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Review

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Introduction

Image-enhanced endoscopies (IEEs), including topical dyes,[1-3] optical filtering[4] and ultra-magnification,[5] allow for various analyses of gastrointestinal lesions, such as the analysis of minute structures and epithelial capillaries on the mucosal surface, and the intensity of fluorescence emitted from intestinal tissues. These novel technologies provide attractive alternatives for identifying the abnormalities in the size, density and shape of crypts and vessels in either the normal intestine or a tumor lesion.

Colorectal cancers arise from the progressive accumulation of genetic and epigenetic alterations. In this sequential process, normal epithelia are believed to initially turn into adenomas, accumulate additional gene alterations, and then transform into carcinomas[6, 7]. Indeed, eliminating all adenomas helps to reduce the incidence of colon cancers[8]. Therefore, adenomas, particularly high grade adenomas which are classified into category 4 or 5.1 according to the Vienna classification[9], are indicated for curable resection.

While colonoscopy is an accepted method for colorectal screening worldwide[10-14], endoscopists miss from 2-6% of advanced adenomas (10 mm or greater in size) or colon cancer, and up to 26-30% of all adenomas when using standard white-light colonoscopy (WLE)[15-18]. The reasons that adenomatous polyps or cancer are missed are thought to be

related to the location of the lesions or the individual skills of the endoscopists[19, 20] as well as the image contrast of neoplasms compared to that of the normal mucosa. IEEs, which can enhance the endoscopic findings of the colon lesions, have the potential to improve the detection and differentiation of colon neoplasms. However, many clinical trials testing the usefulness of IEEs for the diagnosis of colon neoplasms have shown controversial results[21, 22]. The discrepancies among these outcomes of the clinical trials appear to be caused by the technical limitations of each technology as well as variability in the diagnostic skill of the participants in these studies. Many endoscopists have different skill levels with regard to their operation of the colonoscope and judging the endoscopic findings. Therefore, two factors related to the usefulness of these novel technologies need to be evaluated; at which step(s) is that technology applicable for the diagnosis of colon neoplasms (detection, differentiation or staging) and by what level(s) of endoscopists (experts or less-experienced endoscopists) can the technology be employed. The former is associated with the merits and limitations of each technology, and the latter concerns the experience of the endoscopists and the accuracy and reproducibility of the examination (inter and intra-observer agreement). The present review describes the usefulness of each technology with regard to diagnosing colon neoplasms. We searched the pertinent literature with Pubmed using the following terms:

image-enhanced, chromoendoscopy, narrow band imaging, autofluorescence imaging, high-definition, high-resolution and trimodal. All unrelated publications and case reports were excluded and the remaining citations were divided into three types: those that focused on the detection of colon neoplasms (Table 1), those that focused on the characterization of colon neoplasms (Table 2) and those that focused on the inter- and intra-observer agreement of each procedure (Table 3).

Chromoendoscopy

Detection (Table 1)

Chromoendoscopy with non-absorbed indigo carmine or absorbed methylene blue is a relatively classical technique, but still one of the best procedures for enhancing the margin and surface pattern of the lesions. Pan-chromoendoscopy in the colon improves the detection of adenomatous polyps in some studies[1, 2, 23-29]. Brooker JC, et al. reported that the proportion of patients with at least 1 adenoma did not differ between those diagnosed by chromoendoscopy and standard definition white light endoscopy (SD-WL; 33% vs. 25%) while significantly more diminutive adenomas (<5 mm) were detected proximal to the sigmoid colon in the dye-spray group (0.72 vs. 0.27/patient)[23]. Hurlstone DP, et al. showed the total number of adenomatous lesions, and the proportion of patients with at least 1 polyp or more than 2 adenomas to be significantly

higher in chromoendoscopy group than those in SD-WL group (66% vs. 33%, 65% vs. 42% and 10% vs. 3%, respectively)[24].

Lecomte T, et al. showed in a tandem study of 36 patients with hereditary nonpolyposis colorectal cancer syndrome that chromoendoscopy detected an additional 11 adenomas after high definition white light endoscopy (HD-WL) detected 7 adenomas and significantly increased the detection rate of adenomas in the proximal colon (9% vs. 3%)[25]. Three subsequent studies revealed similar results that chromoendoscopy increased the detection rate of small (less than 5 mm) or flat adenomas, but not overall adenomas[26-28]. A recent large study by Pohl J, et al. demonstrated that the proportion of patients with at least one adenoma was significantly higher in the pan-chromoendoscopy group (46.2%) than in the control group (36.3%)[29]. Targeted chromoendoscopy also facilitates the detection of colorectal neoplasms, particularly the flat and depressed type[3, 30, 31].

Concerning inflammatory bowel diseases, several trials have shown that the detection of flat or circumscribed colitis-associated neoplasms was enhanced in patients with long-standing ulcerative colitis[32-36]. Kiesslich R, et al. showed in their randomized-controlled study that the detection rate of dysplasia by targeted biopsies under pan-chromoendoscopy was superior to that of random biopsies under

conventional colonoscopy (32/84 vs. 10/81 patients)[32]. Hurlstone DP, et al. showed in their case-control study that significantly more intraepithelial neoplastic lesions were detected in the magnification chromoendoscopy group in comparison to the controls (69 vs. 24 from 350 patients)[33]. Rutter MD et al. and Marion JF, et al. subsequently revealed usefulness of chromoendoscopy for detection of dysplasia in prospective studies[34, 36]. A statement by Crohn's and Colitis Foundation of America Colon Cancer in the IBD Study Group for the surveillance of ulcerative colitis endorses that the use of chromoendoscopy for the detection of dysplasia[37]. Chromoendoscopy is therefore beneficial for improving the detection rate of either sporadic or colitis-associated neoplasms.

Characterization (Table 2)

Chromoendoscopy with magnification is capable of differentiating adenomas from non-neoplastic polyps by analyzing the surface structure of crypt-openings. Kudo et al. classified the pattern of the crypt openings (pit patterns) into five categories (type I to V) and showed the association between each category and histological features[38-40]. Kudo's classification states that type I and II correspond to non-neoplastic polyps, while type III, IV and V correspond to adenoma or carcinoma. Furthermore, they showed that

neoplasms with the type V pattern have a high risk of a submucosal invasion, which is contraindicative for endoscopic resection. Machida H, et al. showed in their retrospective study that the accuracy of chromoendoscopy for discriminating colon adenoma from hyperplasia (accuracy, 93.4%; sensitivity, 100%; specificity, 75%) was significantly higher than that of SD-WL (accuracy, 79.1%; sensitivity, 83%; specificity, 44%)[41]. Chiu HM, et al. showed the accuracy, sensitivity and specificity of chromoendoscopy in differentiating colon adenomas from hyperplasias to be 91.1%, 91.3% and 90.5% vs. 68.3%, 62.1% and 85.4%, respectively, for SD-WL in one participant and 92.2%, 97.2% and 74.4% vs. 67.2%, 65.2% and 74.4%, respectively, for SD-WL in another participant.[42]. Taken together, chromoendoscopy is therefore considered to be superior to SD-WL for the differentiation of colon polyps while a study directly comparing chromoendoscopy to HD-WL for differentiating colon polyps has not been conducted.

Conversely, concerning the diagnosis of the depth of invasion, Kudo et al. showed that the disappearance of pits on the tumor surface was a key finding associated with submucosal invasion[38, 43], Matsuda et al subsequently showed the high diagnostic accuracy of chromoendoscopy for the prediction of massive submucosal invasion based on the Kudo's classification (sensitivity, 85.6%; specificity, 99.4%; positive predictive

value, 86.5%; negative predictive value, 99.4%; accuracy, 98.8%) from their non-comparative study [44]. Further comparative studies of conventional colonoscopy and chromoendoscopy are therefore necessary to confirm whether chromoendoscopy is useful for predicting the depth of invasion of colon cancer (T staging).

Endoscopists (Table 3)

The evaluation of chromoendoscopic findings is based on the morphological features, and therefore both objectivity and reproducibility are other important factors for assessing the significance of chromoendoscopy. Huang et al. showed a good-to-excellent inter and intra-observer agreement (kappa values (k-value) = 0.716 and 0.810, respectively) for assessing pit patterns using the Kudo's classification, in a study conducted by experienced endoscopists in a Japanese single center[45]. In contrast, East et al. found a fair inter-observer agreement for the Kudo pit pattern (k-value 0.25) in the assessment of 32 photographs of colon polyps (describing both excellent and poor clarity of pit pattern) by two experienced endoscopists, one Japanese trained and the other European trained[46, 47]. Recent our investigation of inter-observer agreement for assessing chromoendoscopic findings revealed a moderate kappa value in the specialist group (0.54) and the resident group (0.47)[47] using photographs selected by a specialist

based on the clarity of the images. The huge discrepancy of the results among these studies is thought to be caused by the selection bias of the photographs and the diverse diagnostic skills of the participants. Using chromoendoscopy in daily practice is associated with other disadvantages such as labor intensity and time consumption[48]. In this respect, chromoendoscopy is inferior to other IEEs such as NBI and AFI. Further multicenter trials are therefore needed to clarify the usefulness of chromoendoscopy for the detection and characterization of colon neoplasms by general endoscopists.

Narrow band imaging

Detection (Table 1)

Narrow-band imaging (NBI) is a new technology in which spectral features are modified by narrowing the bandwidth of spectral transmittance with optical filters. NBI can assess the capillary architecture and microvessels at the touch of a button[49]. Hirata et al. have shown a good correlation between chromoendoscopy and NBI[50]. Six large studies following the report have been conducted[51-56]. Three studies revealed that NBI improved the detection rate of colon adenoma in comparison to HD-WL[51-53]. The additional effect of NBI for detecting colon adenoma was 27–40%[51, 52]. In particular, NBI increased the detection rate of diminutive adenomas[53]. In contrast, another three

studies showed no improvement of the detection rate of adenoma by NBI[54-56]. In the study by Adler et al.[55], while the detection rate of patients with adenoma(s) by NBI was not changed between the initial and late phases, the detection rate in late phase by HD-WL was significantly improved from that in the initial phase. This suggests that a learning effect from NBI improved the detection rate by HD-WL. Conversely, Inoue's study[53] showed a high detection rate for adenoma by NBI, particularly for diminutive adenoma (less than 5 mm). These six studies were all performed by experienced endoscopists, however, the term 'experienced' was arbitrarily defined in each study, which is a potential cause of the controversial results.

Pellisé M, et al. recently showed in their prospective randomized study that NBI provided a similar true-positive rate and an inferior false-positive rate for the detection of dysplasia in patients with long-standing inflammatory bowel diseases. However, the miss rate with NBI tended to be higher than that with chromoendoscopy (31.8% vs. 13.6%), and thus they did not recommend NBI as a standard technique[57]. Further studies of tumor detection, focusing on the learning effect and size of the lesions, in the sporadic as well as colitis-related neoplasms, with less bias by the participants' experiences will indicate the true significance of NBI for the detection of colon neoplasms.

Characterization (Table 2)

Colon adenoma and cancer frequently induce tumor vessels around the lesions along with tumor progression. Therefore, evaluating any abnormalities of the capillary architecture and microvessels by NBI is considered to be a reasonable diagnostic modality for characterizing colon neoplasms. Several classification systems based on either the mucosal (pit pattern) or vascular pattern including abnormal shape and/or the density of vessels are shown for differentiating colon neoplasms from non-neoplastic polyps with NBI. Sixteen studies have so far been reported regarding the use of NBI for characterizing colon lesions[41, 42, 46, 47, 50, 51, 58-67]. These studies and a meta-analysis[68] indicated that the accuracies of NBI, SD-WL, HD-WL and chromoendoscopy were 62-93.4%, 66.5-81.8%, 65-75.9% and 69-95.6%, respectively. NBI appears to be superior to SD-WL, and equal to chromoendoscopy, but its efficacy compared to HD-WL is still controversial. In addition, it has been reported that NBI findings are also useful for evaluating the depth of invasion of colon cancer based on the density and irregularity of the vascular structure[62, 64, 65]. Wada et al. found that irregular and sparse patterns of vascular formation were key findings related to the submucosal invasion, and the sensitivity was 100%, the specificity was 95.8%, and the accuracy rate was

96.1% for detecting invasion when the evaluation was based on this key finding. NBI is therefore helpful to decide the staging of colon cancer (T staging)[65]. However, the predictive ability of the invasion depth by NBI based on either the capillary architecture or pit pattern has not yet been compared with that of chromoendoscopy in a prospective manner. Further studies are needed to elucidate whether NBI possesses the ability to predict the depth of invasion in comparison to conventional methods, including chromoendoscopy.

In contrast to the above study, two observational studies for diagnosing dysplasia in patients with ulcerative colitis were conducted[69, 70]. Matsumoto et al. showed that the tortuous pattern, as determined by NBI colonoscopy, may indicate the presence of dysplasia during surveillance for UC[69]. FJ Van den Broek, et al. showed the usefulness of the pit pattern for the diagnosis of dysplasia in UC[70]. NBI is therefore thought to be a feasible procedure to characterize either sporadic or colitis-associated neoplasms.

Endoscopists (Table 3)

The NBI image is evaluated based on complex findings such as the various irregularities of the structures of numerous capillaries and microvessels. This suggests that the evaluation of NBI image depends on the ability of each endoscopist to analyze

the complex images. Indeed, studies of the inter-observer agreement of NBI on the diagnosis of colon neoplasms have shown controversial results. Chiu HM et al. showed an excellent inter-observer agreement (k=0.86) using 10 images of either chromoendoscopy or NBI assessed by two experienced endoscopists[42]. East et al. showed a moderate-to-good inter-observer agreement for the Kudo pit pattern (k-value 0.48) and vascular pattern intensity (k-value 0.64) in the assessment of 32 polyps by one Japanese and one European endoscopists[46]. Rastogi et al. recently showed no significant difference in the kappa value for inter-observer prediction for the polyp type on NBI between experienced and less-experienced endoscopists, in whom none of the endoscopists had any prior experience with NBI colonoscopy[71]. Our prospective study revealed a moderate inter-observer agreement of NBI for differentiating colon neoplasms from hyperplastic polyps by specialists (k-value 0.54) and a slightly lower value in residents (k-value 0.49)[47]. Higashi et al. showed in their prospective study that the diagnostic accuracy and inter-observer agreement for the differentiation of colon polyps based on Sano and Kudo classification systems using NBI with high magnification improved in less-experienced endoscopist group (who had performed colonoscopies for more than five years but had never used NBI) after expanded training (diagnostic accuracy: from 73% to 90%; k-value: from 0.49 to 0.79), which became

equivalent to that of the highly-experienced endoscopists group (who had routinely used magnification colonoscopy with NBI for more than five years) (k-value 0.85), but not in the non-experienced endoscopist group (with no prior endoscopy experience) (diagnostic accuracy: from 63% to 74%; k-value: from 0.16 to 0.39)[72]. Furthermore, several prospective observational single-centre studies have shown that NBI training sessions, even over a very short-time session (20 minutes), are effective for physicians with various levels of endoscopic experience in differentiating colon neoplasms from hyperplastic polyps by NBI[73, 74]. Therefore, it might also be beneficial for improving the diagnostic skills of less-experienced endoscopists by the establishment of appropriate training programs.

Autofluorescence imaging

Detection (Table 1)

AFI is a novel endoscopic procedure that can capture fluorescence (500–630 nm) emitted from intestinal tissues after delivering an excitation light source of 390–470 nm to the tissue surface. The fluorescence light is transformed to green and the reflected light is transformed to red and blue, proportionally to their intensities, and then the images composed of various intensities of each color are displayed on the monitor in

real-time[75, 76]. The presence of intestinal lesions including colon neoplasms alters the autofluorescence because of changes in either the endogenous fluorophores themselves or a reduction in the permeability of fluorescence emitted from the fluorophores. As a result, a color change is observed in the respective lesions from green to magenta in the AFI images **(Figure 1)**.

The significance of AFI in detecting colon neoplasms remains controversial. While a small study conducted by Matsuda et al. shows an improvement of the polyp detection rate in the right-sided colon in comparison to HD-WL,[76] other investigations revealed AFI to be less useful in detecting colon neoplasms due to the low specificity (35 – 37%)[63, 77]. The specificity of AFI for detecting colon neoplasms is not expected to be sufficient because AFI detects the reduction of fluorescence emitted from intestinal tissue, which is not specific for colon neoplasms,. A poor resolution and insufficient tracking ability are thought to be other limitations associated with AFI. Further improvements in the AFI instruments are therefore needed to improve neoplasm detection in the future.

Characterization (Table 2)

AFI images reflect the changes of endogenous fluorophores themselves as well as the

reduced permeability of fluorescence emitted from the fluorophores. An AFI image is mainly influenced by mucosal and submucosal changes due to intestinal disorders because most of fluorophores captured by AFI are in the submucosal layer of the intestinal wall. AFI is thought to be one useful procedure to differentiate colon neoplasms from non-neoplastic polyps, assess the dysplastic grade of colon adenoma and predict the invasion depth of colon cancer (T staging) **(Figure 2)**.

While some reports initially showed no major improvement in the diagnostic accuracy for discriminating colon neoplasms from non-neoplastic polyps by AFI[63, 78], Van den Broek, et al. showed that AFI improved the diagnostic accuracy for differentiating colon polyps, particularly for non-experienced endoscopists (from 57 to 77%)[66]. Our prospective study demonstrated that AFI helps to differentiate colon neoplasms from hyperplastic polyp, particularly in the resident group (from 69.1 to 89.7%)[47], and subsequently, identified that the fluorescence intensity of AFI image is inversely proportional to the dysplastic grade of colon adenoma[79]. This preliminary investigation suggests that the histological changes of colon neoplasms, including a high density of tumor crypts and cells with an enlargement of nucleus, might disturb the permeability of fluorescence emitted from intestinal tissue (data not shown). Although the usefulness of AFI in characterizing colon neoplasms remains controversial, AFI is

thought to be a useful procedure for characterizing colon neoplasms by less-experienced endoscopists.

Quantifying the intensity of the magenta color is a potential method to objectively evaluate the characterization of colon neoplasms since the assessment of AFI images is dependent on color intensity. Our recent studies calculated the fluorescence index (F index), the intensity of the magenta color adjusted by the intensity of the green color on AFI images, using an image-analytical software package. These studies showed the F index to be a useful marker for discriminating lymphomas from benign lymphoid hyperplasias[80] and predicting the dysplastic grade of colon adenomas[79, 81].

Endoscopists (Table 3)

The evaluation of AFI images is simply based on the intensity of magenta color, regardless of the complex morphological findings. Van den Broek FJ, et al. reported moderate inter-observer agreement for AFI (k-value 0.58) and poor for NBI in non-experienced endoscopists (k-value 0.33) while experienced endoscopist had excellent inter-observer agreement for NBI (k-value 0.77), but fair for AFI (k-value 0.33)[66]. Our prospective study also showed a moderate inter-observer agreement for AFI in either specialists or residents (k-value 0.54 each) and the diagnostic accuracy of AFI in discriminating colon neoplasms from non-neoplastic polyps was particularly

improved in the resident group[47]. AFI appears to be useful to differentiate colon neoplasms from non-neoplastic polyps for less-experienced endoscopists, but the usefulness is questionable for high-experienced endoscopists. This is because AFI simply provides the features of the lesions as intensities of color, which can be easily judged even by less-experienced endoscopists.

Conclusions and future perspectives

The review attempted to assess the role of image enhancing technologies in the diagnosis of colonic neoplasms. Chromoendoscopy has a high value for detecting and characterizing colon neoplasms. However, the procedure is labor intensive and time consuming. NBI is easy to perform and useful for detecting and characterizing colon neoplasms because the detection rate and the diagnostic accuracy for differentiating colon polyps of NBI are equal or superior to either SD or HD-WL, and therefore are comparable with those for chromoendoscopy. AFI has the potential to improve the diagnostic ability for the detection and characterization of colon neoplasms with non- or less-experienced endoscopists,

Each procedure possesses different characteristics for the diagnosis of colon

neoplasms. Chromoendoscopy can detect the shape of crypt openings, so that the technology can evaluate the irregularity of the crypt structure, which is an important histological marker for diagnosing colon adenoma and cancer. AFI reflects the cell density and nucleus enlargement, thus predicting the dysplastic grade of tumor cells. In contrast, NBI can assess the abnormality of vessel and capillary structures, which is frequently observed around colon neoplasms as tumor vessels. Taken together, the combination of these three technologies may thus make it possible to improve the prediction of histological findings distinctive for colon neoplasms.

Recently, novel endoscopic technologies, including optical biopsies and functional imaging, have been newly developed. Quantification of fluorescence intensity or description of tumor-related abnormalities, such as an increased accumulation of nicotinamide adenine dinucleotide, by the multi-wavelength excitation method might mark a new era in this field[77]. Confocal endomicroscopy, which can directly observe the histological findings in real-time, is regarded to be a powerful option to characterize colon neoplasms[35, 82-90]. Further prospective studies with the combination of IEEs or such new technologies are needed to establish the optimal strategy for diagnosing colon neoplasms.

The most important aims of cancer treatment are to increase the survival rate and to

improve the quality of life of the cancer patients, while achieving an improved cost-effectiveness is also important. To date, the fecal occult blood test is the only examination which has been demonstrated to be an effective procedure for decreasing colon cancer death[91-93]. Further analyses are thus needed to show the significance of IEEs for reducing either colon cancer mortality or the treatment-related costs.

Table 1 Summary of the studies concerning the efficacy for the detection of colon neoplsms

Authors	Procedures	Study design	Number of patients	Characteristics of the patients	Participants	Which one is better for detecting colon neoplasms?	Clinical significance
Studies of single procedure (non-IBD patients)							
Kiesslich R, 2001 [2]	SD-WL with chromoendoscopy	Observational study	100	Consecutive patients without visible inflammatory changes	Not discribed		Chromoendoscopy allows easy detection of mucosal lesions in the colon and facilitates visualization of the margins of flat lesions.
Studies of single procedure (non-IBD and IBD patients)							
Rembacken BJ, 2000 [1]	SD-WL with chromoendoscopy	Observational study	1000	902 patients with an avarage risk and 98 with inflammatory bowel diseases	Not discribed		Chromoendoscopy may be useful to detect colon adenoma and cancer.
Studies of single procedure (IBD patients)							
Hurlstone DP, 2005 [33]	SD-WL with chromoendoscopy	Observational study	350	Patients with ulcerative colitis	An experienced endoscopist		Magnification chromoscopy improves the detection of intraepithelial neoplasia in patients with chronic ulcerative colitis.
Comparative studies (non-IBD patients)							
Saito Y, 2001 [3]	SD-WL for the right-sided colon and chromoendoscopy for the left-sided colon	Prospective cohort study	221	Patients with an avarage risk	An American and a Japanese experienced endoscopists	SD-WL < Chromoendoscopy	
Brooker JC, 2002 [23]	SD-WL V.S. Chromoendoscopy	Randomized-controlled trial	259	Patients with an avarage risk	Not discribed	SD-WL <= Chromoendoscopy	Dye-spray increases the detection of small adenomas in the proximal colon and patients with multiple adenomas
Hurlstone DP, 2004 [24]	SD-WL V.S. Chromoendoscopy	Randomized-controlled trial	260	Patients with an avarage risk	2 experienced endoscopists	SD-WL < Chromoendoscopy	Pan-colonic chromoscopy improved detection rates of the total number of adenomatous lesions detected and diminutive and flat adenomas.
Lecomte T, 2005 [25]	HD-WL V.S. Chromoendoscopy	Tandem study	36	HNPCC	An experienced endoscopist	HD-WL < Chromoendoscopy	
Le Rhun M, 2006 [26]	HD-WL V.S. Chromoendoscopy	Tandem study	100	Patients with a history of either familial or personal colonic neoplasia or alarm symptoms after the age of 60 years		HD-WL <= Chromoendoscopy	Although chromoendoscopy improves detection of flat adenomas and hyperplastic polyps, the overall detection of colonic adenomas is not significantly improved.
Lapalus MG, 2006 [27]	HD-WL V.S. Chromoendoscopy	Tandem study	292	Patients with histories of colon neoplasms	6 experienced endoscopists	HD-WL <= Chromoendoscopy	Chromoscopy was not recomennded in a high-risk patient population, although the detection of small adenomas in the proximal colon was improved.
Kahi CJ, 2010 [28]	HD-WL V.S. Chromoendoscopy	Randamized controlled trial	660	Patients with an avarage risk	5 experienced endoscopist	HD-WL <= Chromoendoscopy	Chromocolonoscopy marginally increased overall adenoma detection and yielded a modest increase in flat or small adenoma detection, compared with HD-WL.
Pohl J, 2011 [29]	HD-WL V.S. Chromoendoscopy	Randamized controlled trial	1008	Patients with an avarage risk	5 experienced endoscopists in two medical centres	HD-WL < Chromoendoscopy	
Rex DK, 2007 [54]	HD-WL V.S. NBI	Randomized controlled trial	434	Patients with an avarage risk (50 years or older)	An experienced endoscopist	HD-WL = NBI	
Rastogi A, 2008 [51]	HD-WL V.S. NBI	Back to back colonoscopy	40	Patients with an avarage risk	An experienced endoscopist	HD-WL < NBI	
East JE, 2008 [52]	HD-WL V.S. NBI	Back to back colonoscopy	62	Patients from HNPCC families (Amsterdam II or genetic criteria)	3 experienced endoscopists	HD-WL < NBI	Use of NBI in the proximal colon for patients undergoing HNPCC surveillance improves adenoma detection, particularly those with a flat morphology
Adler A, 2008 [55]	HD-WL V.S. NBI	Randomized controlled trial	401	Patients with an avarage risk	Each examiner had carried out five specific training examinations	HD-WL = NBI	
Inoue T, 2008 [53]	HD-WL V.S. NBI	Randomized controlled trial	253	Patients with an avarage risk	6 experienced endoscopists	HD-WL < NBI	
Adler A, 2009 [56]	HD-WL V.S. NBI	Randomized controlled trial	1256	Patients with an avarage risk	6 experienced examiners	HD-WL = NBI	
Matsuda T, 2008 [76]	HD-WL V.S. AFI	Back-to-back colonoscopy	167	Patients with an average risk	An experienced endoscopist	HD-WL < AFI	
Van den Broek FJ, CGH, 2009 [63]	HD-WL V.S. AFI	Randomized trial of tandem colonoscopy	100	Patients with personal history of adenomas or CRC and family history of CRC	3 standard colonoscopists	HD-WL = AFI	
Kuiper T, 2011 [77]	HD-WL V.S. AFI	Randomized trial of back-to-back colonoscopy	234	Patients with histories of colon neoplasms	8 experienced endoscopists from 6 nonacademic centers	HD-WL = AFI	
Comparative studies (IBD patients)							
Kiesslich R, 2003 [32]	SD-WL with random biopsies V.S. Chromoendoscopy	Randomized-controlled trial	263	Patients with ulcerative colitis	Not discribed	SD-WL < Chromoendoscopy	
Rutter MD, 2004 [34]	SD-WL V.S. Chromoendoscopy	Back to back colonoscopy	100	Patients with ulcerative colitis	An experienced endoscopist	SD-WL < Chromoendoscopy	
Kiesslich R, 2007 [35]	SD-WL with random biopsies V.S. Chromoendoscopy with endomicroscopy	Randamized controlled trial	161	Patients with ulcerative colitis	Not discribed	SD-WL with random biopsies < Chromoendoscopy with endomicroscopy	
Marion JF, 2008 [36]	SD-WL with random biopsies V.S. Chromoendoscopy	Tandem study	115	Patients with inflammatory bowel diseases	Experienced endoscopists	SD-WL < Chromoendoscopy	Chromoendoscopy improved dysplasia yield compared to conventional random and targeted biopsy methods.
Pellisé M, 2011 [57]	Chromoendoscopy V.S. NBI	Randamized controlled trial	80	Patients with inflammatory bowel diseases	2 experienced endoscopists	NBI <= Chromoendoscopy	NBI provided a similar true-positive rate and an inferior fake-positive rate while miss rate with NBI tended to be higher than that with chromoendoscopy

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer

Table 2 Summary of the studies concerning the efficacy for the characterization of colon neoplsms

Authors	Study design	Study design	Number of patients (lesions)	Caracteristics of the patients	Participants	Which one is better for differntiating neoplasms from non-neoplasms?	Clinical significance
Studies of single procedure (non-IBD patients)							
Kudo S, 1996 [38]	Chromoendoscopy	Observational study	(2050)	Not discribed	Not discribed		The magnifying colonoscope provides an accurate instantaneous assessment of the histology of colorectal tumorous lesions
Kato S, 2001 [39]	Chromoendoscopy	Retrospective study	(4445)	Not discribed	Not discribed		The combination of magnifying colonoscopy and dye spraying is helpful in determining the nature of colonic lesions as non-neoplastic, adenomas, or invasive carcinomas.
Hirata M, 2007 [60]	NBI	Retrospective study	163 (189)	Patients who underwent endoscopic or surgical resection	2 experienced		NBI magnification is useful for the prediction of histologic diagnosis.
Katagiri A, 2008 [61]	NBI	Prospective cohort study	104	consecutive patients	An experienced endoscopist		Capillary patterns observed by NBI could be used to assess the degree of atypia in early colorectal neoplasia.
Rastogi A, 2008 [51]	NBI	Back to back colonoscopy	40	Patients with an avarage risk	An experienced endoscopist		This pilot study demonstrates the feasibility of histologic correlation with NBI.
Sano Y, 2009 [62]	NBI	Prospective cohort study	702	Patients with an avarage risk	An experienced endoscopist		Observation of surface MC vessels by magnifying NBI is a useful and simple method for differentiating colorectal nonneoplastic and neoplastic polyps.
Kanao H, 2009 [64]	NBI	Prospective cohort study	223	Patients with colon polyp	3 experienced endoscopists		NBI magnification findings of colorectal lesions were associated with histologic grade and invasion depth.
Wada Y, 2009 [65]	NBI	Prospective cohort study	495	Patients with an avarage risk	2 endoscopists		The NBI system was valuable for distinguishing between neoplastic and non-neoplastic lesions, as well as between cancers and adenomas.
Studies of single procedure (IBD patients)							
Matsumoto T, 2007 [69]	NBI	Prospective cohort study	46	Patients with ulcerative colitis	An endoscopist		The tortuous pattern determined by NBI may be a clue for the identification of dysplasia during surveillance for UC.
van den Broek FJ, Gut, 2008 [70]	NBI	Prospective cohort study	50	Patients with ulcerative colitis	3 experienced endoscopists		Pit pattern analysis by NBI has a moderate accuracy for the prediction of histology.
Comparative studies							
Fu KI, 2004 [40]	Chromoendoscopy V.S. Chromoendoscopy with endomicroscopy	Prospective study	122	Patients with an avarage risk	2 trained endoscopists	Chromoendoscopy < Chromoendoscopy with endomicroscopy	
Machida H, 2004 [41]	SD-WL V.S. NBI V.S Chromoendoscopy	Retrospective study	34	Patients with an average risk	2 experienced endoscopists	SD-WL < NBI = Chromoendoscopy	
Su MY, 2006 [58]	SD-WL V.S. NBI	Obsevational study	78	consecutive patients	Two experienced endoscopists	NBI = Chromoendoscopy	The NBI system identified morphological details that correlate well with polyp histology by chromoendoscopy.
East JE, 2007 [46]	Chromoendoscopy V.S. NBI	Randomized control study	20 (photographs of 33 polyps)	Patients with an avarage risk	One experienced endoscopist in Japanese and one in European	The European endoscopist Chromoendoscopy = NBI The Japanese endoscopist Chromoendoscopy < NBI	The European trained endoscopist showed similar accuracy for both methods. For the Japanese-trained endoscopist, both NBI pit pattern and vascular pattern intensity exceeded chromoedoscopy in terms of overall accuracy.
Hirata M, 2007 [50]	Chromoendoscopy V.S. NBI	Retrospective study	99 (148)	Patients who underwent endoscopic or surgical resection	Not discribed	NBI = Chromoendoscopy	
Chiu HM, 2007 [42]	SD-WL V.S. NBI V.S Chromoendoscopy	Randomized control study	133（180）	Patients with an avarage risk	4 experienced endoscopists	SD-WL < NBI = Chromoendoscopy	
Tischendorf JJ, 2007 [59]	NBI V.S Chromoendoscopy	Randomized control study	99（200）	Patients with an avarage risk	2 endoscopists	NBI = Chromoendoscopy	
van den Broek FJ, Clin Gastroenterol Hepatol, 2009 [63]	HD-WL V.S. NBI V.S. AFI	Randomized trial of tandem colonoscopies	100	Patients with personal history of adenomas or CRC and family history of CRC	3 standard endoscopists	HD-WL = NBI = AFI	
Boparai KS, 2009 [78]	AFI V.S. NBI	Prospective polyp series	7	Patient with hyperplastic polyposis syndrome (HPS)	An experienced endoscopist	AFI < NBI	Differentiation of adenomas from HPs was possible with NBI but not with AFI
van den Broek FJ, AJG, 2009 [66]	HD-WL V.S. NBI V.S. AFI	Randomized control study	107（photographs of 50 polyps）	Patients with personal history of adenomas or CRC and family history of CRC	3 experienced and 4 non-experienced endoscopists	Experienced endoscopists HD-WL = NBI = AFI Less-experienced endoscopists HD-WL = NBI < AFI	
Sato R, 2011 [47]	HD-WL V.S. AFI V.S. NBI	Randomized control study	183 (424 photographs)	Patients with an avarage risk	3 experienced and 3 less-experienced endoscopists	HD-WL < NBI = AFI	AFI and NBI are considered to be feasible tools that can discriminate colon adenoma from hyperplastic polyps, particularl for less-experienced endoscopists.

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer

Table 3 Summary of the studies concerning inter- and intra-observer consistencies

Authors	Evaluated procedure	Materials	Number of cases (photographs)	Caracteristics of the patients	Participants	Inter- and intra-observer agreements
Huang Q, 2004 [45]	Chromoendoscopy	Photographs	154 (220)	Not discribed	6 experienced endoscopists	For experienced endoscopists, the inter- and intra-observer reproducibility of the classification of pit pattern is good (k = 0.716 and 810, respectively)
Chiu HM, 2007 [42]	SD-WL, NBI and chromoendoscopy	Photographs	133 (180)	Patients with an avarage risk	4 experienced endoscopists	There was excellent interobserver agreement in the sub-study (k = 0.86) for all modalities.
East JE, 2007 [46]	Chromoendoscopy and NBI	Photographs	20 (33)	Patients with an avarage risk	One experienced endoscopist in Japanese and one in European	Data on the agreement between endoscopists was fair for chromoendoscopy (k = 0.27), moderate for NBI (k = 0.49), and moderate to good for vascular pattern intensity (k = 0.58).
Rastogi, 2009 [71]	NBI	Photographs	40 (65)	Patients with an avarage risk	2 experienced and 2 less-experienced endoscopists	The kappa value for the interobserver agreement for predicting the polyp type was 0.63. There was no significant difference in the kappa values calculated for the experienced versus the less-experienced endoscopists.
Higashi R, 2010 [72]	Chromoendoscopy and NBI	Photographs	32 (44)	Patients with an avarage risk	4 residents, 4 less experienced endoscopists (LEE) and 4 highly experienced endoscopists	Interobserver agreements in the highly experienced group for NBI and chromoendoscopy were 0.85 and 0.75, respectively. NBI increased the differential diagnostic skill of the less experienced group after expanded training.
Raghavendra M, 2010 [73]	NBI	Photographs	(70)	Patients with an avarage risk	12 residents, 12 gastroenterology fellows 13 gastroenterology faculty	A short, didactic teaching session can achieve high accuracy and good interobserver agreement in the use of narrow-band imaging for determining the histology of colorectal polyps.
Ignjatovic A, 2011 [74]	NBI	Photographs	(30)	Not discribed	21 participants of varying colonoscopy experience, 5 experts in NBI	The kappas were 0.69 overall, 0.79 for fellows, 0.69 for faculty, and 0.62 for residents, consistent with substantial interrater agreement.
van den Broek FJ, AJG, 2009 [66]	HD-WL, NBI and AFI	Photographs	50 (107)	Patients with personal history of adenomas or CRC and family history of CRC	3 experienced and 4 non-experienced endoscopists	Experienced endoscopists had a better interobserver agreement for NBI (k=0.77) than for AFI (k = 0.33), whereas non-experienced endoscopists had a better agreement for AFI (k = 0.58) than for NBI (k = 0.33).
Sato R, 2011 [47]	HD-WL, NBI and AFI	Photographs	183 (424)	Patients with an avarage risk	3 experienced and 3 less-experienced endoscopists	The kappa values for inter-observer agreement of HRE, AFI, and NBI in specialists were 0.56, 0.54, and 0.54, and those in residents were 0.47, 0.54, and 0.49, respectively.

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer

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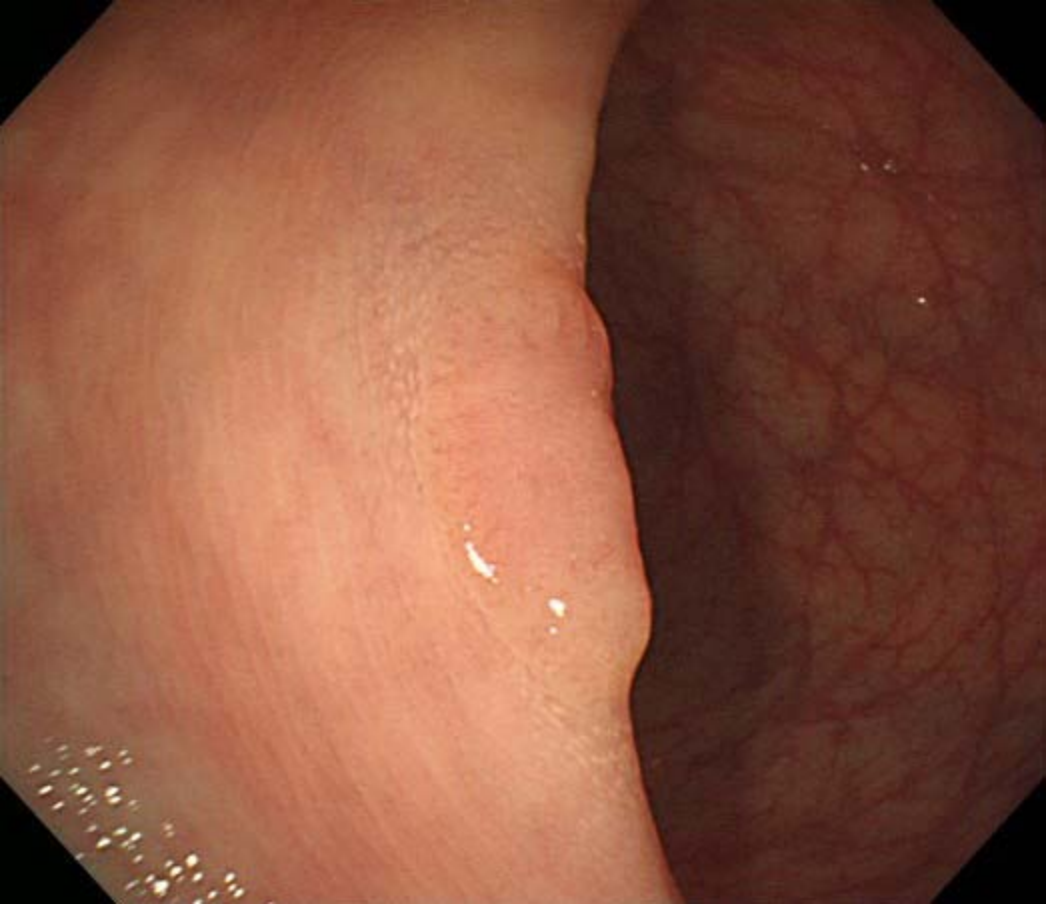
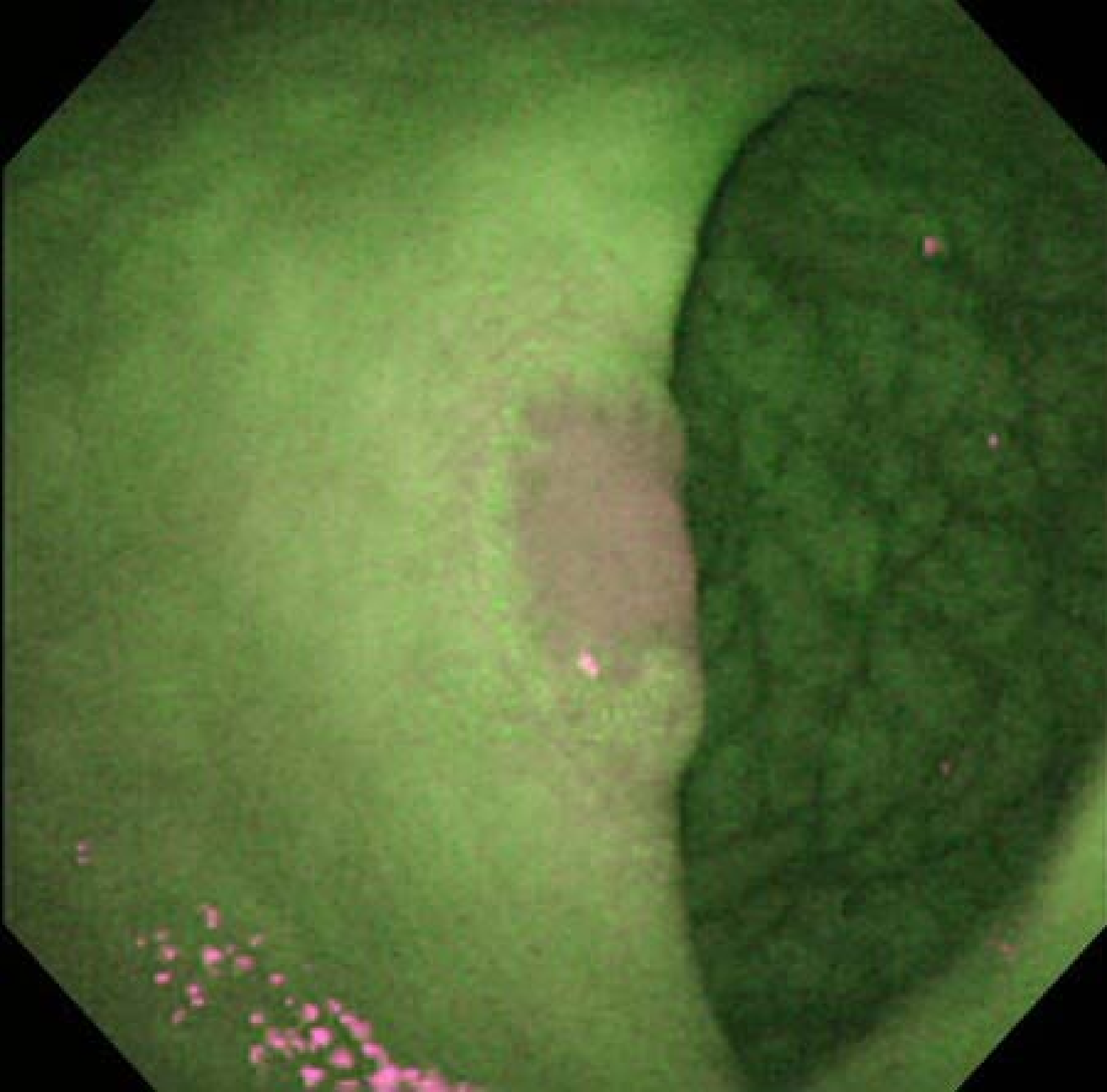
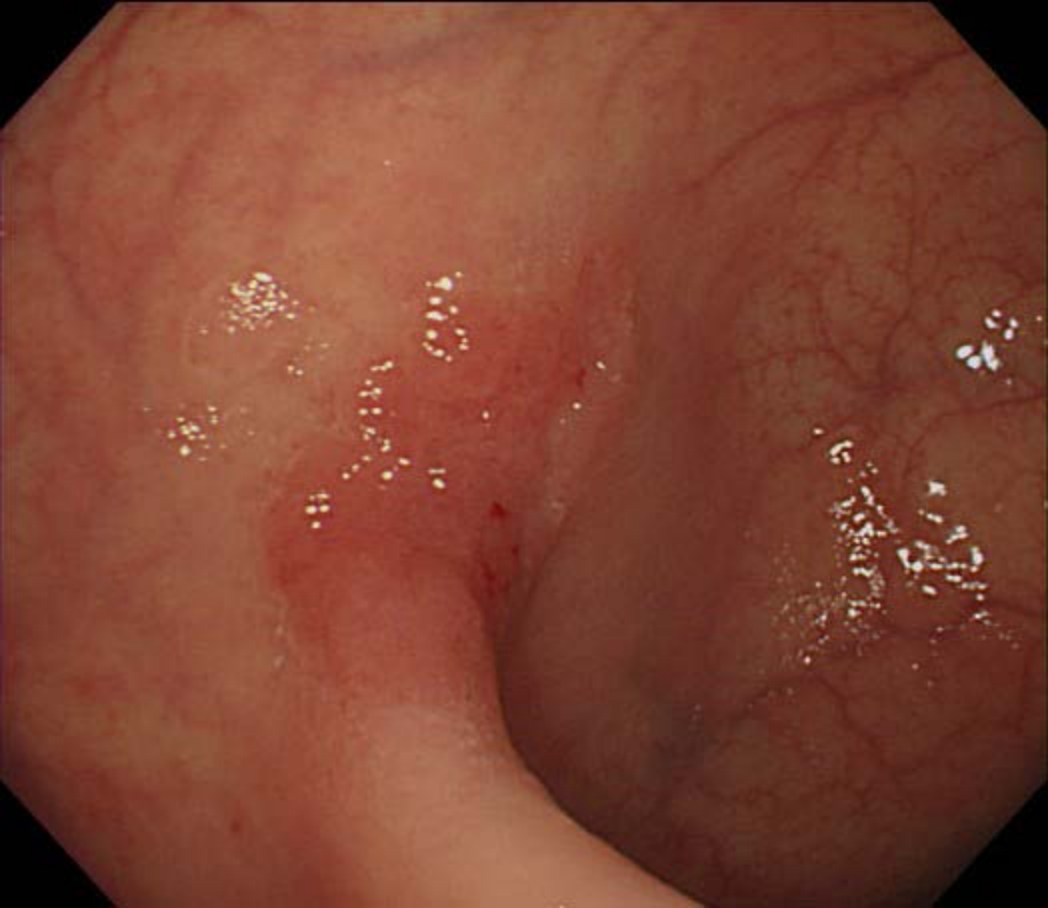
Figure legends

Figure 1. WLE (A) and AFI (B) of a flat and depressed type of colon adenoma. WLE revealed a flat and depressed type of tumor (A). AFI detected only the depressed area as magenta (B), thus suggesting that the tumor cells are limited to the depression area. (These pictures are cited from Fujiya et al. Colonoscopy/Book 1, 2011[94])

Figure 2. WLE (A) and AFI (B) of a flat and depressed type of colon cancer with submucosal invasion. (These pictures are cited from Fujiya et al. Colonoscopy/Book 1, 2011_ENREF_85[94])







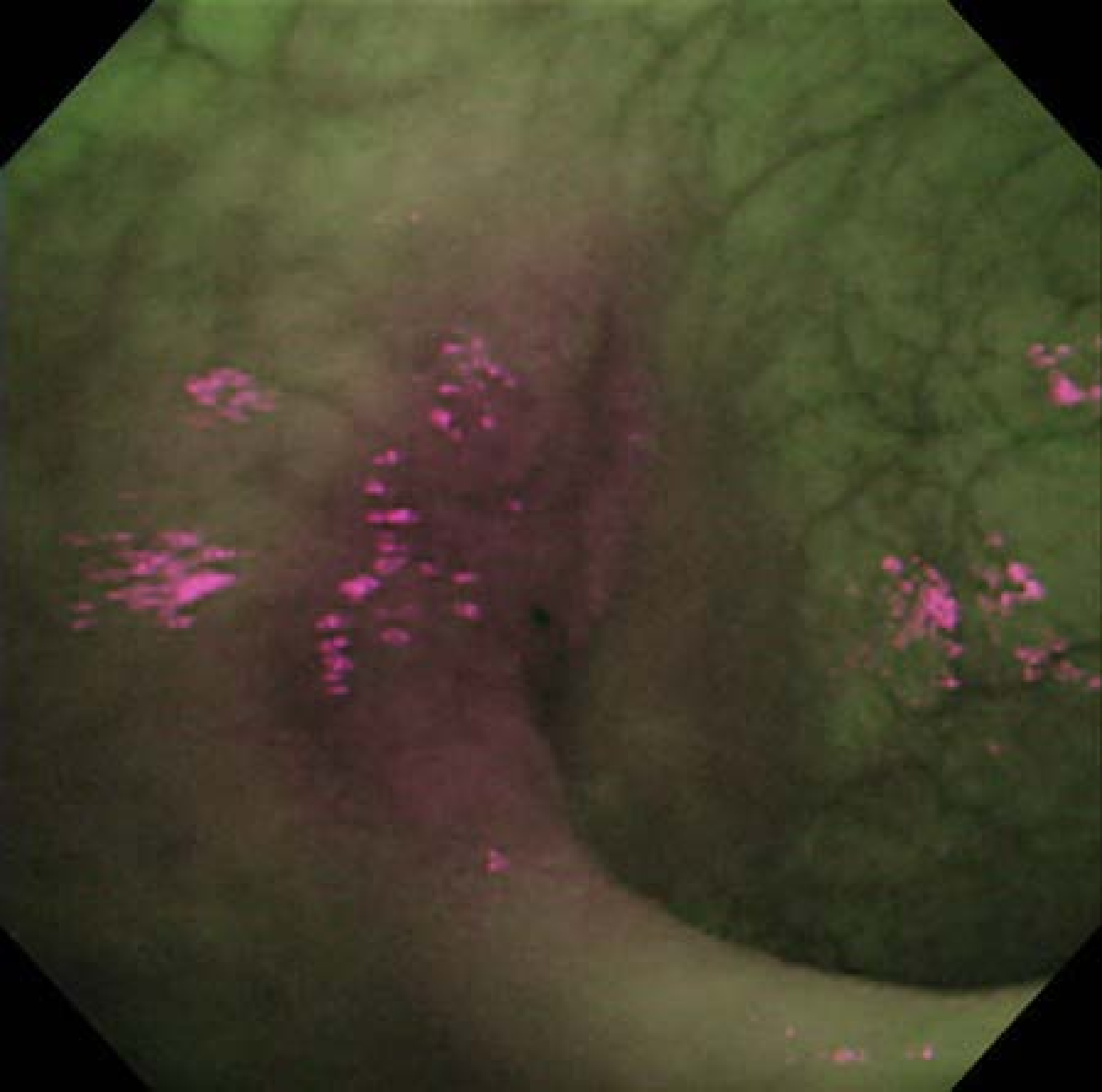


Table 1 Summary of the studies concerning the efficacy for the detection of colon neoplsms

Authors	Procedures	Study design	Number of patients	Characteristics of the patients	Participants	Which one is better for detecting colon neoplasms?	Clinical significance
Studies of single procedure							
Kiesslich R, 2001 [4]	SD-WL with chromoendoscopy	Observational study	100	Consecutive patients without visible inflammatory changes	Not described		Chromoendoscopy allows easy detection of mucosal lesions in the colon and facilitates visualization of the margins of flat lesions.
Studies of single procedure (non-IBD and IBD patients)							
Rembacken BJ, 2000 [1]	SD-WL with chromoendoscopy	Observational study	1000	902 patients with an average risk and 98 with inflammatory bowel diseases	Not described		Chromoendoscopy may be useful to detect colon adenoma and cancer.
Studies of single procedure (IBD patients)							
Hurlstone DP, 2005 [33]	SD-WL with chromoendoscopy	Observational study	350	Patients with ulcerative colitis	An experienced endoscopist		Magnification chromoscopy improves the detection of intraepithelial neoplasia in patients with chronic ulcerative colitis.
Comparative studies (non-IBD patients)							
Saito Y, 2001 [3]	SD-WL for the right-sided colon and chromoendoscopy for the left-sided colon	Prospective cohort study	221	Patients with an average risk	An American and a Japanese experienced endoscopists	SD-WL < Chromoendoscopy	
Brooker JC, 2002 [23]	SD-WL V.S. Chromoendoscopy	Randomized-controlled trial	259	Patients with an average risk	Not described	SD-WL <= Chromoendoscopy	Dye-spray increases the detection of small adenomas in the proximal colon and patients with multiple adenomas
Hurlstone DP, 2004 [24]	SD-WL V.S. Chromoendoscopy	Randomized-controlled trial	260	Patients with an average risk	2 experienced endoscopists	SD-WL < Chromoendoscopy	Pan-colonic chromoscopy improved detection rates of the total number of adenomatous lesions detected and diminutive and flat adenomas.
Lecomte T, 2005 [25]	HD-WL V.S. Chromoendoscopy	Tandem study	36	HNPCC	An experienced endoscopist	HD-WL < Chromoendoscopy	
Le Rhun M, 2006 [26]	HD-WL V.S. Chromoendoscopy	Tandem study	100	Patients with a history of either familial or personal colonic neoplasia or alarm symptoms after the age of 60 years		HD-WL <= Chromoendoscopy	Although chromoendoscopy improves detection of flat adenomas and hyperplastic polyps, the overall detection of colonic adenomas is not significantly improved.
Lapalus MG, 2006 [27]	HD-WL V.S. Chromoendoscopy	Tandem study	292	Patients with histories of colon neoplasms	6 experienced endoscopists	HD-WL <= Chromoendoscopy	Chromoscopy was not recomennded in a high-risk patient population, although the detection of small adenomas in the proximal colon was improved.
Kahi CJ, 2010 [28]	HD-WL V.S. Chromoendoscopy	Randomized controlled trial	660	Patients with an average risk	5 experienced endoscopist	HD-WL <= Chromoendoscopy	Chromocolonoscopy marginally increased overall adenoma detection and yielded a modest increase in flat or small adenoma detection, compared with HD-WL.
Pohl J, 2011 [29]	HD-WL V.S. Chromoendoscopy	Randomized controlled trial	1008	Patients with an average risk	5 experienced endoscopists in two medical centres	HD-WL < Chromoendoscopy	
Rex DK, 2007 [54]	HD-WL V.S. NBI	Randomized controlled trial	434	Patients with an average risk (50 years or older)	An experienced endoscopist	HD-WL = NBI	
Rastogi A, 2008 [55]	HD-WL V.S. NBI	Back to back colonoscopy	40	Patients with an average risk	An experienced endoscopist	HD-WL < NBI	
East JE, 2008 [52]	HD-WL V.S. NBI	Back to back colonoscopy	62	Patients from HNPCC families (Amsterdam II or genetic criteria)	3 experienced endoscopists	HD-WL < NBI	Use of NBI in the proximal colon for patients undergoing HNPCC surveillance improves adenoma detection, particularly those with a flat morphology
Adler A, 2008 [35]	HD-WL V.S. NBI	Randomized controlled trial	401	Patients with an average risk	Each examiner had carried out five specific training examinations	HD-WL = NBI	
Inoue T, 2008 [53]	HD-WL V.S. NBI	Randomized controlled trial	253	Patients with an average risk	6 experienced endoscopists	HD-WL < NBI	
Adler A, 2009 [36]	HD-WL V.S. NBI	Randomized controlled trial	1256	Patients with an average risk	6 experienced examiners	HD-WL = NBI	
Matsuda T, 2008 [76]	HD-WL V.S. AFI	Back-to-back colonoscopy	167	Patients with an average risk	An experienced endoscopist	HD-WL < AFI	
Van den Broek FJ, 2009 [63]	HD-WL V.S. AFI	Randomized trial of tandem colonoscopy	100	Patients with personal history of adenomas or CRC and family history of CRC	3 standard colonoscopists	HD-WL = AFI	
Kuiper T, 2011 [77]	HD-WL V.S. AFI	Randomized trial of back-to-back colonoscopy	234	Patients with histories of colon neoplasms	8 experienced endoscopists from 6 nonacademic centers	HD-WL = AFI	
Comparative studies (IBD patients)							
Kiesslich R, 2003 [32]	SD-WL with random biopsies V.S. Chromoendoscopy	Randomized-controlled trial	263	Patients with ulcerative colitis	Not described	SD-WL < Chromoendoscopy	
Rutter MD, 2004 [34]	SD-WL V.S. Chromoendoscopy	Back to back colonoscopy	100	Patients with ulcerative colitis	An experienced endoscopist	SD-WL < Chromoendoscopy	
Kiesslich R, 2007 [35]	SD-WL with random biopsies V.S. Chromoendoscopy with endomicroscopy	Randomized controlled trial	161	Patients with ulcerative colitis	Not described	SD-WL with random biopsies < Chromoendoscopy with endomicroscopy	
Marion JF, 2008 [36]	SD-WL with random biopsies V.S. Chromoendoscopy	Tandem study	115	Patients with inflammatory bowel diseases	Experienced endoscopists	SD-WL < Chromoendoscopy	Chromoendoscopy improved dysplasia yield compared to conventional random and targeted biopsy methods.
Pellisé M, 2011 [57]	Chromoendoscopy V.S. NBI	Randomized controlled trial	80	Patients with inflammatory bowel diseases	2 experienced endoscopists	NBI <= Chromoendoscopy	NBI provided a similar true-positive rate and an inferior false-positive rate while miss rate with NBI tended to be higher than that with chromoendoscopy

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer

Table 2 Summary of the studies concerning the efficacy for the characterization of colon neoplsms

Authors	Procedures	Study design	Number of patients (Lesions)	Characteristics of the patients	Participants	Which one is better for detecting colon neoplasms?	Clinical significance
Studies of single procedure (non-IBD patients)							
Kudo S, 1996 [38]	Chromoendoscopy	Observational study	(2050)	Not described	Not described		The magnifying colonoscope provides an accurate instantaneous assessment of the histology of colorectal tumorous lesions
Kato S, 2001 [39]	Chromoendoscopy	Retrospective study	(4445)	Not described	Not described		The combination of magnifying colonoscopy and dye spraying is helpful in determining the nature of colonic lesions as non-neoplastic, adenomas, or invasive carcinomas.
Hirata M, 2007 [60]	NBI	Retrospective study	163 (189)	Patients who underwent endoscopic or surgical resection	2 experienced		NBI magnification is useful for the prediction of histologic diagnosis.
Katagiri A, 2008 [61]	NBI	Prospective cohort study	104	consecutive patients	An experienced endoscopist		Capillary patterns observed by NBI could be used to assess the degree of atypia in early colorectal neoplasia.
Rastogi A, 2008 [51]	NBI	Back to back colonoscopy	40	Patients with an average risk	An experienced endoscopist		This pilot study demonstrates the feasibility of histologic correlation with NBI.
Sano Y, 2009 [62]	NBI	Prospective cohort study	702	Patients with an average risk	An experienced endoscopist		Observation of surface MC vessels by magnifying NBI is a useful and simple method for differentiating colorectal nonneoplastic and neoplastic polyps.
Kanao H, 2009 [64]	NBI	Prospective cohort study	223	Patients with colon polyp	3 experienced endoscopists		NBI magnification findings of colorectal lesions were associated with histologic grade and invasion depth.
Wada Y, 2009 [65]	NBI	Prospective cohort study	495	Patients with an average risk	2 endoscopists		The NBI system was valuable for distinguishing between neoplastic and non-neoplastic lesions, as well as between cancers and adenomas.
Studies of single procedure (IBD patients)							
Matsumoto T, 2007 [69]	NBI	Prospective cohort study	46	Patients with ulcerative colitis	An endoscopist		The tortuous pattern determined by NBI may be a clue for the identification of dysplasia during surveillance for UC.
van den Broek FJ, 2008 [70]	NBI	Prospective cohort study	50	Patients with ulcerative colitis	3 experienced endoscopists		Pit pattern analysis by NBI has a moderate accuracy for the prediction of histology.
Comparative studies							
Fu KI, 2004 [40]	Chromoendoscopy V.S. Chromoendoscopy with endomicroscopy	Prospective study	122	Patients with an average risk	2 trained endoscopists	Chromoendoscopy < Chromoendoscopy with endomicroscopy	
Machida H, 2004 [41]	SD-WL V.S. NBI V.S Chromoendoscopy	Retrospective study	34	Patients with an average risk	2 experienced endoscopists	SD-WL < NBI = Chromoendoscopy	
Su MY, 2006 [28]	SD-WL V.S. NBI	Observational study	78	consecutive patients	Two experienced endoscopists	NBI = Chromoendoscopy	The NBI system identified morphological details that correlate well with polyp histology by chromoendoscopy.
East JE, 2007 [46]	Chromoendoscopy V.S. NBI	Randomized control study	20 (photographs of 33 polyps)	Patients with an average risk	One experienced endoscopist in Japanese and one in European	The European endoscopist Chromoendoscopy = NBI The Japanese endoscopist Chromoendoscopy < NBI	The European trained endoscopist showed similar accuracy for both methods. For the Japanese-trained endoscopist, both NBI pit pattern and vascular pattern intensity exceeded chromoendoscopy in terms of overall accuracy.
Hirata M, 2007 [50]	Chromoendoscopy V.S. NBI	Retrospective study	99 (148)	Patients who underwent endoscopic or surgical resection	Not described	NBI = Chromoendoscopy	
Chiu HM, 2007 [42]	SD-WL V.S. NBI V.S Chromoendoscopy	Randomized control study	133（180）	Patients with an average risk	4 experienced endoscopists	SD-WL < NBI = Chromoendoscopy	
Tischendorf JJ, 2007 [59]	NBI V.S Chromoendoscopy	Randomized control study	99（200）	Patients with an average risk	2 endoscopists	NBI = Chromoendoscopy	
van den Broek FJ, 2009 [63]	HD-WL V.S. NBI V.S. AFI	Randomized trial of tandem colonoscopies	100	Patients with personal history of adenomas or CRC and family history of CRC	3 standard endoscopists	HD-WL = NBI = AFI	
Boparai KS, 2009 [78]	AFI V.S. NBI	Prospective polyp series	7	Patient with hyperplastic polyposis syndrome (HPS)	An experienced endoscopist	AFI < NBI	Differentiation of adenomas from HPs was possible with NBI but not with AFI
van den Broek FJ, 2009 [66]	HD-WL V.S. NBI V.S. AFI	Randomized control study	107 (photographs of 50 polyps)	Patients with personal history of adenomas or CRC and family history of CRC	3 experienced and 4 non-experienced endoscopists	Experienced endoscopists HD-WL = NBI = AFI Less-experienced endoscopists HD-WL = NBI < AFI	
Sato R, 2011 [47]	HD-WL V.S. AFI V.S. NBI	Randomized control study	183 (424 photographs)	Patients with an average risk	3 experienced and 3 less-experienced endoscopists	HD-WL < NBI = AFI	AFI and NBI are considered to be feasible tools that can discriminate colon adenoma from hyperplastic polyps, particularly for less-experienced endoscopists.

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer

Table 3 Summary of the studies concerning inter- and intra-observer consistencies

Authors	Evaluated procedure	Materials	Number of cases (photographs)	Characteristics of the patients	Participants	Inter- and intra-observer agreements
Huang Q, 2004 [45]	Chromoendoscopy	Photographs	154 (220)	Not described	6 experienced endoscopists	For experienced endoscopists, the inter- and intra-observer reproducibility of the classification of pit pattern is good (k = 0.716 and 810, respectively)
Chiu HM, 2007 [42]	SD-WL, NBI and chromoendoscopy	Photographs	133 (180)	Patients with an average risk	4 experienced endoscopists	There was excellent interobserver agreement in the sub-study (k = 0.86) for all modalities.
East JE, 2007 [46]	Chromoendoscopy and NBI	Photographs	20 (33)	Patients with an average risk	One experienced endoscopist in Japanese and one in European	Data on the agreement between endoscopists was fair for chromoendoscopy (k = 0.27), moderate for NBI (k = 0.49), and moderate to good for vascular pattern intensity (k = 0.58).
Rastogi, 2009 [71]	NBI	Photographs	40 (65)	Patients with an average risk	2 experienced and 2 less-experienced endoscopists	The kappa value for the interobserver agreement for predicting the polyp type was 0.63. There was no significant difference in the kappa values calculated for the experienced versus the less-experienced endoscopists.
Higashi R, 2010 [72]	Chromoendoscopy and NBI	Photographs	32 (44)	Patients with an average risk	4 residents, 4 less experienced endoscopists (LEE) and 4 highly experienced endoscopists	Interobserver agreements in the highly experienced group for NBI and chromoendoscopy were 0.85 and 0.75, respectively. NBI increased the differential diagnostic skill of the less experienced group after expanded training.
Raghavendra M, 2010 [73]	NBI	Photographs	(70)	Patients with an average risk	12 residents, 12 gastroenterology fellows 13 gastroenterology faculty	A short, didactic teaching session can achieve high accuracy and good interobserver agreement in the use of narrow-band imaging for determining the histology of colorectal polyps.
Ignjatovic A, 2011 [74]	NBI	Photographs	(30)	Not described	21 participants of varying colonoscopy experience, 5 experts in NBI	The kappas were 0.69 overall, 0.79 for fellows, 0.69 for faculty, and 0.62 for residents, consistent with substantial interrater agreement.
van den Broek FJ, 2009 [66]	HD-WL, NBI and AFI	Photographs	50 (107)	Patients with personal history of adenomas or CRC and family history of CRC	3 experienced and 4 non-experienced endoscopists	Experienced endoscopists had a better interobserver agreement for NBI (k=0.77) than for AFI (k = 0.33), whereas non-experienced endoscopists had a better agreement for AFI (k = 0.58) than for NBI (k = 0.33).
Sato R, 2011 [47]	HD-WL, NBI and AFI	Photographs	183 (424)	Patients with an average risk	3 experienced and 3 less-experienced endoscopists	The kappa values for inter-observer agreement of HRE, AFI, and NBI in specialists were 0.56, 0.54, and 0.54, and those in residents were 0.47, 0.54, and 0.49, respectively.

SD-WL; Standard definition white light endoscopy, HD-WL; High definition white light endoscopy, NBI; Narrow band imaging, AFI; Autofluorescence imaging, CRC; Colorectal cancer