A PROSPECTIVE DIAGNOSTIC STUDY ON THE USE OF NARROW BAND IMAGING ON SUSPISCIOUS LESIONS DURING COLONOSCOPIC EXAMINATION IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By:

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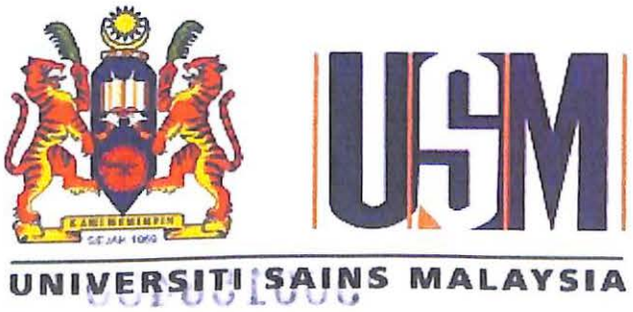

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ABBREVIATIONS

Colorectal Cancer	CRC
Colorectal Adenoma	CRA
Narrow Band Imaging	NBI
White Light Endoscopy	WLE
Confidence Interval	CI
Carcinoma In-situ	CIS
Histopathological Examination	HPE
High Definition	HD
Computed Tomography	CT
Gastrointestinal Tract	GIT
Endoscopic Mucosal Resection	EMR
Endoscopic Submucosal Dissection	ESD
Mucosal Capillary Vessel	MCV
Capillary Pattern	CP
Receiver Operating Characteristic	ROC
Hospital Universiti Sains Malaysia	HUSM
Contrast endoscopy	CE
Sodium Phosphate	NaP
Polyethylene glycol	PEG
Loss of weight	LOW

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ABSTRACT

BACKGROUND: Colonoscopy is the gold standard to detect colorectal neoplasm. There have been multiple attempts to improve diagnostic accuracy partly by image improvement and one of them is narrow band imaging. Based on published reports that NBI have the good diagnostic accuracy, the usage of NBI in differentiating neoplastic and non-neoplastic colorectal lesions was carried out in our hospital (HUSM) for the first time.

OBJECTIVE: To explore the diagnostic validity of NBI colonoscopy as well as associated factors related to the neoplastic and non-neoplastic colorectal lesions.

METHOD: One hundred patients who came mainly for screening colonoscopy with variable lower gastrointestinal symptoms that have suspicious colorectal lesions were included in this study. Only one of the most suspicious lesions in each patient (n=100) was analyzed using NBI colonoscopy based on Sano's classification. These lesions were then either biopsied or resected for histopathological analysis. Endoscopic images were captured electronically and allocated for single reader evaluation. Sensitivity, specificity and diagnostic accuracy of the NBI colonoscopy was assess by comparing it to histopathology results. Other associated factors related to neoplastic and non-neoplastic lesions were analyzed accordingly.

RESULTS: ROC analysis showed that the sensitivity and specificity of the NBI were 88.2% and 71.9% respectively. The analysis also showed that the area under ROC was 0.801, indicating good level of discriminative ability of NBI to differentiate between disease and non-disease. Bowel preparation failed to reach significant association with NBI outcomes; therefore this study suggests that suboptimal bowel preparation is adequate to obtain good outputs of NBI

colonoscopy. There were significant association between LOW and site of lesions to the HPE outcomes even after controlling other variables ($p<0.05$).

CONCLUSION: Our study has shown that NBI system in colonoscopy was capable of distinguishing neoplastic from non-neoplastic colorectal lesions. It indicates an acceptable level of agreement with the gold-standard (i.e. HPE). However the role of NBI in screening and surveillance in Malaysia still need further evaluation and exploration.

ABSTRAK

LATARBELAKANG: Pemeriksaan kolonoskopi adalah standard utama untuk mengesan masalah ketumbuhan usus besar. Banyak penambahbaikan telah dibuat untuk meningkatkan kejituan diagnosis dengan mempertingkatkan kualiti imej antaranya menggunakan pengimejan jalur terhad (NBI; narrow band imaging) sewaktu prosedur kolonoskopi. Banyak data-data yang menunjukkan kelebihan pengimejan jalur terhad ini, dengan itu ia menarik perhatian kami untuk menjalankan kajian mengenainya di Hospital Universiti Sains Malaysia.

OBJEKTIF: Untuk mengkaji kejituan diagnosis menggunakan pengimejan jalur terhad dan faktor-faktor lain yang berkaitan dengan ketumbuhan usus besar.

KAEDAH: Pemeriksaan kolonoskopi menggunakan pengimejan jalur terhad telah dilakukan ke atas seratus orang pesakit yang datang dengan simtom-simtom penyakit usus besar. Hanya satu ratus (n=100) ketumbuhan yang berisiko tinggi dianalisa menggunakan klasifikasi Sano. Ketumbuhan tersebut samada akan diambil tisu atau dibuang untuk dihantar ke makmal patologi untuk dianalisa jenisnya. Gambar endoskopi akan diambil dan diberikan kepada seorang pakar bedah untuk ditelili dan diberikan diagnosis endoskopi. Kepekaan, 'specificity' dan kejituan diagnosis akan dikira apabila dibandingkan dengan keputusan tisu patologi. Faktor-faktor lain yang berkaitan dengan ketumbuhan usus besar juga akan dianalisa.

KEPUTUSAN: Daripada analisa kami menunjukkan kepekaan pengimejan jalur terhad adalah sebanyak 88.2% dan 'specificity' pula sebanyak 71.9%. Kejituan diagnosis berdasarkan kawasan bawah ROC adalah 0.801. Ini menunjukkan kejituan diagnosis menggunakan pengimejan jalur terhad adalah pada tahap yang bagus. Persiapan usus untuk kolonoskopi adalah penting tetapi dalam analisa kami ia tidak berkait secara langsung apabila menggunakan pengimejan jalur

terhad. Faktor – faktor yang didapati berkait secara langsung dengan ketumbuhan usus adalah masalah kurang berat badan dan kawasan di mana ketumbuhan itu berlaku ($p<0.05$).

KESIMPULAN: Kajian kami menunjukan pengimejan jalur terhad ini boleh membezakan ketumbuhan usus yang bahaya atau tidak bahaya apabila dibandingkan dengan keputusan tisu patologi. Kejituan diagnosisnya adalah pada tahap yang bagus berdasarkan data-data yang telah diperolehi. Penggunaan sistem pengimejan jalur terhad ini dalam penyaringan kes-kes baru atau berulang adalah berpotensi tetapi perlukan lebih banyak kajian di Malaysia.

1) INTRODUCTION

1.1) Colorectal cancer

Colorectal cancer is the third commonest cancer related death in Malaysia. Data from Ministry of Health Malaysia showed an increase in colorectal admission rates from 8.1% in 1987 to 11.9 in 1995 (MOH, 1995). Many researches in genetics including experimental and epidemiological data suggest that colorectal cancer develops from complex interactions between environment factors and inherited susceptibility. However, the current hypothesis is that adenomatous polyps (neoplastic lesion) are the precursor of colorectal cancer based on the concept of adenoma-carcinoma sequence (Leslie *et al,* 2002). In general, gastrointestinal tract has a rapid epithelial cell turnover that continues throughout life. Intestinal cells are exposed to a hostile environment either toxins or carcinogens contained in digested food. Thus gastrointestinal epithelium has become an important tissue in cancer biology.

In general population at risk of colorectal cancer can be subdivided into low, average or high risk groups (Table 1).

Table 1: Population at risk of developing CRC. (Modified from Qureshi, Mohamed Akhtar, et al. "Screening for colorectal cancer in malaysia consensus/clinical practice guidelines." *Malay* 143.54.8: 12-40.

Risk	Population
High risk	Personal history of either polyps or colorectal cancer
	Family history of either polyps or colorectal cancer
	Personal history of inflammatory bowel disease
	Family history of cancer in breast, ovarian or uterine

Average risk	Asymptomatic individual aged above 40 years old
Low risk	Asymptomatic individual aged less 40 years old and other then those listed above.

Clinical presentation of CRC depends on the location of the lesion. Majority tumors are asymptomatic and only discovered on routine screening colonoscopy. Right sided colon lesions occasionally cause hematochezia, but more often occult bleeding causing anemia and fatigue. On the other hand, left sided colon lesions more often present as large bowel obstruction with inability to pass flatus or feces, abdominal pain, distention and altered bowel habit. Constitutional symptoms are common like loss of appetite and loss of weight. Rarely, colon cancer present as perforation with focal or diffused peritonitis or as a fistula with pneumaturia or feculent vaginal discharge. These presentations may be difficult to distinguish from those of diverticulitis. In advanced diseases, metastatic symptoms may be present like jaundice, ascites, shortness of breath or hemoptysis (Figueredo *et al*, 2004).

Diagnosis of colorectal cancer when suspected has to correlate well with history and physical signs. Colonoscopy examinations still the gold standard especially in high risk group. An attempt should be made to identify as well as to obtain tissue biopsy of primary lesions and rule out synchronous lesions (3-5%). There are other alternative screening procedures which are less sensitivity like barium enema or CT-colonoscopy especially when endoscopy procedure is not feasible (Kronberg, 1996). Usage of dye staining during colonoscopy or narrow band imaging system with high definition video had increase yield of diagnosis accuracy. Diagnosis only confirmed by evidence from the tissue histopathology examination.

1.2) Premalignant polyps of the colon and rectum

Colorectal polyp may be defined as a mass that arise from the surface of the intestinal epithelium and project into the intestinal lumen. These lesions may be characterized by their gross appearance as sessile (relatively flat) or pedunculated (with stalk). Premalignant polyps are usually referring to adenomatous polyps. The epithelium of adenomatous polyps generally characterized by pathologist in three common varieties: tubular (with branched, tubular appearing glands), villous (with long frond-like projections of surface epithelium) or tubulovillous (containing both tubular and frond-like epithelium) (Corman, 1998).

Tubular adenomas are the most common polyps of large bowel approximately about 85% of all polyps and typically pedunculated. About 10-15% of polyps are tubulovillous and a slightly lesser number around 5% are villous adenomas, which are most often sessile. All these polyps carry a risk of containing malignant cells. Tubular adenomas usually have a risk of 5% and tubulovillous have a risk of 22% containing malignant cells. Sessile villous polyps have greater risk. Both size and induration of these polyps may reflect cancer risk (Haggitt *et al*, 1985). For example a 4cm sessile villous polyp has 40% risk of cancer, whereas same polyp with induration has a 90% risk.

The basic definition of a polyp given above is usually used to initiate a discussion of benign, or at least minimally invasive, early neoplasm. Although polyps may bleed and can (rarely) cause obstructive symptoms by serving as a lead point for an intussusception, their importance lies in close relationship between benign growths and invasive cancer of large bowel. Adenomas are known precursor to invasive cancer and this is based on the understanding of concept adenoma-carcinoma sequence (Fearon *et al*, 1990).

1.3) Colonoscopy examination

To detect colonic neoplasm, colonoscopy is the gold standard (Alder *et al,* 2006). This is among the commonest gastrointestinal procedure to diagnose colorectal diseases. Colonoscopy is a procedure in which a flexible tube (colonoscope) will be inserted into the anus and then is advanced slowly, under visual control, through the rectum, colon until the caecum which is the first part of the large bowel.

Conventional colonoscope is approximately four feet long, equipped with light source (white light), camera and luminal access for mucosal biopsy or other therapeutic procedures. Thickness is roughly around thickness of a finger. Colonoscopy not just helping a surgeon to visualized colorectal lesions but indeed gives the opportunity for surgeon to get a tissue diagnosis as well before embarked to the major surgical procedure. Generally indications for colonoscopy are for screening or surveillance. Screening refers to a process whereby population at risk is tested by simple inexpensive mean to identify those with disease, with or without symptoms (Qureshi *et al,* 1999). Surveillance in contrast, referring to a process where group of patients at high risk of developing disease process and thus need to undergo entire colon evaluation at regular interval (Qureshi *et al,* 1999).

Patients who are indicated for colonoscopy need a good bowel preparation for clarity in visualization of any colorectal lesions. This can be done by giving patient standard bowel preparation depending on institutions. Patients are given detailed instructions about the cleansing preparation. In general, this consists of drinking a special cleansing solution prior to the examination with food restriction. These instructions should be followed exactly as prescribed or the procedure may be unsatisfactory, and may have to be repeated, or a less accurate alternative

test such as barium enema or CT-colonoscopy may be performed in its place (Mandle *et al,* 1993).

The large randomized control trials on population screening have principally employed colonoscopy as the confirmatory investigation with recourse to double contrast barium enema if total colonoscopy was technically unsuccessful (Mande, 1993, Hardcastle, 1996). Now is the era of minimally invasive surgery, thus detection of early neoplasm is the utmost important. However, in good hand of a surgeon diagnostic accuracy via colonoscopy procedure still promising and evolvement of the endoscopic technology really help in improvement of patient management. There have been multiple attempts to improve diagnostic accuracy and one of them is introduction of NBI system into the gastrointestinal endoscopy, with expectation that it will replace former dye staining (Chiu *et al,* 2007).

1.4) Historical aspect of narrow band imaging

Incidence of gastric cancer in Japan is very much higher than the rest of the world and greater attention has been paid to early diagnosis since the beginning of 1950s when "gastrocamera" was first introduced. Those days, the finding of early gastric cancer was not frequent and most of the lesions were identified either deeply ulcerated or polypoid lesion. Detection of those early cancers was more readily possible after technology evolved in the beginning of 1980s following the results of retrospective studies of rapidly growing advanced cancer (Yoshida *et al,* 1981). With this increased appreciation of the superficial lesions, widespread use of biopsy together with careful scrutiny of the mucosa using dye spray

techniques, early gastric cancer which appear just as faint mucosal irregularity or discoloration came to be the most frequent findings in late 1980s.

Such results were applied also to esophageal and colorectal malignancy, and there has been general acceptance in Japan that early malignancies in the alimentary tract may not appear polypoid or ulcerative (Yoshida *et al,* 1981). The desire to better recognize such malignancies, which may be difficult to distinguish from nonspecific inflammation or trauma, had prompted physician to envision new endoscopy technology that is capable of revealing cancer specific images in the surface structure of the mucosa. It is within this context that the field of narrowband imaging (NBI) was developed as promising way to facilitate the endoscopic diagnosis of early neoplastic and pre-cancerous lesions in the alimentary tract (Gono *et al,* 2004).

NBI is an optical image enhancement technology that enhances the vessels in the surface of mucosa and pattern of the mucosal surface by employing the characteristics of light spectrum (Gono *et al,* 2004). The development of NBI goes back to the study of spectroscopy 18 years ago. The national project "Second Term Comprehensive 10-Year Strategy for Cancer Control" started in 1994. Prof.N.Oyama of Tokyo Institute of Technology and Olympus Medical Systems Corp., started the study in which they intended to digitalize the color and structure of mucosa for establishment of more objective / quantitative pathological diagnosis, hence for better diagnostic yield. They obtained and analyzed more than 2000 samples from esophagus, stomach and colon but the spectrum data was not stable (Yoshida *et al,* 1981).

However, throughout the study, they noticed the specific pattern of spectrum when choosing certain narrow band wavelengths. As a result, when employing a narrow band filter, they found excellent light enhancement deep in mucosa at red light wavelength, shallow mucosal

surface at blue light wavelength and in between levels at green light wavelength (Yoshida *et al*, 1981). Based on the findings, study was continued with research and development group of Olympus and finally found that narrow band blue light wavelength matched the light absorption characteristics of blood hemoglobin and enhanced details of the mucosal surface (Yoshida *et al*, 1984). In December 1999, world's first clinical images using NBI were obtained but it was only black and white making it impractical for clinical applications. The challenge was shortly solved by the introduction of newer improved filters and the development of a prototype incorporating a circuit board exclusively for NBI display.

Since these first NBI pictures were achieved, they actively expanded the study in cooperation with multiple research facilities. As a result of this collaborative investigation, the application of NBI diagnosis expanded rapidly. Starting with the diagnosis of colonic tumor and squamous cell carcinoma of esophagus, the applications of NBI were established in other fields such as superficial carcinoma in pharynx, Barrett's esophagus and adenocarcinoma, stomach cancer and inflammatory bowel disease. Multiple studies were published in these areas; the results have been published in academic society proceedings, research committee reports and clinical papers in peer reviewed journals (Sano *et al*, 2001).

In December 2005, the NBI system became commercially available from Olympus and the technology and diagnosis expanded further, not only in Japan, but also worldwide (Gono *et al*, 2004). Endoscopic diagnosis has been rapidly progressing and now advanced to the era of pathology. This is possible because the imaging technology now allows assessment of three dimensional architecture of tissue by fine examination of the mucosal surface with magnifying endoscopy (Gono *et al*, 2004). In coming years, special light observation such as NBI may

further be able to provide even more information about a targeted lesion, in order to clarify the indication of new cancer therapies.

2) REVIEW OF LITERATURE

2.1) Narrow band imaging

There have been multiple attempts to improve diagnostic accuracy of colonoscopy partly by image improvement and one of them is narrow band imaging (NBI). NBI is a newly developed lighting system within the endoscopic set that can enhances the mucosal surface and micro-vessel. The NBI system utilizes light in short, limited wavelengths that allow visualization of the hemoglobin absorption band, such as that indicative of blood vessels, with adequate contrast via a single touch of the control switch (Gono *et al*, 2004) (Figure 1).

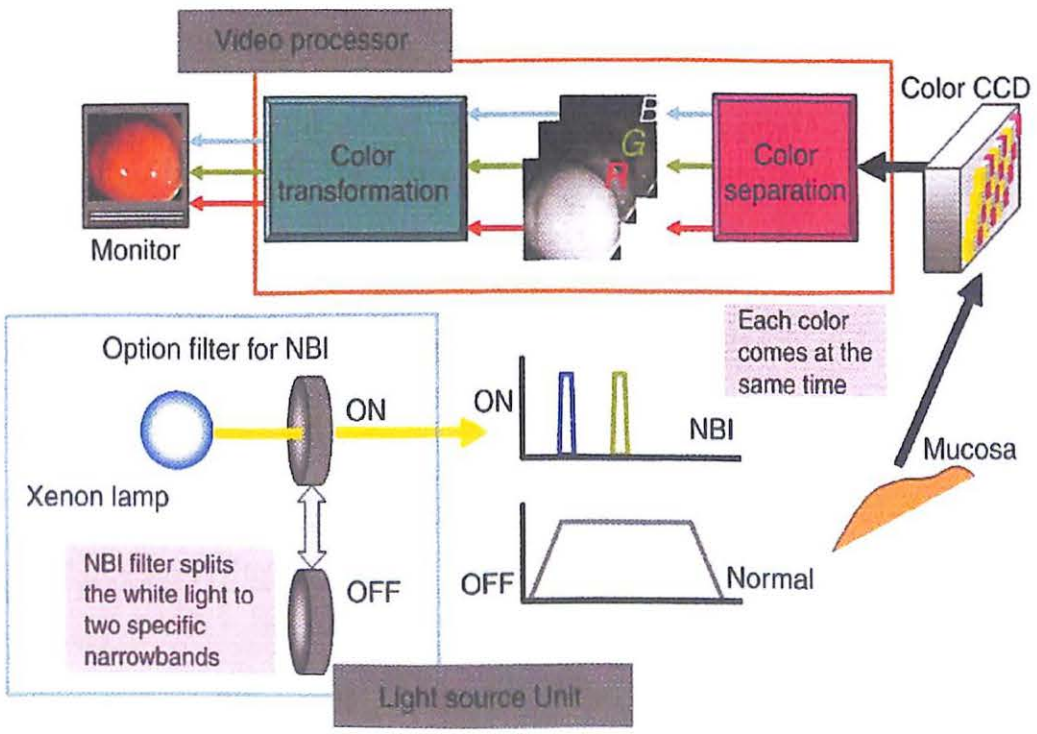

Figure 1: Structure of NBI system. (Reprinted from; Gono *et al.*, 2004. Copyright K. Gono)

In general, our gastro-intestinal tract surfaces are mainly composed of micro blood vessels and mucosa, therefore narrowband illumination can be strongly absorbed by hemoglobin and penetrates surface of the tissue. NBI system uses two discrete band of light, narrow band blue light displays superficial capillary networks; while green light displays subepithelial vessels (Figure 2). Combination of both narrowband light offers an extremely high contrast image of the tissue surface. As a result, capillaries are displayed brown and vein in submucosal are displayed cyan on the monitor (Figure 3). Such enhanced detection of suspicious lesions in the gastrointestinal tract should allow better targeting of biopsy, improved diagnosis and hence lead to more appropriate treatment (Muto *et al,* 2007).

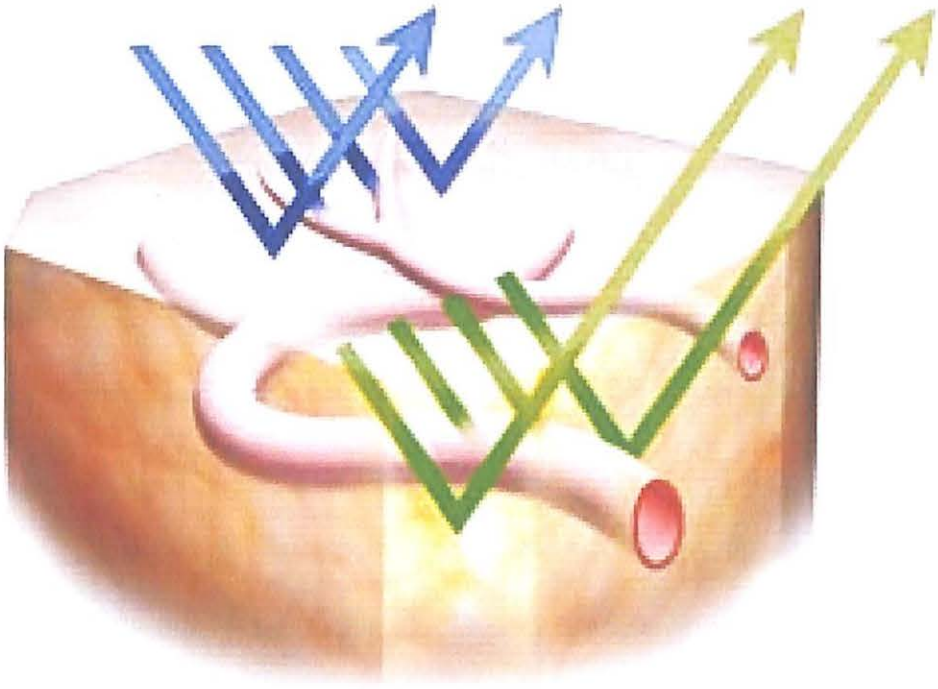

Figure 2: Two different band of light used in NBI system; one blue at 415nm and one green at 540nm.

(Modified_from;http://www.olympus.es/medical/en/medical_systems/applications/urology/bladder/narrow_band_imaging__nbi_/narrow_band_imaging__nbi_.html)

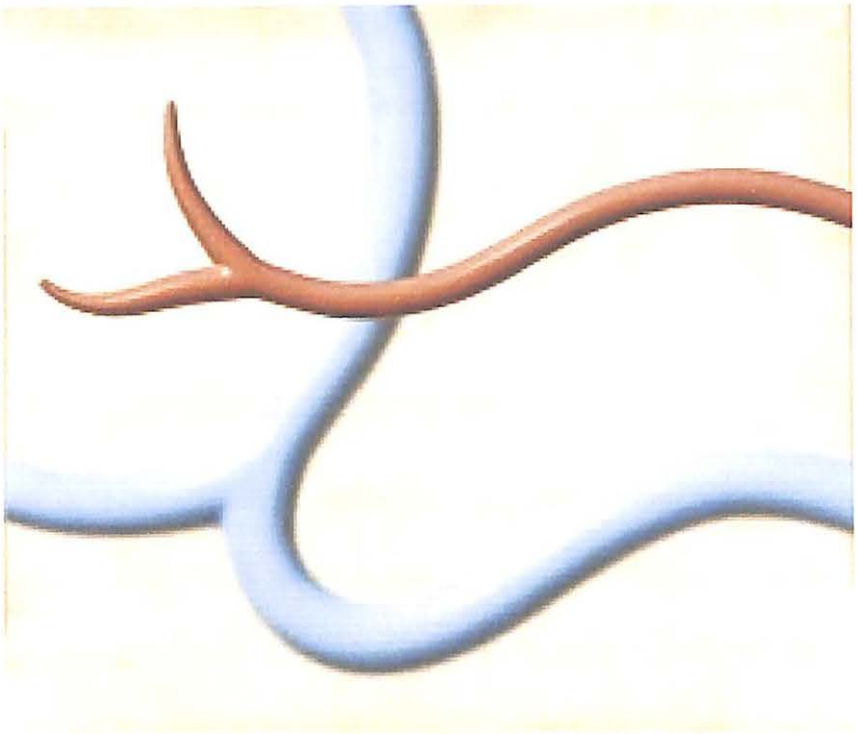

Figure 3: Image NBI on monitor; capillaries on surface displayed brown and vein in the sub surface displayed in cyan.

(Modified_from;http://www.olympus.es/medical/en/medical_systems/applications/urology/bladder/narrow_band_imaging__nbi_/narrow_band_imaging__nbi_.html)

This new NBI system is capable of visualizing neoplastic lesions with real-time image processing during colonoscopy. Chiu *et al*, (2006), reported in a prospective comparative study that the diagnostic accuracy of NBI was significantly higher than that of conventional colonoscopy ($p<0.001$) and was comparable to that chromoendoscopy. Screening colonoscopy has been established as effective means of preventing colorectal cancer in some countries by identification and removal of the precursor lesion which is adenomatous lesion (Kronbrog *et al*, 1996). Therefore introduction of the new NBI system into the gastrointestinal endoscopy may

improve detection and identification of suspicious lesions (Sano *et al*, 2005). All these with the expectation that it will replace dye staining for heightening contrast and therefore highlighting the lesions.

2.2) NBI classification in endoscopy

NBI system in endoscopy has been commercialized since 2005 (Sano *et al*, 2009). Japan was among the pioneer countries who implement it in their colonoscopy examination. This system classified the colonoscopic findings based on the mucosal vascular pattern and pit pattern. Two well-known Japanese classification used until today are Sano-Emura and Kudo's classification. In our study, we used Sano-Emura classification for any suspicious lesions detected during the colonoscopy examination (Sano *et al*, 2009). This classification will be highlighted in detailed on next few paragraphs. Kudo's classification was not used since it may need a higher optical magnification to analyze better the mucosal pit patterns which was not feasible with our present endoscopic set. Other classification includes Paris classification derived from the Japanese classification looking at the endoscopic appearance of superficial neoplasia (intramucosal or submucosal) in the GIT mucosa (Lambert, 2005).

Angiogenesis is a critical transition of premalignant lesion in a hyperproliferative state to the malignant phenotype. Therefore diagnosis based on the angiogenic or vascular morphological changes might be ideal for early detection or diagnosis of neoplasms (Sano *et al*, 2009b). Machida *et al*, (2004) reported in their pilot study that accuracy of endoscopic examination was higher in NBI colonoscopy compared to conventional colonoscopy. The NBI modification provides unique image which emphasizes the capillary pattern as well as the surface structure.

Sano *et al,* (2009) reported that the diagnostic accuracy in NBI endoscopy was similar to that of chromoendoscopy and have described the microvascular classification of colorectal lesion using NBI system (Figure 4).

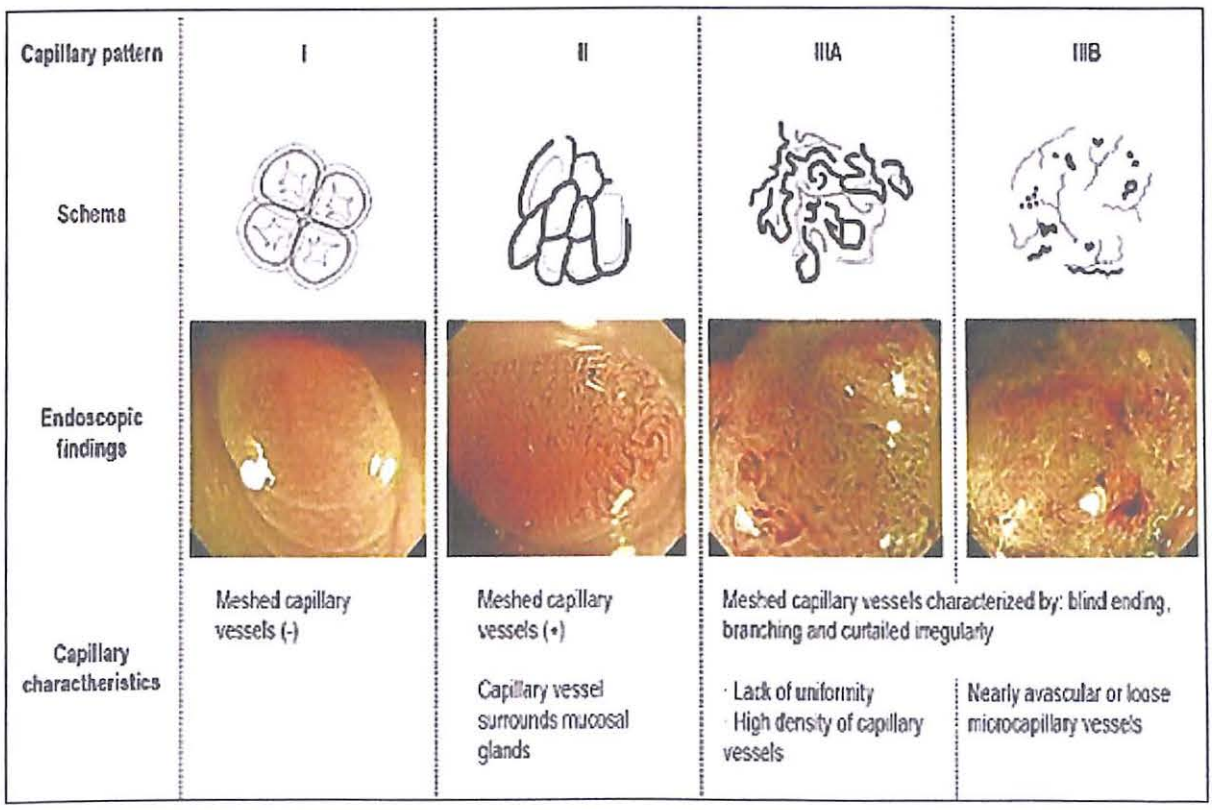

Figure 4: Schematic pictures of capillary patterns in Sano's classification. Capillary pattern I: normal or hyperplastic, II: adenoma, IIIa: high grade dysplasia and IIIb: invasive cancer. Modified from; Uraoka, T., Saito, Y., Ikematsu, H., Yamamoto, K., & Sano, Y. (2011). Sano's capillary pattern classification for narrow-band imaging of early colorectal lesions. *Digestive Endoscopy*, *23*, 112-115.

Machida *et al,* (2004) has outlined the importance of superficial character of colonic lesions which correlate well with the histology findings. Henry *et al,* (2010) reported a sensitivity of 93% and specificity of 88% in differentiating neoplastic and non-neoplastic lesions when analyzing 126 polyps using NBI system when classified according to Sano's classification. Therefore, they concluded that the capillary pattern using NBI colonoscopy without optical

magnification effectively distinguishes neoplastic and non-neoplastic polyps. Higashi *et al,* (2010) demonstrated a significant improvement in diagnostic accuracy using NBI during colonoscopy done by less experienced endoscopist in their prospective study ($p<0.01$).

2.3) Current opinion regarding NBI in colonoscopy

In medicine prevention is always better than cure. In the context of colorectal cancer, many surgeons believe by treating the precursor of colorectal cancer which is adenoma or dysplasia by endoscopic treatment and surveillance endoscopy have shown to decrease the incidence of colorectal cancer based on the adenoma-carcinoma sequence (Corman, 1998, Fearon, 1990). White light or conventional colonoscopy still has the drawbacks of poor performance in some cases with adenoma missing rate about 12% (Kaltenbach *et al,* 2008). Since colonoscopy is the gold standard of diagnosing this lesion, the technologies in endoscopic have evolved from black and white picture until current color high definition camera. Chromoendoscopy has been established in Japan since 1980s, which improves the detection of diminutive and flat colorectal lesions (Kiesslich *et al,* 2001). However, the total colonic dye-spraying technique need a certain degree of technical training that may be necessary for less experienced endoscopists.

To date, even chromoendoscopic had been interchangeably used or replaced in some center by so called newly developed narrow band imaging which is easy by switching the on off button on the endoscope. Sano *et al* was the first to report in 2001 the efficiency of using NBI in gastrointestinal tract. Another prospective study conducted by Sano *et al,* (2009) evaluated the usefullness of meshed capillar vesssels (MCV) observed by NBI magnification for

differrentiating between neoplastic and non-neoplastic colorectal lesions of polyps < 10mm that are the most common and difficult to diagnose accurately. In addition, Horimatsu *et al*, (2006) reported that the appearance of visualized MCVs during magnifying NBI colonoscopy could be used to identify angiogenesis in colorectal low grade adenomas and hyperplastic polyps base on immunohistochemical analysis. These two studies showed the capibility of NBI to differentiate between neoplastic and non-neoplastic lesion using real-time image processing dring colonoscopy without the need for any dye spraying or staning.

Hirata *et al*, (2007) stated that at higher magnification with contrast endoscopy (CE), such as NBI, the visualized surface patterns of the GI mucosa were shown to correlate well with the underlying histology. The development of refine endoscopic technology to enhance contrast of the visualized mucosa is a necessary and welcome step forward. This technology aids the development of a new paradigm of endoscopic diagnosis, rather than pathologic diagnosis which play a central role. Advanced endoscopic technology, when coupled with good science, skilled technique, and elegant art, will permit colonoscopy to continue to be at the forefront in the quest against colorectal neoplasms (Higashi *et al*, 2010).

The enthusiasm to improve the diagnostic characteristics of colonoscopy must be equally matched with effort to improve the efficiancy of colonoscopy therapy. Contrast endoscopy will allow us to achieve these aims by providing us with the tool to diagnose colorectal neoplasms accurately in order to apply the appropiate therapy. Based on the sano's capillary pattern classification, accurate endoscopic diagnosis will, in turn, be useful for medical decision-making of the most appropriate treatment; i.e: no treatment for pattern I, endoscopic treatment for II, IIIa, and surgery for IIIb (Uraoka *et al*, 2011). Perhap in the near future, NBI colonoscopy will become new gold standard in screening and surveilance endoscopy.

2.4) Current Issue in optimal bowel preparation

Adequacy of bowel preparation is important factor to ensure optical clarity during colonoscopy examination to avoid missing any significant pathology that may occur in colon. Currently, the two major classes of bowel preparations are polyethylene glycol solution (PEG) and sodium phosphate formulations (NaP). A study by Qureshi *et al,* (2000) suggested that PEG gut lavage was an effective bowel preparation. They concluded in their study, a statistically significant factors that resulted in poor bowel preparation included age < 20 years and > 60 years ($p<0.0001$), and inpatient ($p<0.0193$). The quality of the preparation is not however uniform and a number of studies report a rate of suboptimal cleansing of 10 – 33%. Other possible cause of poor bowel preparation is the length of time between lavage and examination (Qureshi *et al, 2000).*

A study from Aoun *et al,* (2005) patient who received a PM/AM split dose of 4-L PEG were significantly more likely to receive a preparation rated excellent than patients who received the entire 4-L dose the evening before colonoscopy (44% vs 6%, respectively). Other study compared 4-L PEG with NaP split-dosing regimens and found out not only that NaP yielded a better bowel preparation, but that longer times between doses (6 hours vs 12-24 hours) resulted in improved colon cleansing (presumably due greater fluid intake) (Rostom *et al,* 2006). The most concern factor regarding administration of a single dose entirely the day before colonoscopy is impaired visualization due to residual fecal matter. A study by Frommer, (1997) showed that oral NaP solution taken split dose resulted significantly lower fecal material in the right colon compared with single dose day before procedure (4% vs 30%, $P < 0.001$, respectively).

In a comparative study by Khan *et al,* (2008), it was reported that patients who took a split-dose of purgative were more often satisfied with the bowel cleansing than those who took a single-dose of purgative (63% vs 46%, P <0.0001; respectively). Regardless of any type of solution used, the aim of bowel preparation is to facilitate successful complete colonoscopy. In a retrospective study by Lebwohl *et al,* in 2011, although minority of patient underwent colonoscopy with suboptimal bowel preparation but the adenoma missing rates were high (up to 42%). This suggest suboptimal bowel preparation substantially decreases colonoscopy effectiveness. It is well documented that a good bowel preparation before colonoscopy improves the rate of detection of colonic polyps (Burke, 2007 and Froehlich *et al,* 2005)

2.5) NBI colonoscopy in clinical study

Various study of NBI has been done in assessment of mucosal lesion. Any mucosal tissues from different organ are potential of undergo NBI assessment based on many ongoing study in mucosal assessment. In context of colorectal lesions several studies have shown the benefit of NBI in differentiating neoplastic and neoplastic lesions. Wada *et al,* (2010) did a study to clarify the value of the NBI system in tissue characterization and differential diagnosis. A total of 617 lesions was assessed by NBI colposcopy system and they could differentiate neoplastic and non-neoplastic with sensitivity of 90.9% and specificity of 97.1%. They concluded that NBI system was valuable for distinguishing between neoplastic and non-neoplastic lesions, as well as between cancers and adenomas. Based on the study, the vascular patterns analysis can also be a promising tool for determining treatment selection, either endoscopy or surgery.

Another study done by Higashi *et al,* (2010) on NBI system with the objective of evaluating diagnostic skills of less-experienced endoscopists (LEE) group to differentiate diminutive (≤5mm) colorectal polyp after expanded training program. It involved 32 patients and 44 colorectal polyps. The results revealed that the diagnostic accuracy was significantly higher after expanded training in LEE group especially when using high magnification NBI and it is equivalent to highly-experienced endoscopist. Rogart *et al,* (2008) conducted a prospective observational study to compare white light with NBI for differentiation of colorectal polyps and to assess the learning curve. A total number of 265 polyps were found and assessed. Their results showed 80% diagnostic accuracy when using NBI and 69% accuracy when using white light to diagnosing adenoma.

In the era of minimally invasive surgery, detection of precancerous or early cancer is always of utmost importance for surgeon. Chromoendoscopy has been established well as adjunct to colonoscopy to increase sensitivity and now there are growing evidences of NBI system which can produce equivalent diagnostic accuracy. A meta-analysis done by East *et al.* (2008b) when compared between chromoendoscopy and NBI for the *In Vivo* diagnosis of neoplasia showed both to be equivalent in diagnostic precision and highly accurate. Twenty studies were identified with total of 10 556 patients and 9 471 biopsies were included in the analysis. Overall, sensitivity of chromoendoscopy was 0.96 (95% CI 0.95-0.96), specificity was 0.77 (95% CI 0.75-0.79) and sensitivity of NBI was 0.93 (95% CI 0.91-0.95), specificity was 0.84 (95% CI 0.78-0.89). NBI, a push-button technology using a simple microvascular based classification system, is likely to replace chromoendoscopy for lesion assessment, perhaps even replacing histopathology for small, low risk lesions.

Similar study done by Tischendorf *et al.*, (2007) reported that NBI in combination with magnifying endoscopy is a promising tool for the differentiation of neoplastic from non-neoplastic colorectal polyps in vivo without the necessity of using dye. Using vascular patterns for differentiation, NBI with magnification correctly identified 93.7 % of neoplastic polyps and 89.2 % of non-neoplastic colorectal lesions, whereas magnifying chromoendoscopy had a specificity of 95 % but a sensitivity of only 66.7 %. With the growing interest of improving diagnostic accuracy many center have utilized either conventional chromoendoscopy or digital chromoendoscopy which is also known as NBI endoscopy system. Despite various methods of contrast enhancement for clarity of mucosal display and assessment, the final aim is still for diagnostic precision as to detect early and probably prevention can be done before sinister complication occurred.

2.6) Advantages of NBI system in endoscopy

In addition to its diagnostic accuracy, NBI also showed many other beneficial advantages not just within the context of detecting colorectal lesions per say but to other subspecialties as well. Imaizumi *et al*, (2012) conducted case series study using NBI in surgical treatment of laryngeal papillomatosis showed that the border between normal mucosa and the papilloma could be clearly identified, allowing precise excision and without further recurrence. Hayashi *et al*, (2010) had done a study on 46 patients with primary unknown cervical lymphnodes metastasis that showed histologically squamous cell carcinoma and found 26 suspicious lesions during NBI of upper endoscopy that not visible with conventional white light scope. From 26 lesions biopsied, 16 was histologically squamous cell cancer, 10 lesions were located in the

hypopharynx and the remaining six lesions were located in the oropharynx. Therefore they concluded that NBI endoscopy can detect possible primary cancer in patients with primary unknown cervical lymphnodes metastasis.

A pilot study by Baruetto & Audlin, (2008) on the use of NBI for identification of endometriosis during pelviscopy (laparoscope) showed 14 out of 20 patients had lesions identified with NBI that were not identified with visible light. A total number of 38 biopsies were taken using NBI and 20(53%) of them were identified histologically as endometriosis. They concluded NBI in laparoscopic procedure is an effective tool for evaluating and identifying endometriosis implants that are not visible with white light endoscopy. A prospective randomized trial by Naselli *et al,* (2010) using NBI during transurethral resection (TUR) of non-muscle invasive bladder cancer had proven to reduce recurrence by 10% at 1 year. The study populations composed of 148 patients randomized to NBI TUR (76 cases) and white light (WL) TUR (72 cases). Results showed that the 1-yr recurrence-risk was 25 of 76 patients (32.9%) in the NBI and 37 of 72 patients (51.4%) in the WL group.

The use of NBI system also has been established in detecting upper gastrointestinal pathology. For colorectal lesions, Kudo and Sano's classification has begun to be widely adopted by many endoscopists because it appears valuable in the histological prediction from the observation of pit patterns or capillary patterns (Kudo, 1996 & Sano, 2001). The were numerous studies from investigators around the world and especially in some Asian countries by using NBI system in upper endoscopy. Despite that, there is still no consistent classification diagnosis system for magnifying endoscopy (ME)-NBI before the endoscopic removal of esophageal and gastric lesions; each medical institution tends to adopt its own classification. A review article by Kosaka *et al,* (2012) on the use of magnifying endoscopy with NBI system in upper

gastroenterology have shown to be a good adjunct for identifying and demarcating residual/local recurrent gastric neoplasms after endoscopic treatment. The histopathological diagnosis of the location and demarcation of all neoplasms corresponded to endoscopic findings.

As a rule of thumb, minimally invasive surgery is an ideal approach for precancerous or early cancer. Therefore detection modalities need to be improved and should be more vigilant even during screening procedure so that detection could be better. Earlier prospective pilot study by Uraoka *et al*, (2010) demonstrated that NBI colonoscopy significantly improved detection of flat lesions, which are more likely to be missed, particularly on the right side of the colon. Anagnostopoulos *et al.* (2007) reported that high resolution magnification endoscopy with NBI allows clear visualisation of microstructural and microvascular patterns within Barrett's oesophagus, and allows targeted biopsy with a high yield of specialized intestinal metaplasia and high grade dysplasia. The positive results of clinical test in colonoscopy and esophagoscopy indicated that NBI will be useful as a supporting method for observation of the endoscopic findings for early cancer (Gono *et al*, 2004). Based on the literature review, clinical importance of the NBI may give greater advantages for screening tool once learning curve of utilizing the new imaging technique has been completely achieved.

2.7) NBI in screening and surveillance colonoscopy

In the context of screening colonoscopy, they are looking at the ability of the endoscopy to detect lesion (Paggi *et al*, 2009). Technology evolved rapidly with aim of better detection. Studies on the detectability of colorectal neoplastic lesions using NBI have been reported in East and Western countries. Some published opinions and conclusions remain controversial at present

time (Paggi, 2009 & East, 2008). A prospective pilot study (Uraoka *et al*, 2010) demonstrated that NBI colonoscopy significantly improved detections of flat lesions, which are more likely to be missed, particularly in right sided of the colon. However, Adler *et al* in 2009 reported in their large randomized trial on NBI versus white light HD for screening colonoscopy, NBI could not show any objective advantage over white light.

To detect small lesions during screening colonoscopy is rather challenging. To date, many attempts have been made by endoscopist to improve detection ability. Even then until now no other method can replace the gold standard of mucosal biopsy. However there were several data which showed NBI, a novel endoscopic technology that can highlights superficial mucosal capillaries and improves contrast for adenomas which may be suitable for screening colonoscopy (Sano, 2001 & Machida, 2004). Paggi *et al,* (2009) reported in their randomized control trial that the routine use of NBI in screening colonoscopy did not increase the adenoma detection rate but it seems to improve the detection of flat adenomas. They found the flat adenoma detection rates were 21.4% and 9.3% in the NBI and WLE groups, respectively (p=0.019).

NBI usage in colonoscopy not just limited to screening purposes. The usage in surveillance colonoscopy is increasing in trend. There are upcoming data that show the advantages of it during surveillance procedures. Colonoscopy surveillance for hereditary non-polyposis colorectal cancer (HNPCC) reduces death rates, but early interval cancer still occur probably due to missed small, aggressive adenomas (East *et al*, 2008a). They reported in their study that NBI usage for patients undergoing HNPCC surveillance appears to improve adenoma detection, particularly those with a flat morphology. They concluded that NBI may help to reduce interval cancer rates.

Since surveillance colonoscopy referring to evaluation of patient at high risk of developing disease process, therefore entire colon need to be assessed. It is a standard practice to have annual follow-up surveillance examination to detect additional new adenomas as well as missed synchronous adenomas (East *et al*, 2008a). This is where good colonoscopy system is needed as well as the additional detection ability. Matsumoto *et al*, (2009) reported that the detection of diminutive colorectal neoplasia in Familial Adenomatous Polyposis were significantly higher in NBI than WLE ($p=0.04$). In another pilot study they reported that their surveillance colonoscopy of ulcerative colitis patients were able to show distinguish features for the identification dysplasia (Matsumoto *et al*, 2007). Probably with the upcoming data of contrast enhanced colonoscopy, we need more additional studies with refine technique so that NBI have the important impact in screening as well as for surveillance colonoscopy.

3.0) OBJECTIVES OF STUDY

3.1) General Objective

To explore the diagnostic validity of NBI colonoscopy as well as associated factors related to the neoplastic and non-neoplastic colorectal lesions.

3.2) Specific Objective

1. To identify the sensitivity, specificity and discriminative validity of NBI colonoscopy in detection of neoplastic and non-neoplastic colorectal lesions as compared to HPE results.

2. To determine association between bowel preparation and NBI results.

3. To determine association between age and HPE outcomes.

4. To determine association between site of lesions and HPE outcomes

4) MATERIAL AND METHODS

4.1) Study design

This is a prospective diagnostic study and was carried out at endoscopic unit of Universiti Sains Malaysia, Kubang Kerian by surgical team after approval by the University's Ethical Committee from January 2012 until October 2012.

4.2) Inclusion and exclusion criteria

All adult patients that undergo colonoscopic examination and detected to have suspicious lesions will be considered for enrollment into this study. No randomization will be made. Exclusion criteria consist of the followings:

1. Known case of inflammatory bowel disease
2. Surveillance colonscopy
3. No HPE results
4. Scope without NBI.
5. Poor bowel preparation

4.3) NBI-colonoscopy procedure

A total of one hundred patients that fulfilled inclusion criteria were included in this study and only one of the most suspicious lesions in each patient (n=100) were analyzed using our Olympus Endoscopic Video System (EXERA-II) (Figure 5). They came mainly for screening