Review Article

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Practical Use of Digital Chromoendoscopy for GI Tract Diseases Including GERD

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INTRODUCTION

Evolving from fiber optic flexible endoscope to video-endoscope, GI endoscopy practice is going to change tremendously with a new technology that supports the use of zoom, magnification, and high resolution of captured images. In addition, dye staining with lugol solution, methylene blue and indigocarmine are facing a replacement with one touch wavelength adjustment. This revolution can be called as magnification digital chromoendoscopy (MDC). The MDC technique, hopefully will replace all cumbersome conventional endoscopies that involve in tissue staining with un-washable dyes and make the procedure become friendlier for our daily endoscopic practice soon.

This article will address on the concept and practical use of this new technique for GI endoscopy. It also will provide channel for future research for those who are interested in this field.

Concept of chromoendoscopy

The idea of using dye for tissue staining in GI endoscopy is mainly for enhancement of the contrastness on different GI mucosa. Currently, dyes that used for this purpose can be categorized into 2 groups according to the type of tissue staining.

1. Vital stained dye is the dye that is absorbed into the cell and interacts with components in the cell. Then color of the mucosa of the absorbed cells either abnormal or normal cells can change differently. The good example of this type of dye is lugol stain. Lugol stain can interact with carbohydrate containing structures inside the cell and color of the mucosa changes into brown or dark stain. The practical use of this stain is for detecting abnormal squamous mucosa including high grade dysplasia and early squamous cell carcinoma of the esophagus that do not absorb this dye (Figure 1). Methylene blue is used in Barrett's epithelium detection (Figure 2). Congo red will turn into dark color when the pH of the mucosal area dropped to acidic level (Figure 3). This use is helpful to define the area of atrophic gastritis that can lead to gastric cancer.

2. Non-vital stained dye can not get absorbed into the cells. However, majority of the dye can show the contrast enhancement by filling into the grooves and folds of GI tract mucosa. Many early GI cancers start with small dimple or bump which is difficult to be detected by the conventional endoscope. The prototypes for this dye are indigocarmine and cresyl violet (Figure 4). Pioneer of their use is flat and depressed lesions detection of colon cancer.

Concept of digital chromoendoscopy

White light that we generally see can be visibly shaded into 7 colors. Different colors carry different wave lengths and the dept of penetration into mucosal layer is depended on the wavelength. For instance, violet has the shortest wavelength at 400 nm. Therefore, violet is not able to penetrate tissue as deep as red which has a wavelength of 700 nm. Blue, green and yellow are colors that have wavelength lie in between

Key words : Magnification digital chromoendoscopy, MDC, FICE, AFI, auto fluorescence imaging.

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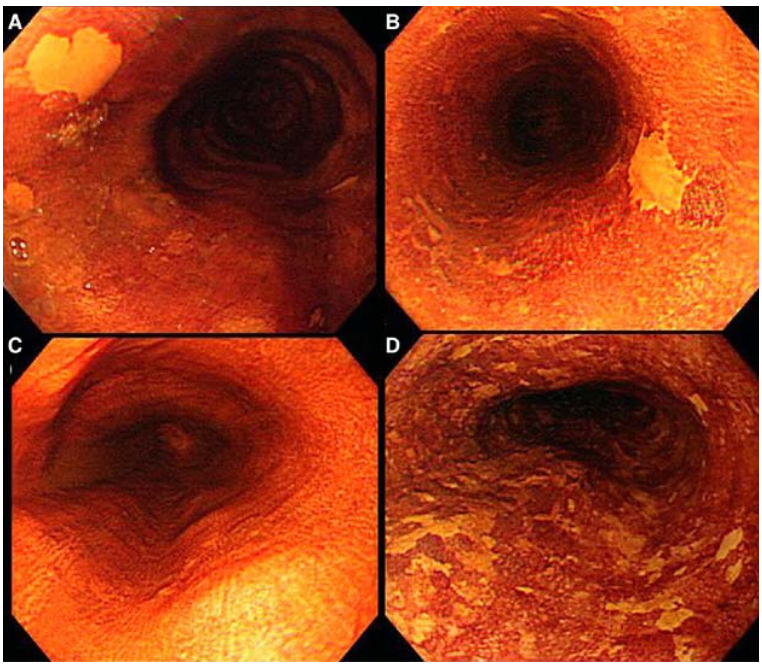

Figure 1. Lugol unstained area representing dysplasia of the squamous mucosa of the esophagus (copied from Kaneko K *et al*. Study of p53 gene alteration as a biomarker to evaluate the malignant risk of Lugol-unstained lesion with non-dysplasia in the oesophagus. BJC 2007;96:492-8)

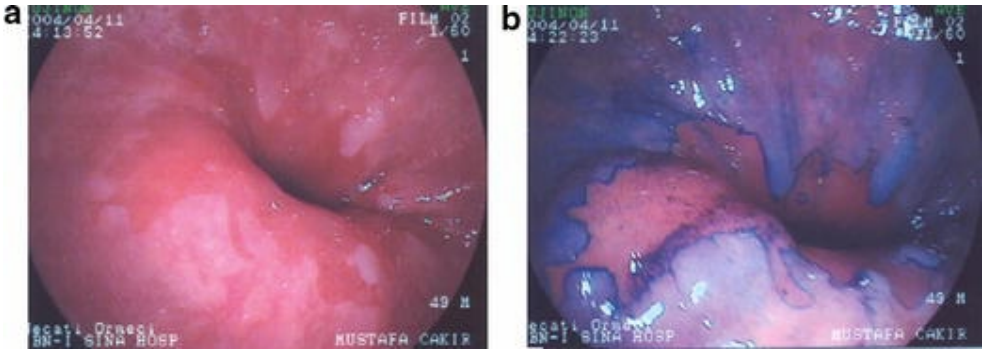

Figure 2. Methylene blue can help the delineation of short segment Barrett's mucosa. (Copied from Ormeci N *et al*. The usefulness of chromoendoscopy with methylene blue in Barrett's metaplasia and early esophageal carcinoma. Surg Endosc 2008;22:693-700)

Figure 3. Left lower corner representing acid producing area that stained positive in black with congo red. (Modified from Sekine H *et al*, Regional differences in the recovery of gastric acid secretion after Helicobacter pylori eradication: evaluations with Congo red chromoendoscopy. Gastrointest Endosc 2006;64:678-85)

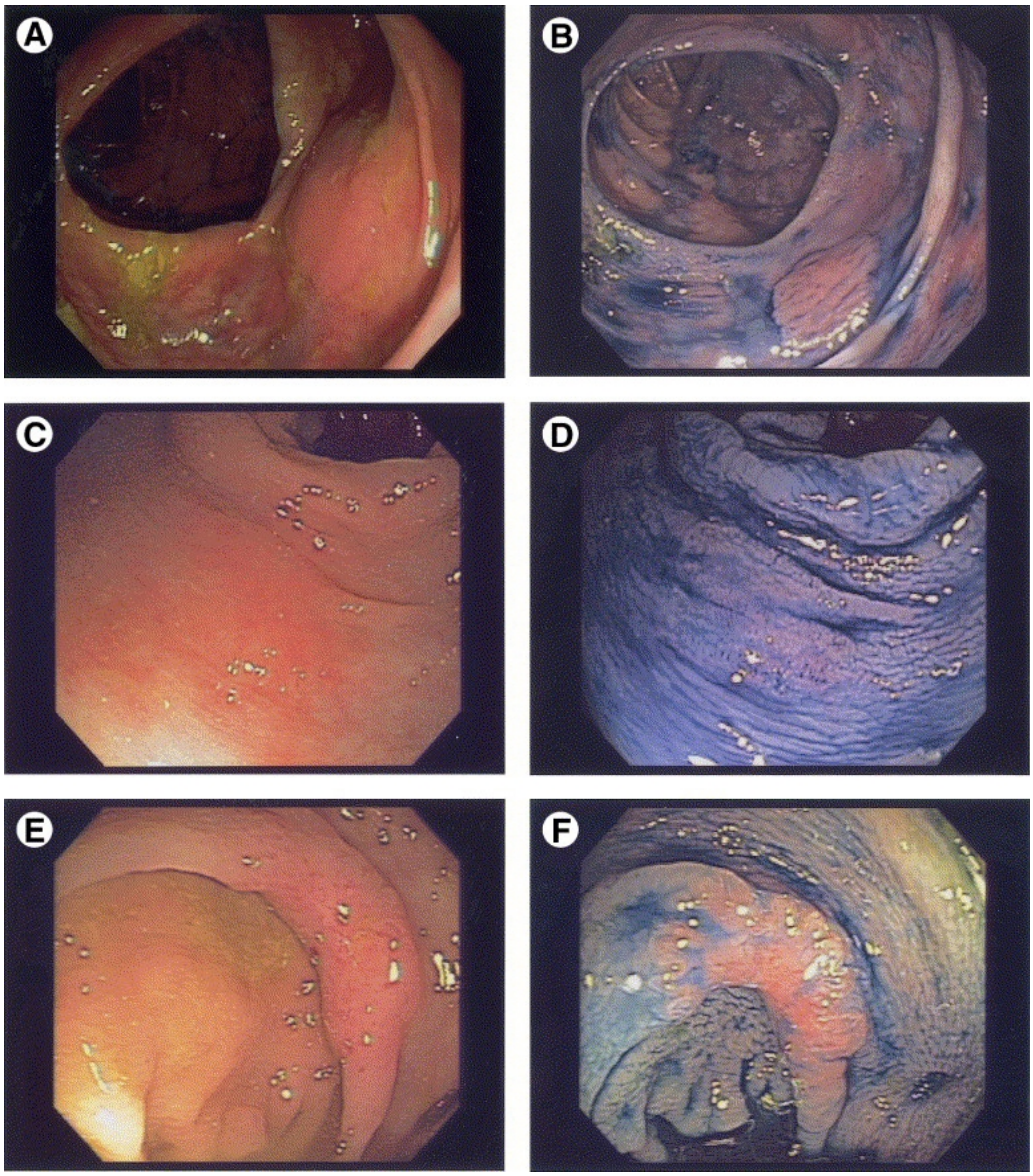

Figure 4. A Flat lesion in the colon under white light endoscopy
B Indigocarmine staining enhanced the flat lesion
C Another flat lesion in the colon under white light endoscopy
D Indigocarmine staining enhanced this flat lesion
E Depressed lesion in the colon under white light endoscopy
F Indigocarmine staining enhanced this depressed lesion

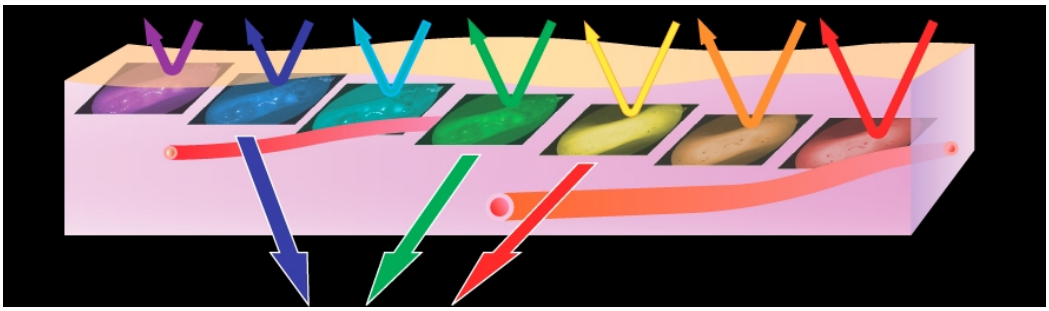

Figure 5. Dept of light penetration by different wavelength of lights

violet and red. Thus the dept of penetration of these colors become progressively deeper into the mucosa respectively (Figure 5). Generally, the range of penetration by these colors is between 0.15 and 0.30 mm.[1]

Hemoglobin is the main substance responsible for the absorption of visible light, with an absorbable peak in the blue part of the spectrum (415 nm). Mucosal structures with high hemoglobin content (ie, blood vessels) absorb the 415 nm light and hence become darker and produce different contrast to the brighter surrounding mucosa that reflects the light. Thus any hypervascularized tissues including malignant mass or inflammatory mass would absorbed this blue light stronger than others. We can use this concept to detect early cancer or inflammatory process by selecting the blue wave length to shy on the object (afferent system) or reprocessing the objective picture after white light illumination and select only blue part after white light shining (efferent system)(Figure 6). The representative of blue light shining (afferent system) is narrow band imaging (NBI) that introduced by Olympus Company. Currently, there are 2 systems available in the market; Excera II (180 series) and Lucera II (280 series). Excera system uses a colorship charge coupling device (CCD) and use and additional filter that selecting only blue band (415 nm) when switching the system (Figure 7 and 8). This system is widely available outside Japan. By contrast, Lucera system contains 2 filters; one is an RGB filter for black and white CCD and the other is an NBI filter. This system is mainly available only for Japanese endoscopists and for some research units.

The efferent system is relied on the computer system that enhanced the image contrast by reprocessing the captured picture. By selecting only preferred spectrum of wavelength the computer can generate a new picture that highlighted the area of inflammation and cancer. There are 2 systems that currently available; Intelligent chromoendoscopy (Fujinon [FICE]) and I-scan (Pentax). FICE generates a very large number of wavelength permutation with increments of 5 nm. They are 10 stations that factory assigns for use. These stations are adjustable according to users' preference (Figure 9). The advantage of the efferent system is this preferred wavelength is adjustable. However, there has been no standard guideline that supported the use

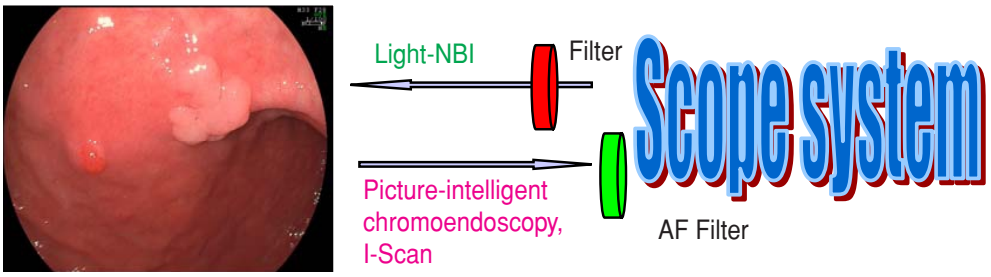

Figure 6. Demonstrating afferent and efferent systems concept

Figure 7. NBI scope before mode switching

Figure 8. NBI scope after switching mode to blue light

of these different colors. Another question be answered is at what wavelength is the most appropriate for different GI tract locations and lesions.

Another system that looked promising is called autofluorescence imaging (AFI) system. AFI is a technique that relied on different components of different tissue light reflection. Collagen, flavoprotein, NADH, and prophyrin are autoflurescense substances that variably distribute in many tissues. For instance, high metabolism tissue like cancer contains more prophyrin than flavin and tissue is of cancer is usually thicker than normal, after excitation by blue light (390-470 nm) all the excitation green reflection (540-560 nm) is absorbed. Then, the picture of cancer area is shown as purple (Figure 10). By contrast, normal tissue can reflect and project green light very well.

Limitation of use

The interpretation of images produced by MDC requires familiarity and learning curve. Categorization of many findings from MDC for many pathological conditions is still uncertain and not becoming standardized yet. In contrast to white light counterpart, MDC produced less bright image particularly in large

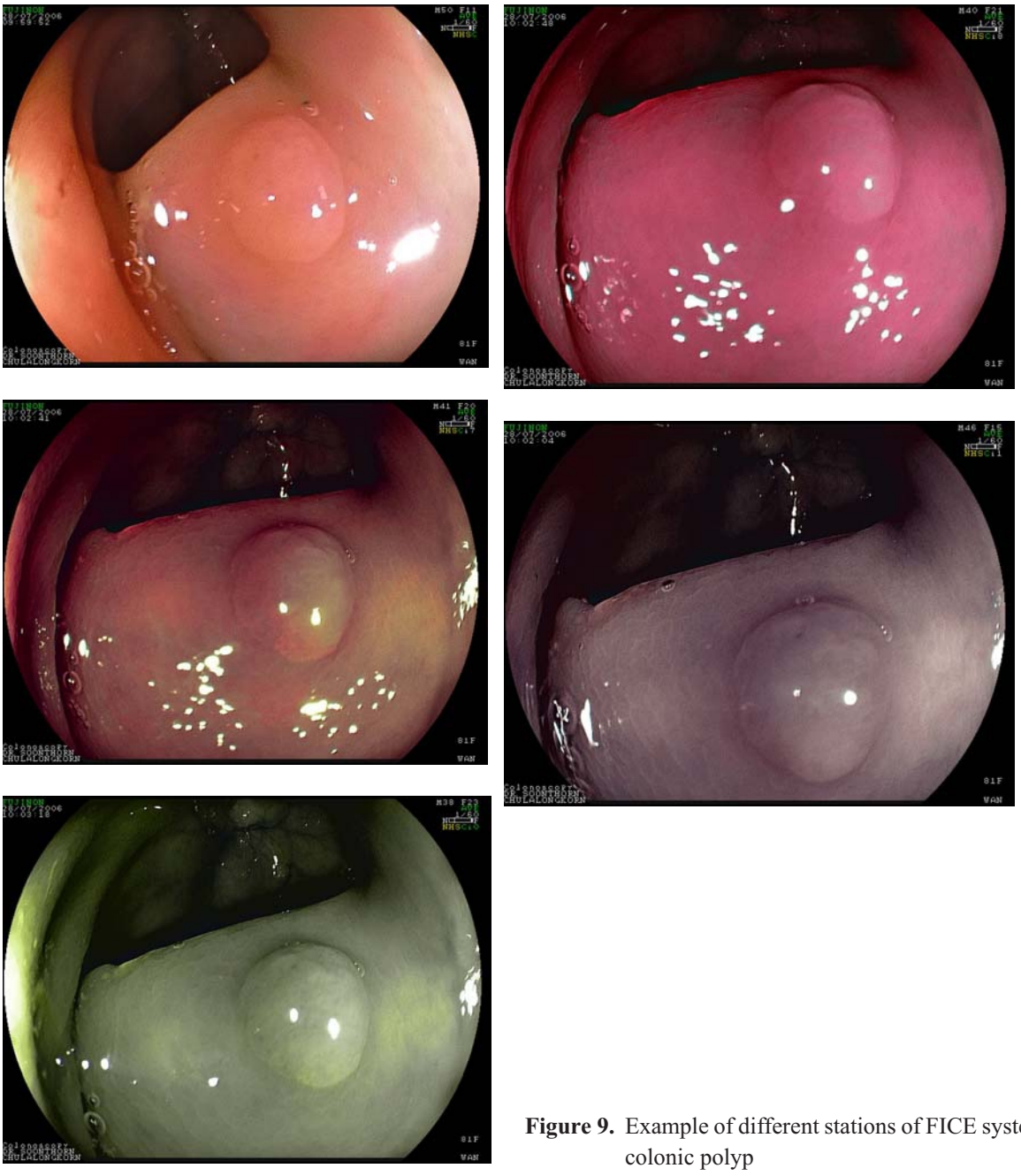

Figure 9. Example of different stations of FICE system for colonic polyp

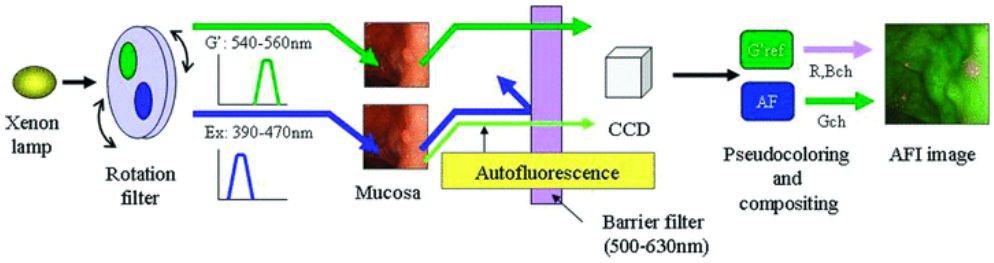

Figure 10. Demonstrating the concept of AFI

luminal diameter area like stomach. In addition, the maximum benefit usually obtains only from zoom view (50-100X). Unfortunately, the current selling models contain almost solely of non-magification scopes. Moreover, with the zoom view, to allow optimal inspection of the mucosa, the scope tip needs to be closer than white light system. Therefore, plastic cap attachment is mandatory to maintain the distant between scope tip and the mucosa.

Another consideration is the presence of bile and blood (especially after biopsy), the inspected view would be obscured because these fluids significantly absorb the MDC wavelength. Moreover, some pixelated distortion may occur during swift motion of the scope. Lastly, even with many stations provided by the company, the appropriate station for each organ and pathological lesion requires more studies to formulate the best guideline.

Practical use of MDC from top to bottom

1. Esophagus: Majority of patients with reflux symptoms in Asia do not have abnormal endoscopic finding by conventional endoscope. However, some reports have confirmed that these patients may have small degree of inflammation confirmed by histology[2-4]. MDC system may be useful for an early detection of this minimal change reflux disease (MERD). Recently by using an intelligence chomoendoscopy without magnification, our group has shown that a triangular indentation into the squamous mucosa extended from the villiform columnar mucosa at the squamocolumnar junction was useful as a positive finding in patients with MERD. With wavelength at station 0 (415 nm) and station 4 (560, 500, 475 nm), the sensitivity for MERD detection were 77.78% and 64.71% respectively (Figure 11).

By contrast, white light endoscopy had a lower sensitivity at 57.14%[5]. Sharma *et al*, reported the usefulness of NBI system for detection of GERD. They found that a significantly higher proportion of patients with GERD had increased number, dilatation, and tortuosity of intrapapillary capillary loops (IPCLs)[6] (Figure 12).

They also found that GERD patients had more microerosions and increased vascularity of the Z line (Figure 13)[6].

The same group did a study of Barrett's esophagus detection by NBI. NBI pictures were graded according to different luminal pattern (ridge/villous, circular and irregular/distorted) (Figure 14) and vascular pattern (normal and abnormal), and compared with biopsy findings.

A good correlation of NBI reading was confirmed by having the sensitivity, specificity, and positive predictive value of ridge/villous pattern for Barrett epithelium detection were 93.5%, 86.7%, and 94.7%, respectively[7]. Different form NBI, AFI showed a poorer result in Barrett epithelium detection. The sen-

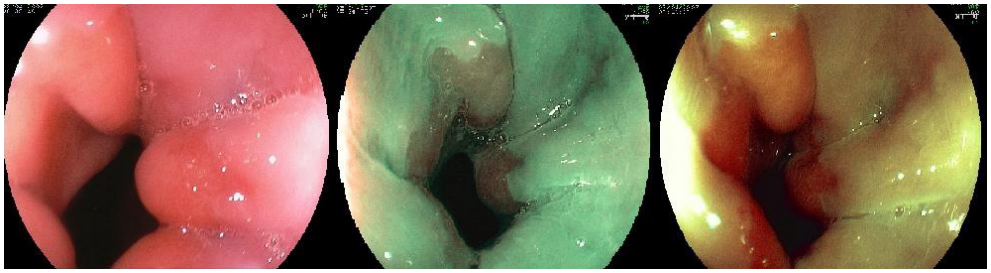

Figure 11. Demonstrating triangular indentation detected by FICE

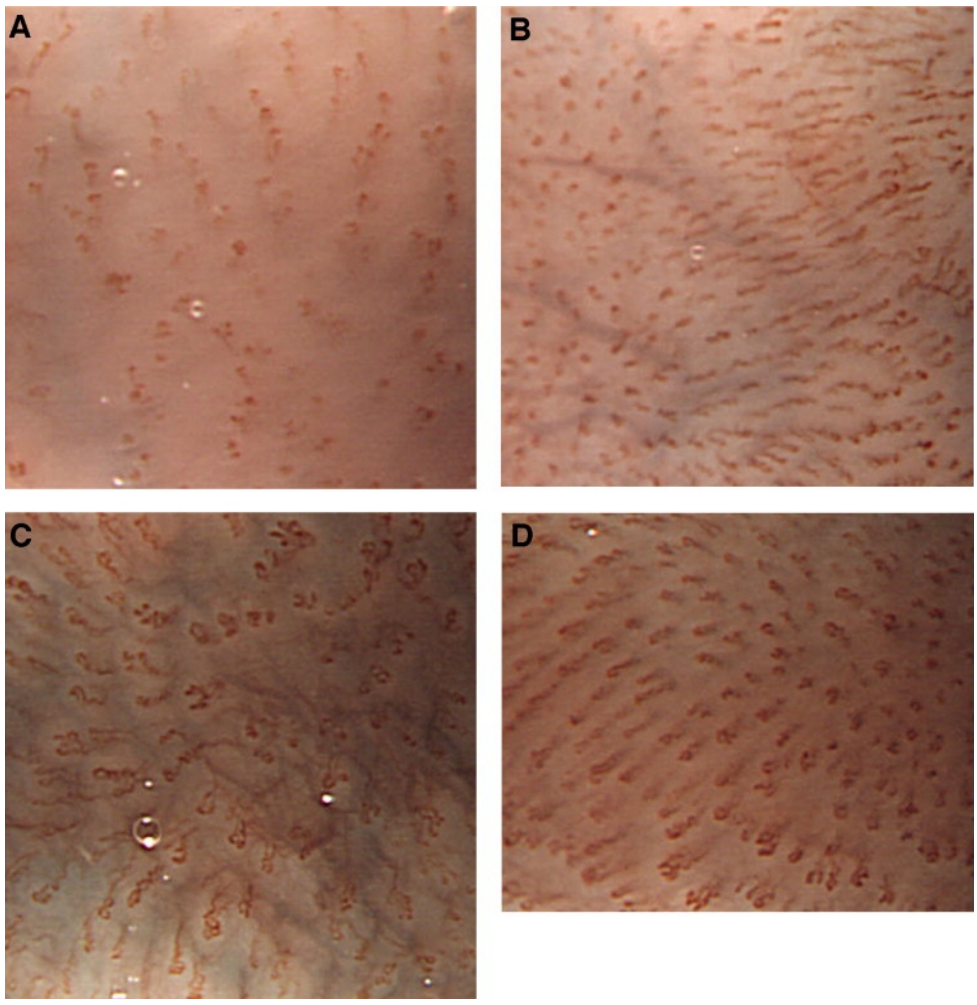

Figure 12. (A) NBI endoscopy images showing normal IPCLs, (B) increased number of IPCLs, (C) tortuous IPCLs, and (D) dilated IPCLs. (copied from Sharma P *et al*, A feasibility trial of narrow band imaging endoscopy in patients with gastroesophageal reflux disease. Gastroenterology 2007;133(2):454-64)

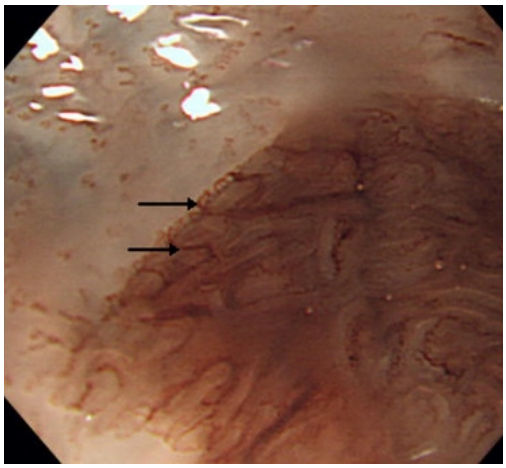

Figure 13. NBI endoscopy image depicting increased vascularity at the squamocolumnar junction (arrows).(copied from Sharma P *et al*, A feasibility trial of narrow band imaging endoscopy in patients with gastroesophageal reflux disease. Gastroenterology 2007;133(2):454-64)

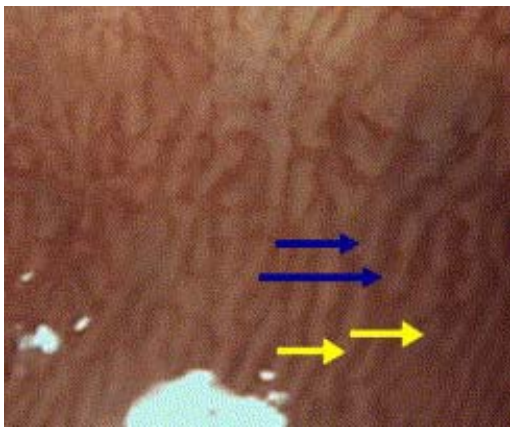

Figure 14. Ridge/villous pattern is illustrated by the darker longitudinal line (ridge - blue arrows) and the lighter longitudinal line (villous, yellow arrows). (Copied from Sharma P, et al The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus. Gastrointest Endosc 2006;64:167-75)

sitivity, specificity, PPV and NPV were reported as 42%, 92%, 12%, and 98.5% respectively[8]. Interestingly, the addition of AFI to standard endoscopy was found to increase the detection rate of both positive patients and positive early cancer lesions in patients with Barrett's oesophagus and the false positive rate of AFI decreased after additional detailed inspection with NBI[9]. Until now, there has been no report on the benefit of MDC for squamous cell carcinoma detection. However, there are few reports on the value of this technique in head and neck cancer[10,11]. We are awaiting for the result of direct comparison study between lugol staining and MDC for squamous esophageal cancer detection.

2. Stomach: A cascade of gastric cancer starts from atrophic gastritis, intestinal metaplasia and then dysplasia. Smoking elderly with Helicobacter infection is prone to contain these pre-malignant conditions[12]. However, standard endoscopic surveillance may have a limitation to target these lesions. It may be of benefit to perform a surveillance endoscopy in high risk population like in Japan. However, the implementation of nationwide mass screening in low-incidence countries may not be cost-effective. In addition, a routine random biopsy may guarantee the effectiveness of early cancer detection. Recently, we demonstrated the benefit of using MDC with NBI technology to target biopsy of the suspicious area for gastric intestinal metaplasia in Thai high risk patients[13]. We demonstrated that light blue crest, villous pattern, and large long crest lesions (Figure 15) that detected by MDC posed a high validity score for sensitivity, specificity, PPV, NPV and accuracy at 91.3%, 73%, 67.7%, 93.1%, and 80% respectively[13].

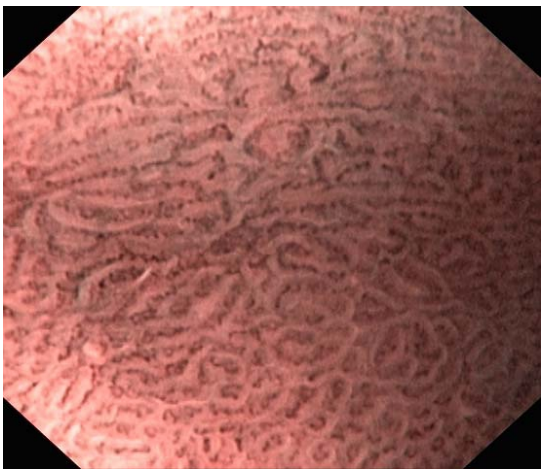

Figure 15. Light blue crest detected by magnify NBI

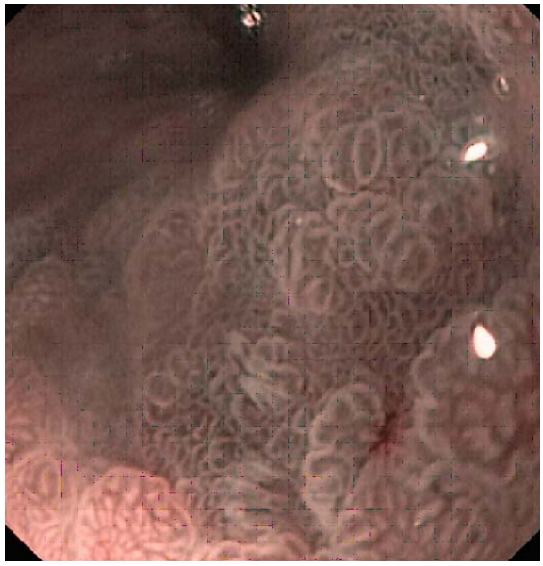

Figure 16. Villous pattern detected by magnify NBI

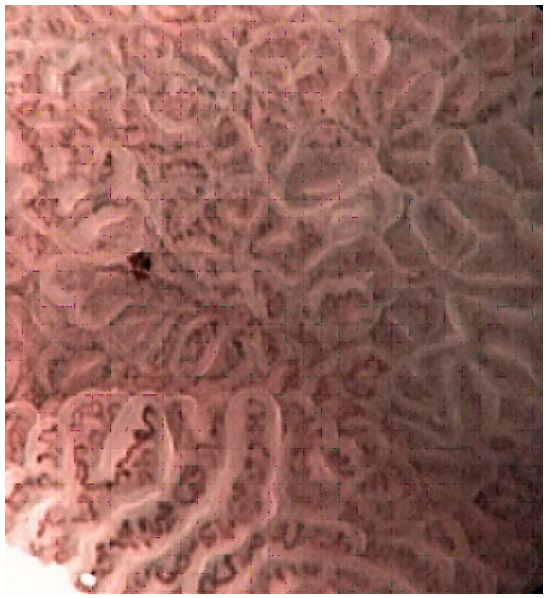

Figure 17. Large long crest detected by magnify NBI

Another study from Japan demonstrated the advantage of efferent system made by Fujinon company[14]. They demonstrated that this system was able to facilitate the detection rate of depressed type early gastric cancers in 26 of 27 patients. With 40 fold magification view these lesions were much easier to be recognized even by medical students (Figure 18). Regarding Helicobacter infection detaction, by using the criteria as irregular pattern with decreased density of vessels by magnify NBI, Bansal et al were able to diagnose Helicobacter infection with sensitivity and specificity of 74% and 88% respectively[15].

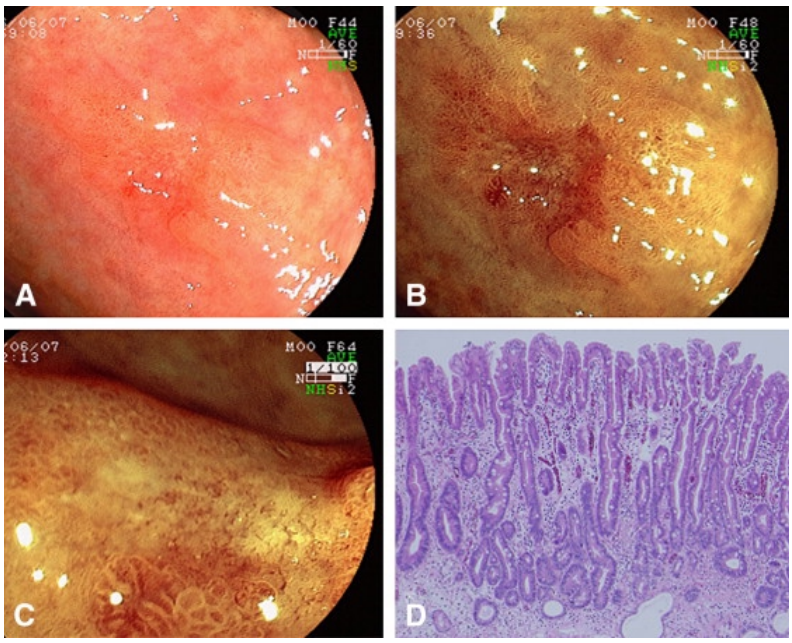

Figure 18. Early gastric cancer depressed type detected by FICE (copied from Osawa H, *et al*. Optimal band imaging system can facilitate detection of changes in depressed-type early gastric cancer. Gastrointest Endosc. 2008;67:226-34).

3. Colon: Colorectal cancer (CRC) is rapidly rising in Asia. There has been no standard guideline until the Asia Pacific Working Group on Colorectal Cancer and international experts launch consensus recommendations[16]. One of the recommendations is to start screening for CRC at the age of 50 years. Regarding, tools for investigation, flexible sigmoidoscopy and colonoscopy are preferred. Double-contrast barium enema carries a suboptimal standard. Currently, CT colonography is not practical and we are awaiting for more data before we can recommend it as a standard tool. In resource-limited countries, FOBT is the first choice for CRC screening. As we are well aware that screening for CRC by FOBT and flexible sigmoidoscopy can reduce mortality rate from this condition[17]. However, to complete the colon examination colonoscopy is the better option.

Recently non-polypoid colonic lesions including lateral spreading and depressed lesions have become more recognizable lesions including many Asian countries[18-21]. These lesions are usually difficult to be detected by a standard endoscopy. Overall, they are more likely to contain carcinoma than polypoid lesion. The report prevalence of invasive carcinoma and carcinoma in situ is 0.82[22]. Staining with indigocarmine and/or crystal violet is the standard technique that Japanese endoscopists used to facilitate detecting these obscure lesions[23,24]. To date, there have been more studies on the benefit of MDC for detecting polypoid lesions.[25-28] The overall sensitivity and specificity of NBI for neoplastic polyp detection were at 80-95%, however, only a handful of studies on non-polypoid lesions are available[29,30]. A recent interesting study from Stanford University that ran back to back colonoscopy with and without NBI for colonic neoplasm detection has shown that 35% of the 12% overall missed lesions were non-polypoid lesions[29]. The conclusion from this study is that NBI did not help for detecting flat lesion. Another study from a high volume colonoscopy center also confirmed that NBI did not result in better detection of adenomas including flat lesions by an endoscopist with a known high detection rate using white light endoscopy (65 vs 67%)[30] Up until now, there was only one study that show the benefit of efferent system for colonic polyp detection[31]. By using low and high magnifications of FICE system for differentiating colonic adenoma (figure 19), Pohl J et al revealed the sensitivity of 89.9% and 96.6%, specificity of 73.8% and 80.3%, and diagnostic accuracy of 83% and 90%, respectively. These provided validity scores by FICE showed a significant improvement form white light endoscopy.

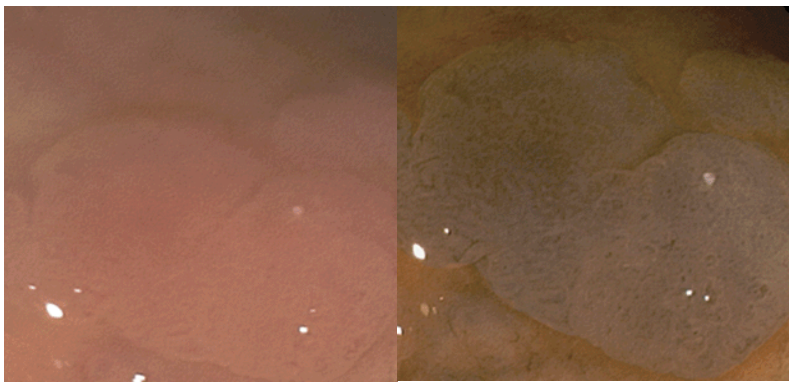

Figure 19. A comparison between white light endoscopy and FICE endoscopy at high magnification. (Modified from Pohl J *et al*. Computed virtual chromoendoscopy for classification of small colorectal lesions: a prospective comparative study. Am J Gastroenterol 2008;103:562-9)

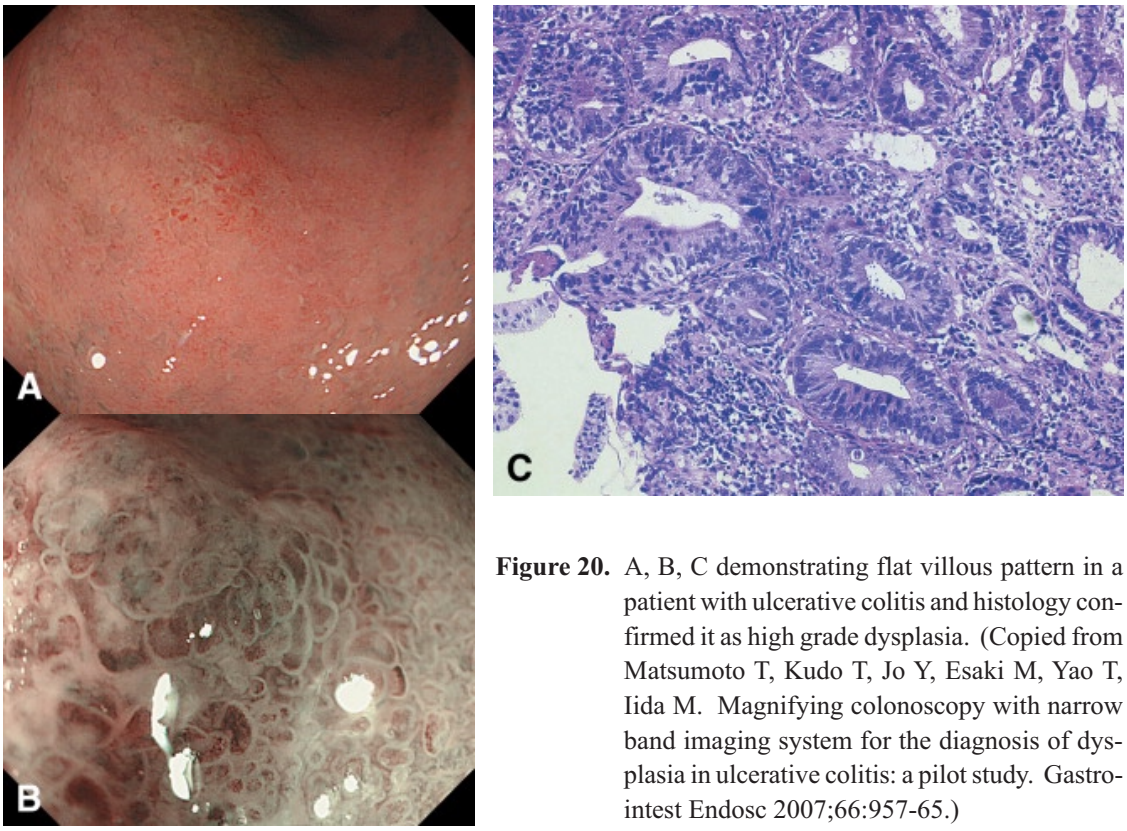

Figure 20. A, B, C demonstrating flat villous pattern in a patient with ulcerative colitis and histology confirmed it as high grade dysplasia. (Copied from Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc 2007;66:957-65.)

Patients with ulcerative colitis (UC) have increased risk for colorectal cancer. The pre-malignant process starts from dysplasia before cancer develops. Surveillance for high grade dysplasia in patient with long standing UC is another area that MDC can add benefit. The current surveillance colonoscopic protocol is to perform a random biopsy at 4 quadrants at every 5-10 cm. This technique is quite cumbersome and requires arduous work of long procedure time. Mutsumoto *et al* reported that tortuous villous pattern detected by NBI during surveillance colonoscopy may be a clue for diagnosis of dysplasia during surveillance for UC (Figure 20)[32]. Unfortunately, a recent study has not confirmed the benefit of NBI yet. A report from the Academic Medical Center, Amsterdam reported the poor sensitivity of the first-generation NBI system for the detection of UC patients with neoplasia[33]. However, the same group report of the benefit of adding AFI for this UC surveillance. They found that dysplasia miss-rates for AFI and conventional en-

doscopy were 0% and 50% respectively (p = 0.036). By using Kudo classification and magnify NBI, this technique had a sensitivity and specificity of 75% and 81%[34].

2. Biliary system and pancreatic duct: Data on MDC and biliary tree are still limited. Generally, biliary endoscopy can be performed either via mother-baby system of ERCP (per-oral) or via percutaneous choledochoscopy. The standard commercially available per-oral system is fiber optic base. Therefore, only research unit that can access the prototype CCD chip MDC- baby scope can perform this procedure. This is a 3.4 mm cholangioscope that uses 2 narrow band filters (415 and 540 nm). This scope does not include red light. A group from Tokyo Medical University Hospital reported that identification of the surface structure and vessels of the mucosal lesions by NBI system was significantly better than with conventional observation ($p < 0.01$ and $p < 0.05$, respectively) (Figure 21). Moreover, only 9.5 % of lesions visualized by white light endoscope were reported as excellent, whereas up to 55% of the lesions defined by NBI were found to

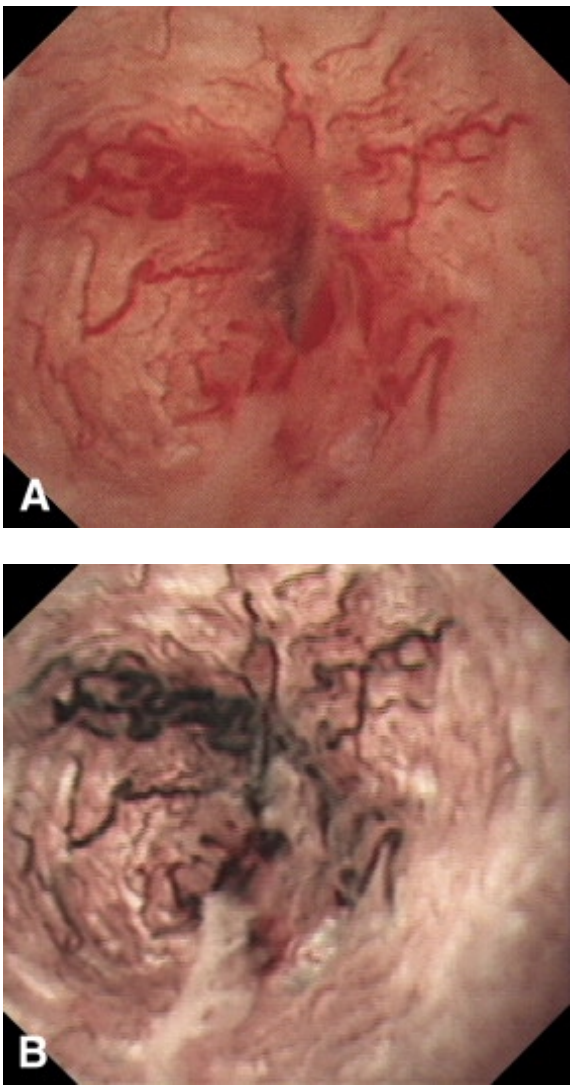

Figure 21. A Malignant stricture detected by white light choledochposcope
B Better vascular networks can be seen from an NBI system.
(Copied from Itoi T, *et al*. Peroral cholangioscopic diagnosis of biliary-tract diseases by using narrow-band imaging (with videos). Gastrointest Endosc 2007;66:730-6.)

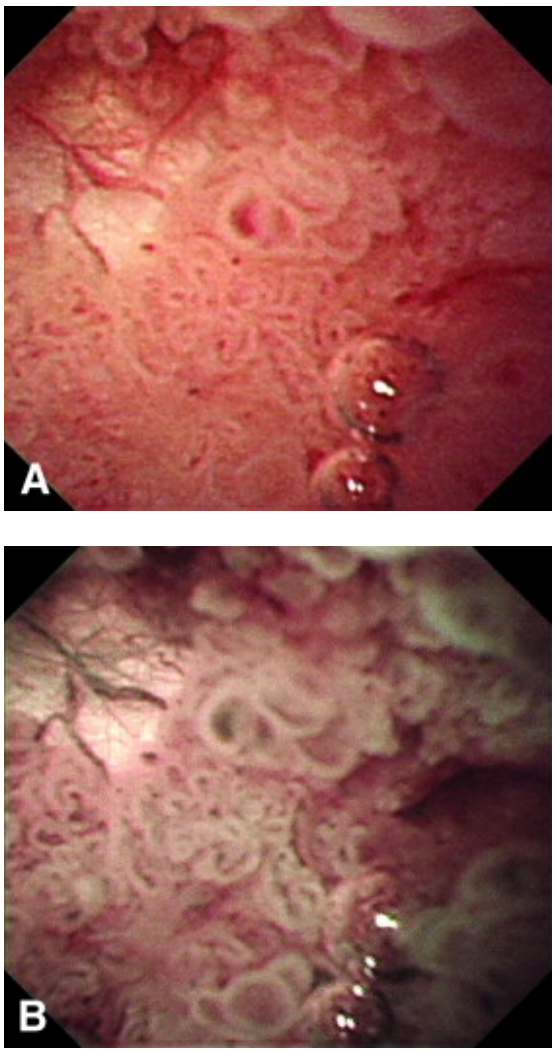

Figure 22. A and B Peroral pancretoscopy in patient witn IPMN; A white light system B NBI system showing a better cpilary and vascular networks of tumors. (Copied from Itoi T, *et al*. Initial experience of peroral pancreatoscopy combined with narrow-band imaging in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas (with videos). Gastrointest Endosc 2007;66:793-7)

be excellent[35]. Of note, the current NBI-baby scope is not equipped with magnification. It can partly compensate by utilizing closer focus length. By not including red light which travels deeper into the mucosa, there is some potential of losing information that can be captured by white light system. The same group also reported on the usefulness of NBI-baby scope for pancreatoscopy, they found that using this scope in patients with IPMN, the images that provided by NBI showed better surface structure and the capillary vessels than by white light endoscopy (Figure 22 A and B). Moreover, NBI identified skip tumor lesions in the tail of pancreas, which were not detected by white light endoscopy[36].

SUMMARY

MDC is an evolving technique that facilitates the enhancement of GI mucosa. The maximum benefit of MDC can be achieved with higher magnification. The current status of image definition and clinical correlation to histological findings are still awaited. To date, there are more published data of afferent MDC (NBI) for esophageal, gastric, colonic, biliary and pancreatic lesions than efferent MDC (FICE and I-scan). With more adjustable wavelength stations, efferent MDC may be a better option for some certain GI lesions. However, there has been limited information at this moment.

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