARD' policy cannot be adopted in countries supporting the US guidelines. An alternative endoscopic technique is proposed here, one that, while decreasing the number of formal histopathological examinations required, is expected to provide information about the histopathological dysplasia of any lesions detected.

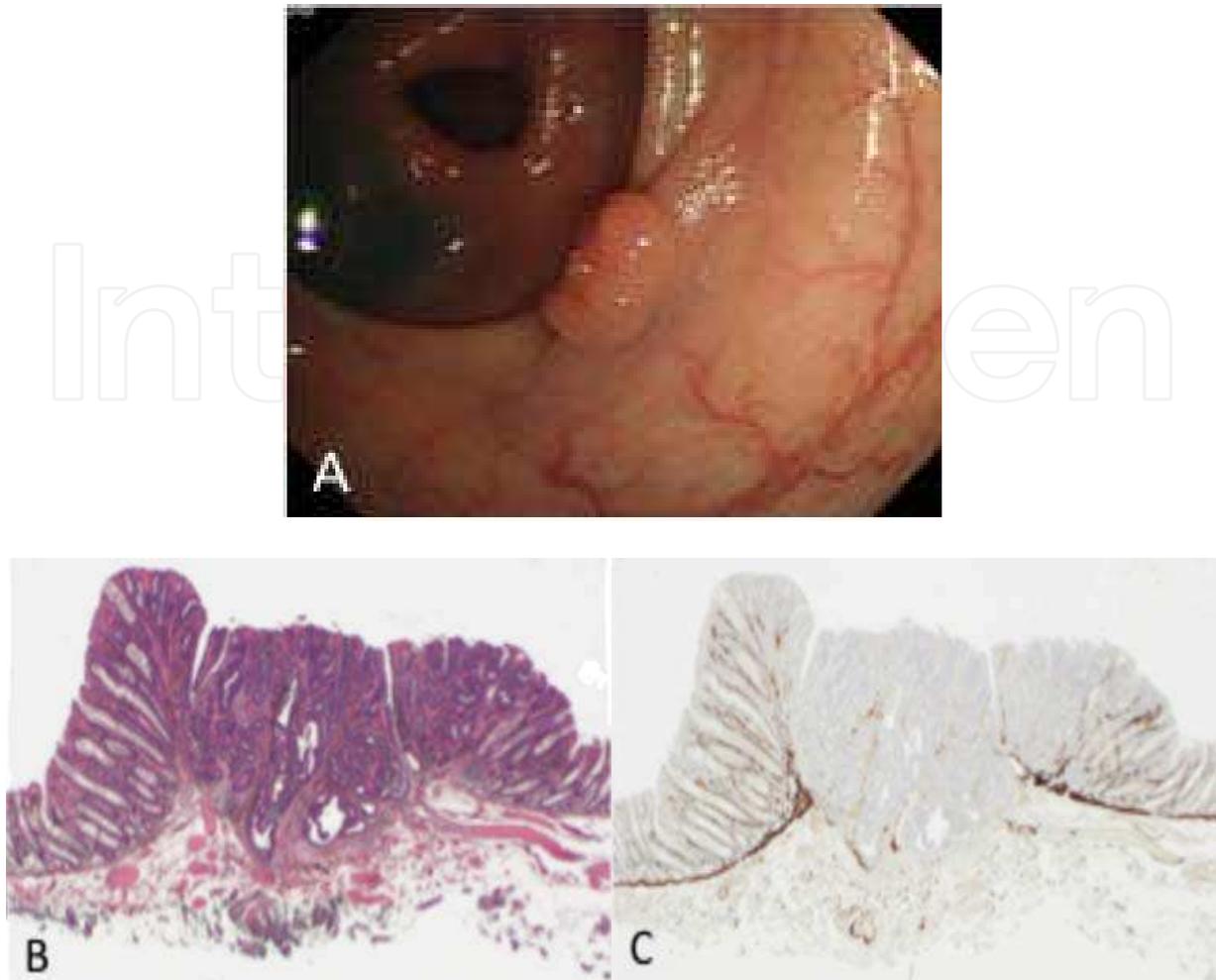


Fig. 8. Small (8 mm) submucosally invasive, polypoid colon cancer. (A) Endoscopic image of a small polypoid (Paris classification, 0-Is) lesion in the sigmoid colon. (B) Microscopic image of endoscopically resected specimen (hematoxylin and eosin stain). The lesion has invaded the submucosal layer. (C) Microscopic image of endoscopically resected specimen (Desmin stain). The muscularis mucosa has been disrupted by the invading carcinoma

#### 4. 'DISCARD with magnifying endoscopy (DISCARD-ME)' policy

Magnifying endoscopy is one method for obtaining histopathological findings by endoscopy *in vivo*. It has been reported that the capillary patterns observed by using NBI with magnifying endoscopy (NBI-ME) can help in assessing the degree of dysplasia in early colorectal neoplasia (Katagiri et al., 2008). Therefore, the present authors believe that NBI-ME provides a more accurate strategy than the conventional 'DISCARD' policy in which NBI is used without ME. Here, a new policy for management of small polyps using NBI-ME; namely the 'DISCARD-ME' policy, is proposed.

##### 4.1 Diagnostic criteria for the 'DISCARD-ME' policy

The diagnostic criteria in the 'DISCARD-ME' policy are basically according to the capillary pattern (CP) classification (Fig. 9), which has been reported to be useful for assessing the degree of dysplasia in early colorectal neoplasia (Katagiri et al., 2008). Lesions with invisible

or faintly visible micro-capillary (MC) vessels are categorized as non-neoplastic (CP Type I), and lesions with clearly visible MC vessels are categorized as neoplastic. Neoplastic lesions are subdivided into low-grade dysplasia (CP Type II) and high-grade dysplasia or carcinoma (CP Type III). In CP type II, the MC vessels is arranged in a round or oval, honeycomb-like pattern. In CP type III, the MC vessels is not arranged regularly in a honeycomb-like pattern and exhibits at least one of the following features: irregular size, complex branching, disruption, or irregular winding.

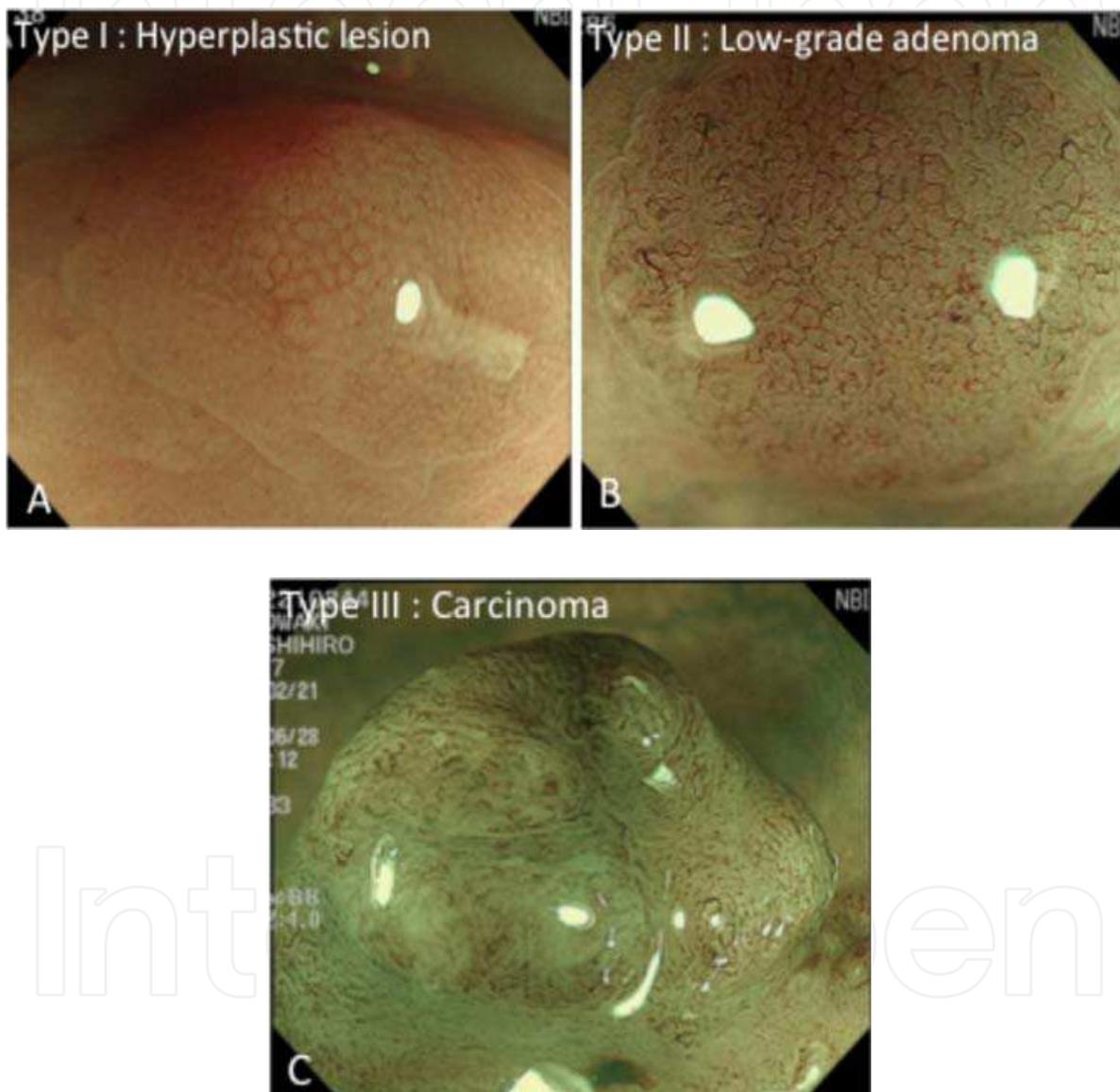


Fig. 9. Capillary pattern (CP) classification using narrow band imaging with magnifying endoscopy (NBI-ME). (A) Type I: NBI-ME image of hyperplastic polyp. The microcapillary (MC) vessels are invisible or faintly visible. (B) Type II: NBI-ME image of low-grade adenoma. The MC vessels are arranged in a round or oval, honeycomb-like pattern. (C) Type III: NBI-ME image of invasive carcinoma. The MC vessels are not arranged regularly in a honeycomb-like pattern and exhibit at least one of the following features: irregular size, complex branching, disruption, or irregular winding

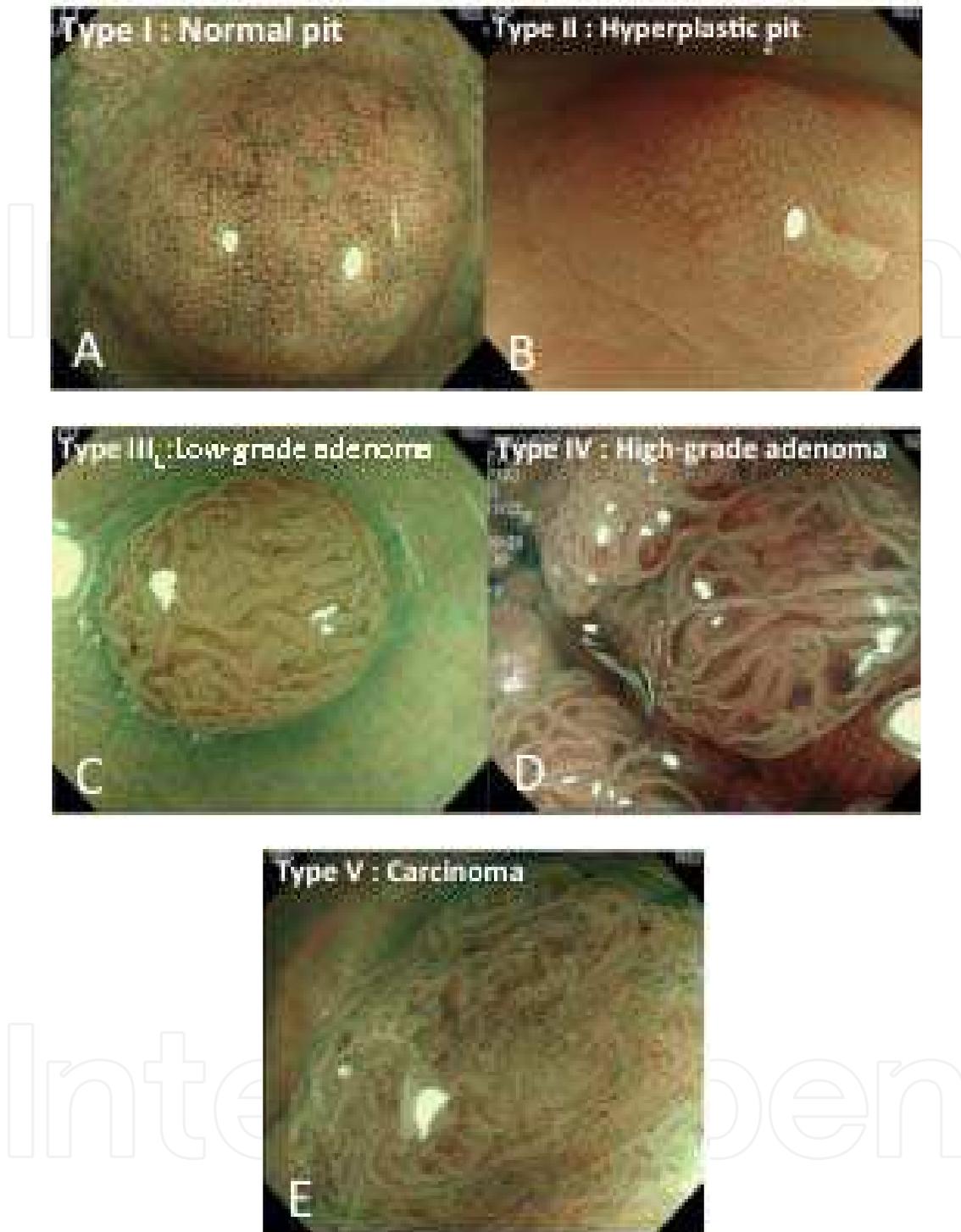


Fig. 10. Pit pattern classification of surface pattern observed by narrow band imaging with magnifying endoscopy (NBI-ME). (A) Type I: NBI-ME image of submucosal tumor (granular cell tumor). The surface pattern is normal, round and regular. (B) Type II: NBI-ME image of hyperplastic polyp. The surface pattern is star-like, slightly dilated and regular. (C) Type III: NBI-ME image of low-grade adenoma. The surface pattern is tubular, long and narrow, not branched and regular. (D) Type IV: NBI-ME image of villous high-grade adenoma. The surface pattern is branched, dendritic, villous or gyrus-like. (E) Type V: NBI-ME image of invasive carcinoma. The surface pattern is irregularly arranged and shaped

When the microvascular architecture cannot be assessed, the pit pattern classification of surface pattern is applied, because Hirata et al. have reported that determination of the pit patterns of colorectal neoplasia by NBI-ME is almost the same as that achieved by standard magnification with chromo-endoscopy (Hirata, et al., 2007, Fig. 10). According to the pit pattern classification, lesions with Type I and II pit patterns are categorized as non-neoplastic, and lesions with Type III, IV and V pit patterns as neoplastic (Kudo, et al., 1994). Neoplastic lesions with a Type III pit pattern are categorized as low-grade adenomas and lesions with Type IV and V pit pattern as high-grade adenomas, villous adenomas or carcinomas. In cases where different histologic categories have been assigned by the CP and pit pattern classifications, the more severe category is adopted.

#### 4.2 Strategy of 'DISCARD-ME' policy

Where the 'DISCARD-ME' policy has been adopted, when colonoscopists have detected a colorectal polyp during a screening colonoscopy, they can predict the polyp type (non-neoplastic, low grade adenoma, suspicious of high grade adenoma or carcinoma) by careful observation using NBI-ME and the above-described criteria. In addition to predicting histopathology, colonoscopists can make the following decisions for polyp management on the basis of the optical diagnosis using NBI-ME (Fig. 11): (1) whether to 'resect and discard' polyps (for serrated lesions in the proximal colon or low-grade adenomas; no formal histopathology required); (2) whether to 'resect and send' them for histopathology (if they cannot decide on the type of polyp or are concerned about high-grade adenoma or carcinoma), or (3) whether to 'leave it *in situ*' (for diminutive recto-sigmoid non-neoplastic lesions).

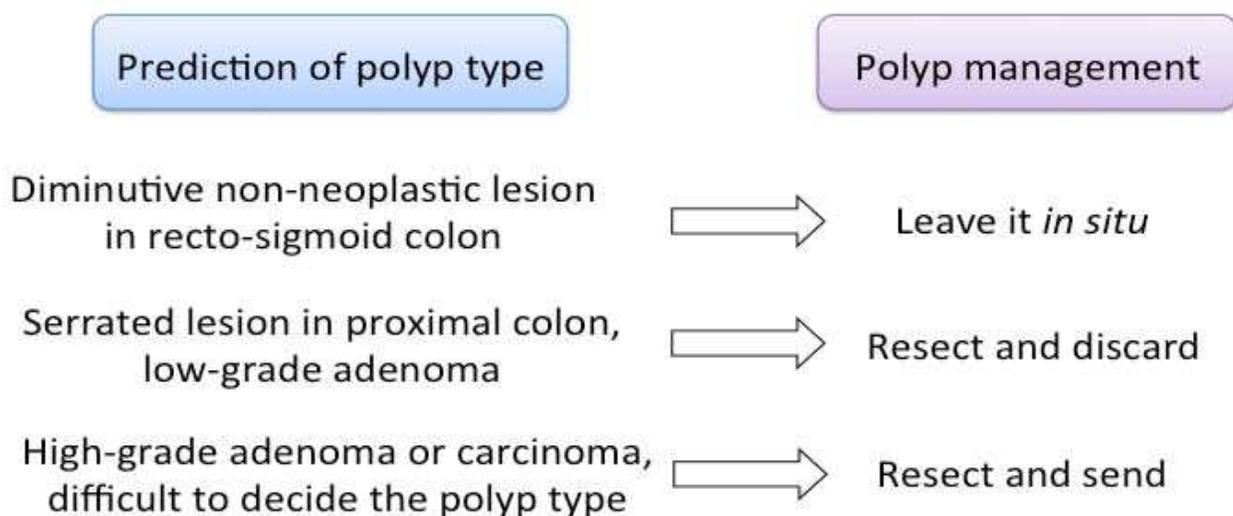


Fig. 11. Strategy of the 'DISCARD-ME' policy

#### 4.3 A 'proof of principle' pilot study for the 'DISCARD-ME' policy

A prospective 'proof-of-principle' pilot study was conducted by the present authors to investigate the feasibility of the 'DISCARD-ME' policy. Forty-one patients undergoing colonoscopy for investigation of a positive screening FOBT, or who had been referred for surveillance colonoscopy after endoscopic resection of colorectal neoplasms, were enrolled.

In this pilot study, 105 lesions were detected. The histopathological diagnoses of two lesions were not obtained, histological diagnosis being available for the other 103 lesions (24 non-neoplastic lesions, 77 low grade adenomas, 1 high-grade adenoma, and 1 non-invasive carcinoma).

In 13 lesions (13%) which were endoscopically diagnosed as suspicious for high-grade adenoma or carcinoma, a decision was made to 'resect and send'. Of these 13 lesions, one was histopathologically diagnosed as high-grade adenoma and one as intramucosal carcinoma. Among the lesions for which the endoscopically made decisions were to 'resect and discard' or 'leave *in situ*', there were no high-grade adenomas or carcinomas. Therefore, it was concluded that decisions for management without formal histopathology could safely be made in 88% of small polyps (Fig. 12). The sensitivity of 'resect and send' for high-grade adenoma and carcinoma was 100%, and its specificity was 90%.

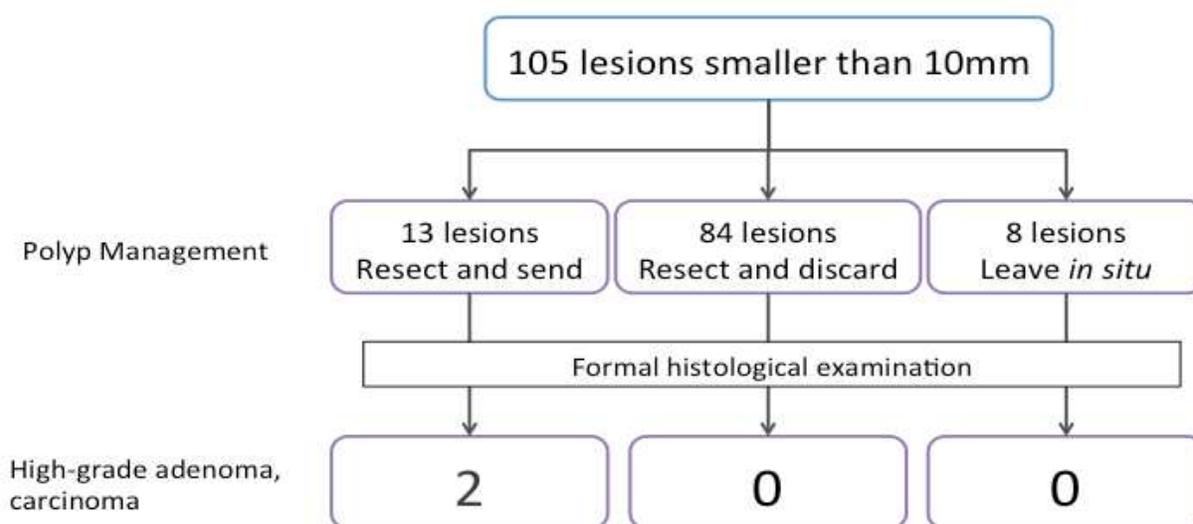


Fig. 12. Flow diagram of the pilot study. In this pilot study, 'resect and send' could safely have been selected for the 13 lesions that included the 2 high-risk lesions, and histopathological examination was omitted for the remaining 88% of lesions

Minimally invasive submucosal cancer is morphologically similar to intramucosal carcinoma, from which it is sometimes difficult to distinguish. Submucosal cancer should be assessed by histopathological examination for lymphovascular involvement and the vertical margin of the resected specimen to determine the need for additional surgery to prevent lymph node metastasis. With the 'DISCARD' policy without NBI-ME, there is a risk of small submucosal carcinomas being discarded, whereas the 'DISCARD-ME' policy could prevent inappropriate discarding. Furthermore, the 'DISCARD-ME' policy could be adopted in countries supporting the US guidelines, because these countries do not discard high-risk lesions.

## 5. Conclusion

The combination of AFI and TH results in more accurate detection of colorectal neoplasms. These new modalities lead to high yield colonoscopy, and the increase in detected lesions, resulting in more time, labor and cost being expended on the histopathological diagnosis of small indolent low-grade adenomas. The 'DISCARD-ME' policy using NBI-ME may

decrease the time, labor and cost of histopathological diagnosis without running the risk of discarding lesions that require formal histopathological diagnosis for assessment of the possibility of lymph node metastasis. These new diagnostic technologies may contribute to a new 'high yield and discard' era in surveillance colonoscopy.

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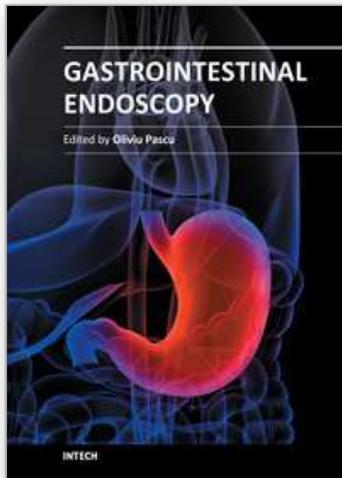
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## **Gastrointestinal Endoscopy**

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Endoscopy has had a major impact in the development of modern gastroenterology. By using different data it provided a better understanding of pathogenic mechanisms, described new entities and changed diagnostic and therapeutic strategies. Meanwhile, taking advantage of many technical advances, endoscopy has had a developed spectacularly. Video-endoscopes, magnification, confocal and narrow-band imaging endoscopes, endoscopic ultrasounds and enteroscopes emerged. Moreover, endoscopy has surpassed its function as an examination tool and it became a rapid and efficient therapeutic tool of low invasiveness. InTech Open Access Publisher selected several known names from all continents and countries with different levels of development. Multiple specific points of view, with respect to different origins of the authors were presented together with various topics regarding diagnostic or therapeutic endoscopy. This book represents a valuable tool for formation and continuous medical education in endoscopy considering the performances or technical possibilities in different parts of the world.

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