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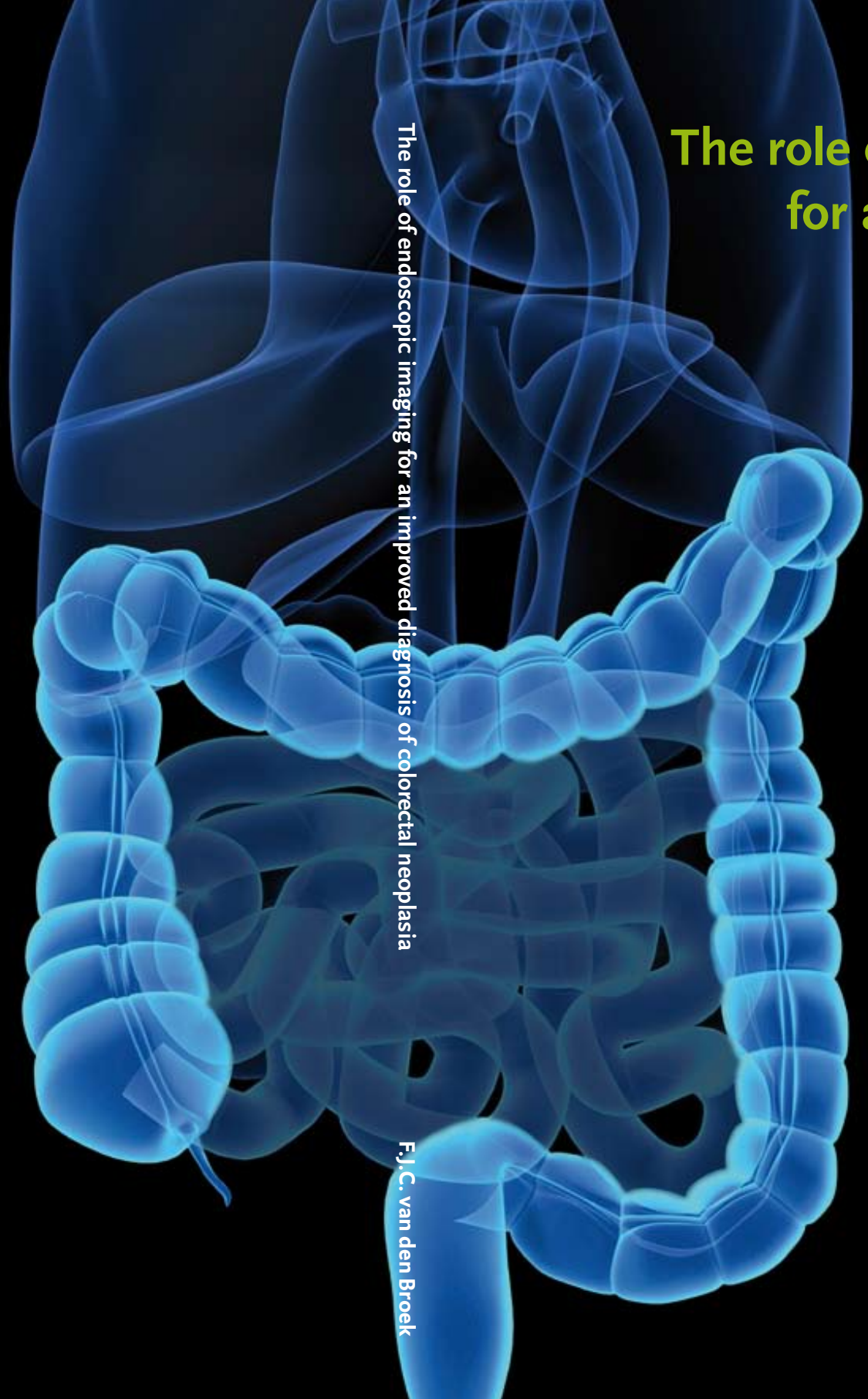
The author of this thesis, Frank van den Broek, was born on September 28, 1978 in Venray. He graduated from medical school at the Radboud University Nijmegen Medical Center in 2002 and worked as a surgical resident at the St Lucas Andreas Hospital in Amsterdam, the Westfries Gasthuis in Hoorn and the VU medical center in Amsterdam. During the same period he performed scientific research on improving the diagnosis of acute appendicitis at the Academic Medical Center in Amsterdam. In April 2006, he started off his PhD project at the department of gastroenterology and hepatology at the Academic Medical Center, resulting in the present dissertation. This thesis encloses a critical appraisal of the published literature and several original studies on the role of endoscopic imaging (e.g. narrow-band imaging, autofluorescence imaging and probe-based confocal laser endomicroscopy) for an improved diagnosis of colorectal neoplasia. After finishing his scientific work in July 2009, he continued his training in surgery at the Kennemer Gasthuis in Haarlem and the VU medical centre in Amsterdam. He is living together with Iris Ketel.

JANUARY 2010



The role of endoscopic imaging for an improved diagnosis of colorectal neoplasia

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Frank J.C. van den Broek

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THE ROLE OF ENDOSCOPIC IMAGING FOR AN IMPROVED DIAGNOSIS OF COLORECTAL NEOPLASIA

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Promotor:	Prof. dr. P. Fockens
Copromotores:	Dr. E. Dekker
	Dr. J.B. Reitsma
Overige Leden:	Prof. dr. W.A. Bemelman
	Prof. dr. P.M.M. Bossuyt
	Prof. dr. E.J. Kuijpers
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Voor mijn moeder

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Introduction and outline of the thesis

Introduction

Colorectal cancer (CRC) is one of the most common cancers in western countries. In the year 2006, the Netherlands accounted for 11,231 new cases and 4,709 deaths due to this disease. Since the recognition that most CRCs arise from premalignant adenomas during a certain time span, this window of opportunity has been used to early detect and remove these precursor lesions. At this moment, conventional white-light colonoscopy is the standard of care for the detection of premalignant lesions. However, some lesions are difficult to detect due to several limitations of current colonoscopy which will be briefly summarized.

- If the colon is not properly prepared prior to colonoscopy, lesions may stay covered by faeces and remain invisible for the endoscopist. Proper bowel cleansing therefore is a prerequisite for an accurate colonoscopy.
- An optimal examination technique must be used and may be defined as quick and secure insertion of the colonoscope into the cecum, applying adequate distension of the colonic wall, cleaning up pools of debris, proper inspection of the entire colonic mucosa including the proximal side of folds and taking sufficient time for withdrawal.
- Some intrinsic polyp characteristics make their detection more difficult. Flat colorectal lesions for instance are easily overlooked. Until 1998, flat and depressed lesions were believed to be uniquely present in the Asian population. In that year a study was published in which colonoscopies in an English population were performed by local endoscopists in conjoint with experienced Japanese endoscopists. Fuji *et al* demonstrated that in the West up to 40% of adenomas were of the flat and depressed type too.[1] As confirmed by others, these lesions had apparently been overlooked in the West for many years.[2,3] Next to flat lesions, diminutive polyps are easily overlooked as well. Miss-rates among small polyps are much higher, as outlined in a systematic review of back-to-back colonoscopies.[4]

Due to the abovementioned limitations, adenoma miss-rates have been reported to be as high as 15-32%.[4] When starting off the scientific research presented in this thesis it thus was clear that the sensitivity of colonoscopy for the detection of adenomas needed to be improved.

Next to improving the sensitivity of colonoscopy with respect to its ability to detect premalignant colorectal lesions, many harmless non-neoplastic lesions are being detected during colonoscopy as well. In fact, about half of all removed polyps are non-neoplastic (mostly hyperplastic) polyps. As no reliable differentiation can be made between non-neoplastic and premalignant polyps during conventional colonoscopy, all harmless lesions are nowadays removed by endoscopic resection and sent for pathology as well. The disadvantage of this current approach is that patients are exposed to the risk of endoscopic removal of non-neoplastic polyps. Since removal of polyps is accompanied by a risk of perforation or bleeding of 0.04-1.1% and 0.48-8.6% respectively, the detection of non-neoplastic lesions leads to unnecessary risks, higher pathology costs and an increased workload for endoscopists and pathologists.[5-8] Accurate differentiation during ongoing endoscopy has the advantage that instantaneous decisions can be made, such as

performing immediate endoscopic resection of a premalignant lesion whereas an innocent non-neoplastic lesion may be left *in situ*.
Several endoscopic imaging techniques have been developed in the past decade which may facilitate endoscopists to improve the detection of flat and small lesions as well as to enable real-time differentiation between neoplastic and non-neoplastic lesions.

– Narrow band imaging (NBI) is an endoscopic imaging technique enhancing the mucosal morphology and vascularisation by applying an optical filter to the endoscopic light. This technique may improve the contrast between neoplastic and non-neoplastic tissue and hence could facilitate the detection as well as the differentiation of colonic lesions.
– Autofluorescence imaging (AFI) is another endoscopic imaging technique during which blue light is used for illumination. Blue light excites certain molecules ('fluorophores') in the colon that will subsequently emit autofluorescence light. As the autofluorescence light differs between neoplastic and non-neoplastic mucosa, AFI could be used to improve the contrast of neoplastic mucosa as well as to differentiate between diverse polyps.
– Confocal laser endomicroscopy (CLE) is a technique which may be considered as in-vivo histopathology, having a field of view of about half a millimeter. As only a limited surface area is visualized by CLE, it is unfeasible for the primary detection of lesions but it could accurately be used for differentiating neoplastic from non-neoplastic lesions.

In the year 2006, the author of this thesis joined the department of Gastroenterology and Hepatology at the Academic Medical Centre of Amsterdam to investigate the role of novel endoscopic imaging techniques for an improved diagnosis of premalignant colorectal lesions. To address this purpose, several research methods have been used that are summarized in three parts:

I Critical appraisal of existing literature on endoscopic imaging
II Studies evaluating endoscopic imaging techniques for polyp detection and differentiation
III Studies evaluating these techniques regarding endoscopic surveillance in ulcerative colitis

In **part I** we describe our findings of the published literature with respect to the evidence for using novel endoscopic imaging techniques. From our critical appraisal of the literature we concluded that several different study designs have been used by others and hence were available for our own studies too. In order to perform high quality research ourselves, we critically judged and discussed these different study designs regarding their validity and efficiency. Subsequently, we used the most valid and efficient study designs in our own scientific research which is presented in **part II and III** of this thesis. In these parts we questioned ourselves whether conventional colonoscopy should be replaced by NBI and/or AFI to reduce the miss-rates of premalignant lesions and to obtain an almost perfect sensitivity for the detection of these lesions. In addition, we questioned whether NBI, AFI and/or CLE could assist the endoscopist in differentiating neoplastic from non-neoplastic lesions during ongoing endoscopy.

Outline of the thesis

When starting off our scientific research in 2006, our main purpose was to determine the role of novel endoscopic imaging techniques for an improved diagnosis of premalignant colorectal lesions.

Part I: Critical appraisal of research in endoscopic imaging

Before initiating our research, we assessed the available evidence on the role of endoscopic imaging in the colon. In chapter 1 the literature on new developments in colonic imaging regarding the detection of neoplasia until 2007 is critically reviewed. As the use of narrow-band imaging (NBI) dramatically expanded worldwide after the initiation of our research, we subsequently performed a systematic review of the literature on this technique until 2008 which is described in chapter 2. During our assessment of the existing literature we found a large heterogeneity among study designs that had been used by others. Chapter 3 summarizes the most frequently used study designs to evaluate novel endoscopic imaging techniques regarding the detection of lesions. In this chapter we assess the validity and efficiency of the different designs and provide a methodological recommendation for researchers. This chapter guided our own research on endoscopic imaging which is presented in part II and III of this thesis.

Part II: Role of endoscopic imaging in diagnosis of colonic polyps

In Chapter 4 we describe a randomized cross-over trial comparing autofluorescence imaging (AFI) versus high-resolution endoscopy (HRE) for the detection of adenomas in patients who undergo colonoscopic surveillance for adenomas. In addition, the use of NBI is evaluated with respect to its ability to differentiate between neoplastic and non-neoplastic polyps. In this study we found that endoscopic tri-modal imaging (i.e. the combined use of HRE, AFI and NBI) had a high accuracy for differentiating neoplastic from non-neoplastic polyps. Therefore, the endoscopic image evaluation study in chapter 5 aimed to assess the value of combining HRE with AFI and NBI for an improved differentiation of adenomas and non-neoplastic colonic polyps among experienced and non-experienced endoscopists. An algorithm is presented in this study that combines information obtained by AFI and NBI in order to improve the overall diagnostic accuracy. As the role of endoscopic imaging may be different in patients with hyperplastic polyposis syndrome (HPS), we evaluated endoscopic tri-modal imaging for the differentiation of polyps in these particular patients in chapter 6. Subsequently, in chapter 7 we compared NBI to HRE in a randomized cross-over study regarding their miss-rates of polyps in patients with HPS. In this chapter NBI is also evaluated with respect to the differentiation of subtypes of polyps in these patients.

Part III: Role of endoscopic imaging in surveillance of ulcerative colitis

As the detection of neoplasia in patients with longstanding UC has been a challenge for decades, a lot of efforts have been made in order to improve colonoscopic surveillance in this population. However, since UC-associated neoplasia is considered difficult to detect, it is still recommended to take random biopsies in these patients at this moment. In chapter 8 we present our retrospective study evaluating the yield and clinical impact of random biopsies that were taken

during conventional colonoscopic surveillance of patients with UC over the last 10 years in our hospital. In chapter 9 we present our first randomized cross-over trial comparing prototype first-generation NBI to conventional colonoscopy for the detection of neoplasia in patients with UC. After our first study, we initiated a second randomized cross-over study comparing HRE and AFI for neoplasia detection in UC patients which is described in chapter 10. In this chapter we additionally evaluated NBI for its accuracy for the differentiation of neoplastic and non-neoplastic mucosa. Chapter 11 subsequently describes our most recently performed randomized cross-over trial comparing new-generation (and commercially available) NBI to high-definition endoscopy for the detection of neoplasia in patients with UC. Finally, in chapter 12 we present a pilot study evaluating the feasibility and diagnostic test accuracy of probe-based confocal laser endomicroscopy during colonoscopic surveillance of patients with UC.

Reference List

1 Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? Endoscopy 1998;30:437-443.

2 Kudo SE, Takemura O, Ohtsuka K. Flat and depressed types of early colorectal cancers: from East to West. Gastrointest Endosc Clin N Am 2008;18:581-93, xi.

3 Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-1035.

4 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.

5 Levin TR, Zhao W, Conell C, Seeff LC, Manninen DL, Shapiro JA, Schulman J. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145:880-886.

6 Heldwein W, Dollhopf M, Rosch T, Meining A, Schmidtsdorff G, Hasford J, Hermanek P, Burlefinger R, Birkner B, Schmitt W. The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. Endoscopy 2005;37:1116-1122.

7 Su MY, Hsu CM, Lin CJ, Ho YP, Chiu CT, Chen PC, Lien JM, Wu CS, Tung SY. Endoscopic treatment of colorectal neoplasms: a simple and safe procedure to lower the incidence of colorectal cancers. Dig Dis Sci 2008;53:1297-1302.

8 Consolo P, Luigiano C, Strangio G, Scaffidi MG, Giacobbe G, Di GG, Zirilli A, Familiari L. Efficacy, risk factors and complications of endoscopic polypectomy: Ten year experience at a single center. World J Gastroenterol 2008;14:2364-2369.

PART I

Critical appraisal of research in endoscopic imaging

CHAPTER 1

Review article: New developments in colonic imaging

Frank J.C. van den Broek
Paul Fockens
Evelien Dekker

Alimentary Pharmacology and Therapeutics 2007; 26 (Suppl 2): 91-99

ABSTRACT

Background: Colonoscopic detection and removal of neoplasia from the colorectum prevents the development of colorectal cancer. Sporadic adenomas and neoplasia associated with ulcerative colitis are frequently missed during colonoscopy, as a result of which interval cancers might develop.
Aim: To review new developments in colonoscopic imaging concerning the detection of neoplasia.
Methods: Medical databases were searched for relevant publications, dealing with advanced endoscopic imaging techniques during colonoscopy.
Results: Pancolonic chromoendoscopy has shown to increase the detection of sporadic adenomas and ulcerative colitis associated neoplasia, at the expense of longer examination times. As chromoendoscopy is labour intensive and time-consuming, its widespread use has been hampered. Narrow band imaging is a novel endoscopic imaging technique, which enhances mucosal and vascular details. Recent studies indicate that narrow band imaging has a high yield for neoplasia; however, no improvement compared to standard colonoscopy has been demonstrated. Autofluorescence imaging is another new technique for which blue endoscopic light is used to induce mucosal autofluorescence. So far, preliminary results have shown promising results of autofluorescence imaging for neoplasia detection.
Conclusion: Whether chromoendoscopy or novel advanced imaging techniques will change current colonoscopic practice depends on results of future studies comparing these different colonoscopic techniques.

Introduction

Colorectal cancer (CRC) is one of the most common cancers in western countries.[1, 2] Most CRC's are preceded by premalignant adenomas, providing an opportunity for early detection and removal of these precursor lesions.[3] Colonic clearing of adenomas reduces the incidence of CRC by approximately 80%.[4, 5] However, recent reports have shown that some patients under close colonoscopic surveillance still develop CRC at short intervals.[6-8] This may be explained by the fact that small adenomas are frequently missed during standard colonoscopy, as outlined in a systematic review of back-to-back colonoscopies.[9] Furthermore, flat and depressed lesions were scarcely detected in western countries until colonoscopies were performed in conjoint with Japanese endoscopists, who demonstrated that up to 40% of adenomas in western hospitals were of the flat and depressed type.[10, 12] These lesions had apparently been overlooked for many years, which is an omission since flat and depressed lesions have a substantial rate of submucosal invasion even when they are small.[11, 13]

Premalignant lesions which are particularly at risk to be missed are those in patients with longstanding ulcerative colitis (UC). In spite of a well known stage of premalignant neoplasia before developing CRC, neoplasia in UC frequently develops in flat and non-suspicious appearing mucosa.[14-18] Therefore, most guidelines recommend taking random biopsies in addition to targeted biopsies of suspicious lesions.[19-21] Despite this aggressive approach neoplasia is still frequently being missed, leading to interval cancers between successive surveillance colonoscopies.[22]

The use of novel endoscopic imaging techniques, which are feasible for broad field colonoscopic surveillance, aims to facilitate the detection of sporadic adenomas and neoplasia associated with UC.[23-25] Techniques that improve the detection of premalignant lesions during colonoscopy possibly optimize the potential for CRC prevention. In this review we evaluate the impact of real time endoscopic imaging techniques on the detection of sporadic adenomas and neoplasia in UC, bearing in mind the importance of the highest level of evidence provided by randomized controlled trials.

Chromoendoscopy

Chromoendoscopy (CE) makes use of absorptive or contrast stains, which are being applied to the colonic mucosa by a special spray catheter, during conventional white light endoscopy.[26, 27] The superficial structure of lesions is being enhanced by active mucosal uptake of dyes (absorptive stains) or by pooling of dyes in the colonic pits and ridges of polyps (contrast stains). The most used and investigated dyes in published series are methylene blue (absorptive) and indigo carmine (contrast).

Sporadic colorectal adenomas

A head to head comparison of pan colonic dye spraying and standard colonoscopy (SC) for the detection of sporadic adenomas has been performed in three randomized controlled trials.[28-30] Brooker et al randomized 259 patients to undergo either pan CE or SC. Among patients

undergoing CE more adenomas were detected compared to SC (125 versus 49), with a nearly significant difference (p=0.060). In subgroup analysis of only diminutive (<5mm) adenomas CE resulted in a significant (p=0.026) increased detection. However, this improvement was accompanied by a 2-fold increase in extubation time (9:05 *vs.* 4:52 minutes; p<0.0001). Since prolonged colonoscopic withdrawal times are known to be associated with higher adenoma detection rates[31], increased inspection time might have been a confounding factor in the results of this study. In a second study performed by Hurlstone *et al*, 260 patients were randomized to CE or SC.29 The use of CE led to a significant (p<0.05) increase in the detection of adenomas (112 *vs.* 57), without a difference in extubation times (17 *vs.* 15 minutes; p>0.1). However, all examinations were performed by only two experienced endoscopists, who had extensive training in Japanese chromoendoscopy techniques. The value of CE in 'conventionally' trained endoscopists remained to be cleared. In the third study, Lapalus *et al* performed back-to-back colonoscopies in 292 patients, using SC in the first pass and randomizing patients to CE or SC in the second pass.[30] By using additional CE more adenomas were detected compared to additional SC (115 *vs.* 87), but the difference was not significant (p=0.18). Subgroup analysis of adenomas <5mm again showed a significant increased detection by CE (p=0.009), but also in this study CE was associated with prolonged examination times.

From the three randomized studies we can conclude that CE increased the overall detection of adenomas, although statistically significant only in one study in which specifically trained endoscopists performed all examinations. Furthermore, there was a significant increase in the detection of diminutive adenomas at the cost of longer procedures, possibly acting as confounder. Other studies investigated the additional value of CE after a first examination with SC in back-to-back study designs and showed detection of extra adenomas at the second examination with CE.[32-35] However, it is known that SC is not infallible for adenoma detection and that a second inspection with SC will also increase the yield for adenomas.[36] In a more recent study comparing standard resolution endoscopy (performed in only one pass) to high resolution endoscopy with subsequent CE (in two passes), the latter techniques together failed to demonstrate an increased detection of adenomas despite prolonged examination time.[37] Therefore, the superiority of CE compared to SC with respect to the detection of adenomas remains to be proven in standard clinical practice with average experienced endoscopists.

Neoplasia associated with ulcerative colitis

At this moment two randomized trials have been performed comparing CE with SC for the detection of neoplasia in patients with longstanding UC.[38, 39] In the first study 165 patients with UC were randomly assigned to undergo surveillance with either methylene blue CE or SC.[38] Among patients undergoing CE there was a 3-fold increase (p=0.003) in detected neoplastic lesions, which especially concerned neoplasia in flat mucosa. However, the mean examination time for CE was 44 ± 12.2 minutes versus 35 ± 9.3 minutes for SC (not significant). In the second randomized study, performed by the same investigators, 153 patients with UC were randomized to CE or SC.[39] In this study CE was combined with confocal endomicroscopy for instant endoscopic diagnosis of lesions after detection by CE. Chromoendoscopy led to a significant (p=0.005) 5-fold increase in yield for neoplasia. The examination time for CE plus confocal microscopy was 42 minutes versus 31 minutes for SC alone, which was not significantly different

despite assessing a mean number of 70 confocal images per patient during ongoing endoscopy. Furthermore, 14 of the 19 detected neoplastic lesions in the CE arm of the study were invisible for conventional white light endoscopy and only visible after application of the dye, implying that an inspection with SC was also performed in these patients. Therefore, a significant increase in examination time in the CE arm of the study would have been expected. Unfortunately, no information was provided about endoscopists and their experience in each randomization arm. Since colonoscopies in the CE arm of the study encompassed an increased workload without an increase in examination time, this might well be a result of very experienced endoscopists performing CE plus confocal microscopy.

Next to the above mentioned trials, other non randomized studies also reported on the value of CE for neoplasia detection in UC.[40-42] Hurlstone *et al* performed a prospective study in 350 UC patients making use of dye spraying in a targeted fashion.[41] Subtle mucosal changes detected on SC were selectively highlighted by indigo carmine. The (non-randomized) control group consisted of 350 disease-matched patients undergoing SC only. Chromoendoscopy detected 69 neoplastic lesions compared to 24 by SC ($p<0.0001$). The authors concluded that CE represents the optimal tool for UC surveillance. However, there are a few remarks to this study. First, all CE procedures were performed by only one experienced endoscopist and all SC's were performed by other consultant endoscopists. Instead of comparing CE to SC, the results may also reflect differences in endoscopists. Second, CE was associated with a significant 2-fold increase in examination time, possibly confounding the results. Third, since both the intervention and control group underwent SC for primary inspection (before selectively applying dyes), subtle mucosal changes in the control group apparently were not sampled for histology. This statement is being strengthened by the fact that in the CE group almost twice as many targeted biopsies were taken after highlighting subtle mucosal changes with indigo carmine. This leads to an underestimation of neoplasia in the control group, since the amount of biopsies taken is associated with sampling error.[19] From this study we can conclude that SC is sufficient for raising suspicion about certain mucosal changes, but these suspicious areas should either be sampled for pathology or be enhanced by CE in order to determine whether neoplasia is suspected. In another study by Rutter *et al* back-to-back colonoscopies were performed in 100 UC patients, utilizing SC in the first pass and CE in the second pass.[40] All procedures were performed by one endoscopist and inspection times for SC and CE were comparable. In the first pass 2 neoplastic lesions were detected and in the second pass with CE 7 additional neoplastic lesions were detected ($p=0.06$).

In conclusion, the use of CE in surveillance of patients with UC increases the yield for neoplasia, but the highest level of evidence is only available from one experienced study group. Methodological inadequacies in other studies preclude recommendations for clinical practice. The role of increased inspection time and experience of endoscopists should be elucidated before recommending CE for surveillance of UC in general.

Narrow band imaging

Narrow band imaging (NBI) is a recently developed real time imaging technique, for which optical filters are being applied to the endoscopic light creating narrowed wavelength bands of blue

(400-430 nm) and green (530-550 nm) light for illumination of the mucosa. Furthermore, the intensity of the blue light component is being increased. Since blue light has only a superficial penetration depth into the mucosa and is the main colour absorbed by haemoglobin, this setting allows for detailed mucosal imaging with enhancement of small superficial capillaries.[43-45] Since the mucosal morphology is being enhanced without the use of dye spraying but with a push on a button on the endoscope, this technique is referred to as 'digital' or 'optical' chromoendoscopy.[46]

Sporadic colorectal adenomas

The use of NBI for analyzing colonic pit patterns of detected lesions has proven to be comparable to chromoendoscopy.[47-50] However, its use for the primary detection of sporadic adenomas has to be elucidated. So far, two randomized controlled trials have been performed.[51, 52] Rex and Helbig randomized 434 patients to undergo NBI or SC with high definition colonoscopes, results of which have been accepted for publication in *Gastroenterology*.[53] Narrow band imaging did not increase the detection rate of adenomas compared to SC (403 versus 395 adenomas), but the overall detection rate of adenomas in the studied patients exceeded all previous published series. One possible reason for this high yield is that all procedures were performed by one highly experienced endoscopist with a known high adenoma detection rate. Another explanation is that all procedures were performed with high definition colonoscopes with 170 degree angle of view, which have a 3-fold greater pixel density in their video-chip than high resolution endoscopes. Therefore, the question which remains to be answered is whether average experienced endoscopists can improve their colonoscopic performance by using NBI.

In another randomized study of 401 patients, adenomas were detected in 22.7% of patients with NBI and in 16.7% with SC (p=0.129).[52] Only in the first 100 cases NBI had a significantly improved performance compared to SC. The authors concluded that there might be a learning effect from NBI for SC.

At this moment, several studies are being performed investigating the value of NBI for adenoma detection.[54-60] The results of these studies have to be awaited and compared to the above mentioned trials with emphasis on experience of endoscopists. Furthermore, trials comparing CE and NBI are warranted to elucidate whether NBI (digital CE) can replace CE as a more convenient enhancement technique.

Neoplasia associated with UC

To date, there has only been performed one randomized cross over study comparing NBI and SC for the detection of neoplasia in patients with UC.61 In this study NBI failed to demonstrate a significant increase in neoplasia detection at the cost of more false positive findings among 42 patients with UC. Both NBI and SC missed about one third of all patients with neoplasia. Only the concomitant use of both techniques detected all but one patient with neoplasia, who had neoplasia only in random biopsies. However, in this study a prototype first generation NBI system was used, having insufficient imaging quality compared to newer systems (Evis Exera II or Evis Lucera, Olympus Medical Systems, Tokyo, Japan). Since CE, which is a candidate for routine use in UC surveillance, is a labour intensive and time consuming technique, NBI should be evaluated further in prospective studies. This research should focus on comparison of SC, CE and NBI in patients with longstanding UC, taking into consideration examination time and experience of endoscopists.

Autofluorescence imaging

When the colonic mucosa is being illuminated by ultraviolet (wavelength <400 nm) or short visible light (mostly blue) it produces autofluorescence (AF) light. This AF light has a longer wavelength than the illumination light and is produced by certain molecules ('fluorophores') in the colonic mucosa. Different groups of fluorophores produce AF of different wavelengths.[62] Except the constitution of fluorophores, mucosal AF is also influenced by tissue architecture (mucosal thickening), light absorption properties (haemoglobin is the main light absorber in the gastrointestinal tract), biochemical environment and metabolic status of the tissue.[63] Since AF of neoplastic mucosa differs from normal colonic tissue, AF can be used for discriminating these two tissue types.

Pioneering studies to AF of the colonic mucosa focused on point spectroscopic measurements.[64, 65] Fluorescence point spectroscopy proved to be highly accurate for discriminating neoplastic and non-neoplastic mucosa, but was not feasible for broad field surveillance.[66-69] Information gained by fluorescence spectroscopy was used to develop a real time fibre-optic fluorescence imaging system, but improvements in resolution and contrast were needed for practical use.[70-73] Recently, video endoscopic autofluorescence imaging (Olympus Medical Systems, Tokyo, Japan) has been developed, which to date has only been studied for the detection of neoplasia in Barrett's esophagus.[74, 75] Furthermore, the original fibre-optic based fluorescence imaging system has been improved (LIFE-GI, Xillix technologies corp, British Colombia, Canada).

Sporadic colorectal adenomas

So far, no papers have been published regarding autofluorescence imaging (AFI) for colonic adenoma detection. Two randomized studies have been performed which were reported in abstract form only.[76, 77] Both studies used prototype video endoscopic equipment (Olympus) incorporating AFI and high resolution SC in one system. A push on a button on the endoscope switches between the two endoscopic modes. Van den Broek *et al* investigated 87 patients with AFI and SC in back-to-back colonoscopies (per colon segment), randomizing for AFI or SC in the first pass.[76] Adenoma miss rates for AFI and SC were 27% and 30% respectively (p=0.515). A same study design was applied by Matsuda *et al*, only investigating the ascending and transverse colon.[77] In this study the adenoma miss rate for AFI was 29% versus 47% for SC (p=0.018). There apparently exists some incongruence about whether AFI can improve the detection of adenomas. In both studies, examination time for AFI and SC were equal. In the study performed by Matsuda *et al*, all procedures were performed by only one endoscopist versus 3 endoscopists in the study by van den Broek *et al*. Whether the improved adenoma detection by AFI in the second study is a result of only one endoscopist has to be clarified in further prospective comparative studies.

In addition to those studies, one non randomized back-to-back colonoscopy study has been performed in 30 patients with familial CRC syndromes, using SC in the first pass and fiber-optic AFI (Xillix) in the second.[78] The inspection with AFI was done by a second endoscopist and lesions were only sampled in the second pass, enabling paired analysis of data. In case of lesions seen on SC but missed by AFI, a third pass was performed for sampling these lesions as well. The authors found a doubling of the adenoma detection rate by AFI compared to SC

(30 *vs.* 16 adenomas). Autofluorescence imaging only missed one lesion, which was detected by SC. However, no information was provided in the abstract about experience of endoscopists in the SC and AFI pass, neither about the procedural times. Furthermore, the method how lesions detected in both passes were defined as being the same was not disclosed. Nevertheless, AFI seems sufficiently effective to be studied in larger trials. Again, experience of endoscopist and procedural time should be taken into account in these studies and comparisons should be made between CE, NBI and AFI after all.

Neoplasia associated with UC

The use of AFI for surveillance of patients with UC has been investigated in two studies, both reported as abstracts.[79, 80] Seaman *et al* performed SC in 17 patients, followed by a second inspection by AFI. The use of AFI increased the number of detected neoplastic lesions from 2 to 5 at the cost of a 3-fold increase in false positive biopsies.[79] No information was provided about examination time and experience of endoscopists. Van den Broek *et al* performed back-to-back colonoscopies (per colon segment) with AFI and SC in 50 patients with longstanding UC, who were randomized for the order of techniques.[80] Autofluorescence imaging detected 8 out of 9 (89%) neoplastic lesions versus 4 out of 7 (57%) by SC (not significant). Since both studies had a small sample size, these favourable results should be interpreted with caution and confirmed in larger prospective trials.

Summary and future directions

Colonoscopic surveillance of patients with an increased risk of developing adenomas or CRC is part of standard clinical practice. The aim of surveillance is the early detection and subsequent removal of premalignant lesions in order to prevent the occurrence of CRC. In patients with UC, the presence of neoplasia even warrants performing a colectomy. However, early premalignant lesions are frequently being missed by standard colonoscopy and interval cancers may occur despite intensive surveillance. Therefore, the main requirement for colonoscopy is to have a high sensitivity for the detection of those precursor lesions.

Chromoendoscopy is a relatively old and established technique, which has proven to increase the detection of both sporadic adenomas and neoplasia associated with UC in prospective randomized trials. However, only a few randomized studies have shown significant increased detection rates. Furthermore, those studies must be interpreted with caution, since highly experienced endoscopists performed the chromoendoscopic procedures and examination time possibly acted as confounder. Chromoendoscopy seems to be a candidate for implementation in surveillance programs for high risk patients, but it is a labour intensive and time consuming technique, which so far has prevented its wide spread use. Future studies to CE should focus on its value in daily clinical practice by average experienced endoscopists.

Narrow band imaging imitates CE but is a more convenient technique since a push on the button of the endoscope, instead of using dyes, highlights the mucosal structures and superficial capillaries of neoplastic lesions. However, only few studies in highly experienced hands have been performed with NBI so far. Since NBI is commercially available and is worldwide

distributed, more studies are foreseen which hopefully will provide definite results on its value in daily clinical practice. Of major clinical importance will be comparative studies between CE and NBI, since NBI is a more practical technique compared to CE.

So far, autofluorescence imaging is only available in prototype endoscopic equipment. In pilot studies AFI seems valuable for the detection of sporadic adenomas as well as for the colonoscopic surveillance in UC. Whether this technique will grow into clinical practice depends on results of prospective studies, which are being performed.

Reference List

1 Wilmink AB. Overview of the epidemiology of colorectal cancer. Dis Colon Rectum 1997;40:483-493.

2 Potter JD. Colorectal cancer: molecules and populations. J Natl Cancer Inst 1999;91:916-932.

3 Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525-532.

4 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, . Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.

5 Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48:812-815.

6 Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000;342:1149-1155.

7 Robertson DJ, Greenberg ER, Beach M, Sandler RS, Ahnen D, Haile RW, Burke CA, Snover DC, Bresalier RS, Keown-Eyssen G, Mandel JS, Bond JH, Van Stolk RU, Summers RW, Rothstein R, Church TR, Cole BF, Byers T, Mott L, Baron JA. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005;129:34-41.

8 Alberts DS, Martinez ME, Roe DJ, Guillen-Rodriguez JM, Marshall JR, van Leeuwen JB, Reid ME, Ritenbaugh C, Vargas PA, Bhattacharyya AB, Earnest DL, Sampliner RE. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med 2000;342:1156-1162.

9 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.

10 Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? Endoscopy 1998;30:437-443.

11 Saitoh Y, Waxman I, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, Pasricha PJ. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120:1657-1665.

12 Tsuda S, Veress B, Toth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. Gut 2002;51:550-555.

13 Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211-1214.

14 Ransohoff DF, Riddell RH, Levin B. Ulcerative colitis and colonic cancer. Problems in assessing the diagnostic usefulness of mucosal dysplasia. Dis Colon Rectum 1985;28:383-388.

15 Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS, Dean PJ, Kimmey M, Perera DR, Rabinovitch PS. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology 1992;103:1611-1620.

16 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-535.

17 Tytgat GN, Dhir V, Gopinath N. Endoscopic appearance of dysplasia and cancer in inflammatory bowel disease. Eur J Cancer 1995;31A:1174-1177.
18 Rutter M, Bernstein C, Matsumoto T, Kiesslich R, Neurath M. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. Endoscopy 2004;36:1109-1114.
19 Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:314-321.
20 Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002;51 Suppl 5:V10-V12.
21 Labianca R, Beretta GD, Mosconi S, Milesi L, Pessi MA. Colorectal cancer: screening. Ann Oncol 2005;16 Suppl 2:ii127-ii132.
22 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006;130:1030-1038.
23 Dekker E, Fockens P. Advances in colonic imaging: new endoscopic imaging methods. Eur J Gastroenterol Hepatol 2005;17:803-808.
24 Kiesslich R, Hoffman A, Neurath MF. Colonoscopy, tumors, and inflammatory bowel disease - new diagnostic methods. Endoscopy 2006;38:5-10.
25 Wallace MB, Sullivan D, Rustgi AK. Advanced imaging and technology in gastrointestinal neoplasia: summary of the AGA-NCI Symposium October 4-5, 2004. Gastroenterology 2006;130:1333-1342.
26 Jung M, Kiesslich R. Chromoendoscopy and intravital staining techniques. Baillieres Best Pract Res Clin Gastroenterol 1999;13:11-19.
27 Bruno MJ. Magnification endoscopy, high resolution endoscopy, and chromoscopy; towards a better optical diagnosis. Gut 2003;52 Suppl 4:iv7-11.
28 Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, Cardwell CR, Williams CB. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56:333-338.
29 Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376-380.
30 Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy 2006;38:444-448.
31 Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533-2541.
32 Stergiou N, Frenz MB, Menke D, Riphaus A, Wehrmann T. Reduction of miss rates of colonic adenomas by zoom chromoendoscopy. Int J Colorectal Dis 2006;21:560-565.
33 Kiesslich R, von BM, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001;33:1001-1006.
34 Lecomte T, Cellier C, Meatchi T, Barbier JP, Cugnenc PH, Jian R, Laurent-Puig P, Landi B. Chromoendoscopic colonoscopy for detecting preneoplastic lesions in hereditary nonpolyposis colorectal cancer syndrome. Clin Gastroenterol Hepatol 2005;3:897-902.

35 Hurlstone DP, Karajeh M, Cross SS, McAlindon ME, Brown S, Hunter MD, Sanders DS. The role of high-magnification-chromoscopic colonoscopy in hereditary nonpolyposis colorectal cancer screening: a prospective "back-to-back" endoscopic study. Am J Gastroenterol 2005;100:2167-2173.
36 Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-28.
37 Le Rhun M., Coron E, Parlier D, Nguyen JM, Canard JM, Alamdari A, Sautereau D, Chaussade S, Galmiche JP. High resolution colonoscopy with chromoscopy versus standard colonoscopy for the detection of colonic neoplasia: a randomized study. Clin Gastroenterol Hepatol 2006;4:349-354.
38 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.
39 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.
40 Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53:256-260.
41 Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005;37:1186-1192.
42 Hurlstone DP, McAlindon ME, Sanders DS, Koegh R, Lobo AJ, Cross SS. Further validation of high-magnification chromoscopic-colonoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2004;126:376-378.
43 Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004;9:568-577.
44 Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38:76-81.
45 Gheorghe C. Narrow-band imaging endoscopy for diagnosis of malignant and premalignant gastrointestinal lesions. J Gastrointestin Liver Dis 2006;15:77-82.
46 Sano Y, Muto M, Tajiri H, Ohtsu A, Yoshida S. Optical/Digital chromoendoscopy during colonoscopy using narrow-band imaging system. Dig Endosc 2005;17:S43-S48.
47 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.
48 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.
49 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.

50 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.

51 Helbig CD, Rex D. Narrow band imaging (NBI) verus white-light (WL) for colon polyp detection using high definition (HD) colonoscopes. 63 ed. 2006:AB213.

52 Adler A. Narrow Band Imaging (NBI) Influences the Learning Curve for Conventional Endoscopy - Final Results of a Prospective Randomized Study in the Detection of Colorectal Adenomas. 65 ed. 2007:AB116.

53 Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-47.

54 East JE, Suzuki N, Stavrinidis M, Palmer N, Guenther T, Thomas HJ, Saunders BP. Narrow band imaging (NBI) for colonoscopic surveillance in hereditary non-polyposis colorectal cancer (HNPCC) syndrome: a back-to-back study. Gastrointest Endosc 2007;65:AB126.

55 East JE, Suzuki N, Stavrinidis M, Palmer N, Guenther T, Saunders BP. Narrow band imaging improves adenoma detection in patients at high risk for adenomas: a randomised trial. Gastrointest Endosc 2007;65:AB95.

56 Kaltenbach TR, Friedland S, Soetikno RM. A new benchmark in the colorectal neoplasm miss rate during colonoscopy: results of a randomized controlled trial of wide angle view (170) colonoscopy comparing narrow band imaging and white light. Gastrointest Endosc 2007;65:AB127.

57 Rastogi A, Bansal A, Wani SB, Callahan P, Pandya PK, Mathur S, Sharma P. Does narrow band imaging (NBI) colonoscopy increase the detection rate of colon polyps? - A pilot feasibility study. Gastrointest Endosc 2007;65:AB259.

58 Shutian Z, Peng L, Zhonglin Y, Li Y, Ming J, Yongdong W, Xiaomei L, Yinglin N, Yongjun W, Hong Z. Detecting colorectal lesions at colonoscopy: a randomized con trolled comparison trial between conventional imaging, narrow band imaging and pancolonic indigo carmine and acetic acid dye. Gastrointest Endosc 2007;65:AB314.

59 Repici A, Hervoso CM, Preatoni P, Gambaro C, Danese S, Omodei P, Barbera R, De Caro G, Comunale S, Stefanelli T, Malesci A. A prospective study comparison of narrow band imaging (NB() versus chromoendoscopy with indigo carmine (IC) versus white light (WL) colonoscopy in the detection of adenomatous colonic lesions. Gastrointest Endosc 2007;65:AB351.

60 Rodriguez-Luna H, Gilani N, Ramirez FC. The role of high definition narrow band imaging endoscopy in the screening of colorectal neoplasia: initial experience with 100 consecutive patients. Gastrointest Endosc 2007;65:AB349.

61 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, Van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.

62 DaCosta RS, Andersson H, Wilson BC. Molecular fluorescence excitation-emission matrices relevant to tissue spectroscopy. Photochem Photobiol 2003;78:384-392.

63 DaCosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. Curr Opin Gastroenterol 2005;21:70-79.

64 Cothren RM, Richards-Kortum R, Sivak MV, Jr., Fitzmaurice M, Rava RP, Boyce GA, Doxtader M, Blackman R, Ivanc TB, Hayes GB, . Gastrointestinal tissue diagnosis by laser-induced fluorescence spectroscopy at endoscopy. Gastrointest Endosc 1990;36:105-111.

65 Kapadia CR, Cutruzzola FW, O'Brien KM, Stetz ML, Enriquez R, Deckelbaum LI. Laser-induced fluorescence spectroscopy of human colonic mucosa. Detection of adenomatous transformation. Gastroenterology 1990;99:150-157.
66 Schomacker KT, Frisoli JK, Compton CC, Flotte TJ, Richter JM, Deutsch TF, Nishioka NS. Ultraviolet laser-induced fluorescence of colonic polyps. Gastroenterology 1992;102:1155-1160.
67 Cothren RM, Sivak MV, Jr., Van DJ, Petras RE, Fitzmaurice M, Crawford JM, Wu J, Brennan JF, Rava RP, Manoharan R, Feld MS. Detection of dysplasia at colonoscopy using laser-induced fluorescence: a blinded study. Gastrointest Endosc 1996;44:168-176.
68 Mycek MA, Schomacker KT, Nishioka NS. Colonic polyp differentiation using time-resolved autofluorescence spectroscopy. Gastrointest Endosc 1998;48:390-394.
69 Mayinger B, Jordan M, Horner P, Gerlach C, Muehldorfer S, Bittorf BR, Matzel KE, Hohenberger W, Hahn EG, Guenther K. Endoscopic light-induced autofluorescence spectroscopy for the diagnosis of colorectal cancer and adenoma. J Photochem Photobiol B 2003;70:13-20.
70 Wang TD, Crawford JM, Feld MS, Wang Y, Itzkan I, Van DJ. In vivo identification of colonic dysplasia using fluorescence endoscopic imaging. Gastrointest Endosc 1999;49:447-455.
71 Brand S, Stepp H, Ochsenkuhn T, Baumgartner R, Baretton G, Holl J, von RC, Paumgartner G, Sackmann M. Detection of colonic dysplasia by light-induced fluorescence endoscopy: a pilot study. Int J Colorectal Dis 1999;14:63-68.
72 Haringsma J, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, Watanabe H, Sato N, Marcon N, Wilson BC, Cline RW. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53:642-650.
73 Wang TD, Triadafilopoulos G. Autofluorescence imaging: have we finally seen the light? Gastrointest Endosc 2005;61:686-688.
74 Kara MA, Peters FP, ten Kate FJ, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc 2005;61:679-685.
75 Kara MA, Peters FP, Fockens P, ten Kate FJ, Bergman JJ. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointest Endosc 2006;64:176-185.
76 van den Broek FJ, Hardwick JC, Reitsma JB, Kara MA, Fockens P, Dekker E. Endoscopic TriModality Imaging (ETMI) for the detection and classification of colonic polyps. Gastrointest Endosc 2007;65:AB93.
77 Matsuda T, Saito Y, Ikehara H, Mashimo Y, Parra-Blanco A, Fu K, Gotoda T, Saito D. Does autofluorescence imaging videoendoscopy system improve the colonoscopic adenoma detection rate? - A prospective study. Gastrointest Endosc 2007;65:AB346.
78 Ramsoekh D, Haringsma J, Van Leerdam ME, Poley JW, Kuipers EJ. Autofluorescence endoscopy improves detection of adenomas in patients with familial colorectal cancer: preliminary results of a back-to-back colonoscopy study. Gastrointest Endosc 2007;65:AB99.

79 Seaman DL, Gostout CJ, Smyrk TC, Sandborn WJ, Loftus EV, Rajan E, Lewis JT. Blinded comparison of white light surveillance colonoscopy to endoscopic autofluorescence imaging (AFI) and narrow band imaging (NBI) for detection of dysplasia in patients with chronic ulcerative colitis and/or concurrent primary sclerosing cholangitis (PSC) or known colorectal dysplasia or cancer: preliminary results of a pilot clinical trial. Gastrointest Endosc 2007;65:AB349.

80 van den Broek FJ, Hardwick JC, Reitsma JB, Stokkers PC, Fockens P, Dekker E. Endoscopic TriModality Imaging (ETMI) for detection and classification of neoplasia in patients with longstanding ulcerative colitis. Gastrointest Endosc 2007;65:AB256.

CHAPTER 2

Systematic review of narrow band imaging for the detection and differentiation of neoplastic and non-neoplastic lesions in the colon

Frank J.C. van den Broek
Johannes B. Reitsma
Wouter L. Curvers
Paul Fockens
Evelien Dekker

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Introduction

In the past decades, the perspective of diagnostic endoscopy has changed from diagnosing evident disease to the detection of subtle abnormalities. Modern endoscopic practice predominantly focuses on early detection and treatment of premalignant neoplasia, thereby interrupting the progression into unfavourable stages of malignancy. Endoscopic surveillance of high risk individuals has shown to be effective for preventing late stage esophageal and gastric cancer, as well as preventing colorectal cancer.[1-3] Although the detection of gastrointestinal neoplasia at an early and curable stage is of crucial clinical importance, the endoscopic visualization of early neoplasia can be difficult, which may lead to neoplasia miss-rates and interval cancers between two successive endoscopies.[4-7]

New imaging modalities, such as narrow band imaging (NBI), may allow for better detection of these early neoplastic lesions and thus improve the effectiveness of endoscopic surveillance and screening. Since NBI utilizes short wavelength (essentially blue) endoscopic light, which penetrates the mucosa only superficially and is mainly absorbed by hemoglobin, this technique highlights mucosal surface patterns and microvascular details (see figures 2-5; and video).[8, 9] The enhanced contrast provided by NBI can theoretically improve the detection of small and subtle mucosal lesions. In addition to a possible effect on detection, NBI has the potential for endoscopic differentiation of lesions ('endo-pathology') as well. Accurate differentiation during ongoing endoscopy has the advantage that on-table decisions can be made. In case of a presumed premalignant lesion, endoscopic resection may be performed immediately, whereas innocent non-neoplastic lesions may be left *in situ*.

Only recently, NBI has become commercially available leading to an accelerated uptake throughout the world. This systematic review summarizes the data on the performance and clinical utility of NBI during colonoscopy. The aims of this systematic review were to evaluate NBI concerning both the detection of premalignant lesions and the differentiation between neoplastic and non-neoplastic lesions.

Criteria for selecting studies

Eligible studies

Clinical trials or observational studies, assessing the performance of NBI colonoscopy with regard to the detection and/or the differentiation of lesions in the colon, were eligible for inclusion in this review. All patients undergoing colonoscopy were included, regardless of indication (screening, surveillance, symptoms).

Outcome measures

Studies reporting on the *detection* of neoplasia (adenomas) with NBI had to contain information on at least one of the following outcome measures: (1) the total number of detected neoplastic lesions; (2) the number or proportion of detected patients with at least one neoplastic lesion. With respect to these outcome measures of detection, the ideal comparison would be the histopathological evaluation of a complete colectomy specimen after performing NBI. Since this

comparison is unfeasible, NBI was compared to white light endoscopy (WLE) which is considered as current standard for the detection of neoplastic lesions.

With respect to studies reporting on *differentiation* between neoplastic and non-neoplastic lesions, the classification by NBI was compared against the reference standard which is the histopathological examination of biopsies or endoscopic resection specimen of the lesion of interest. Different classification systems co-exist for NBI and all of them were included in this review.[10-14] Studies should provide sufficient data to construct 2x2 tables comparing whether the target condition (neoplasia or adenoma) was present according to NBI (index test) against the final histopathology of the same lesion (reference standard).

Information on inter- and intra-observer agreement with respect to the classification by NBI was extracted, if presented.

Search strategy and selection of studies

Search strategy

Searches were conducted on published literature without calendar year restrictions. Studies were identified through electronic searches of Pubmed and EMBASE. In addition, reference lists of included studies were scanned for additional relevant studies (citation tracking).

The following strategy was used to search PubMed [search last conducted 3 April, 2008]: Narrow band imaging OR (Narrow band AND Endoscop*) OR (Narrow band AND colonoscop*). The following strategy was used to search EMBASE [search last conducted 3 April, 2008]: Narrow band imaging.mp. OR ((Narrow band.mp.) AND (exp INTESTINE ENDOSCOPY/ or exp ENDOSCOPY/ or exp DIGESTIVE TRACT ENDOSCOPY/ or exp GASTROINTESTINAL ENDOSCOPY/)) OR ((Narrow band.mp.) AND (colonoscopy.mp. or exp COLONOSCOPY/)).

Selection of studies

Two authors (FvdB and WC) independently screened the titles and abstracts of all studies identified by the abovementioned search strategy and obtained the full articles for all potentially relevant studies. Only articles published in English were included. The full text of these reports was assessed independently for eligibility. Any disagreement between the two assessors was resolved by discussion.

Assessment of methodological quality

The same two authors independently assessed the methodological quality of the included studies. The following quality items were scored for manuscripts reporting data on the *detection* of abnormalities: concealment of allocation, blinding of observers, patient selection and comparability of groups. A validated quality assessment tool for diagnostic accuracy studies (QUADAS) was used to assess the quality of studies reporting data on the *differentiation* of abnormalities.[15] The QUADAS consist of the following quality items: patient selection (item 1-2), appropriateness of reference standard (item 3-7), possibility for replication of the index test and reference standard (item 8-9), blinding (item 10-11) and applicability of the results in daily practice (item 12-14).[15] Each item of the QUADAS checklist was scored as “yes”, “no”, or “unclear”.

Data extraction

A data collection form was developed to extract relevant information from each included study. Two authors extracted the data separately and resolved differences by discussion until consensus was achieved. Data were extracted concerning study design, aim of study, patient selection, patient characteristics, allocation method and sources of bias. Concerning the *detection* of abnormalities, the numbers of detected neoplastic lesions and/or the numbers of patients with detected neoplasia were extracted. Concerning the *differentiation* of lesions, the total number of true positive (positive findings by NBI confirmed by histology), false positive (positive findings by NBI *not* confirmed by histology), true negative (negative findings by NBI confirmed by histology), and false negative findings (negative findings by NBI *not* confirmed by histology) were noted.

Data analysis

Detection

Two different outcomes were meta-analyzed for randomized studies comparing the detection capability of NBI with WLE: the proportion of patients with neoplasia (at least one adenoma) and the mean number of neoplastic lesions per patient.

The (logit transformed) odds ratio was used to compare the proportion of patients with detected neoplasia between NBI and WLE. The random effects approach of DerSimonian and Laird was used to calculate a pooled estimate with corresponding 95% confidence interval (95%-CI). This random effects model takes into account differences in sample size between studies (more weight to larger studies) and it properly incorporates any variability beyond chance in results between studies. Individual and pooled odds ratios were presented using Forrest plots.

The ratio of the mean number of detected neoplastic lesions by NBI relative to the mean number of detected neoplastic lesions by WLE was also used as outcome measure. The 95%-CI around this ratio was calculated assuming that the number of detected lesions would follow a Poisson distribution. A random effects pooling was performed if sufficient studies were available.

Differentiation

Each index test result by NBI was treated as dichotomous: suspicious (positive index test result) or unsuspicious (negative index test result) for neoplasia (adenoma). If several classification systems were used within one study for evaluating the index test (for example mucosal as well as vascular pattern), the mean number of true positive and negative index test results was used in the pooled analysis. Two-by-two tables were constructed showing the cross-classification of the index test results (NBI) versus the reference standard (histology) in order to calculate sensitivity and specificity (i.e. the underlying parameters of our analyses). To visualize data, Forrest plots were produced showing pairs of sensitivity and specificity together with 95% confidence intervals from each study. Confidence intervals were calculated using the Wilson score method. All analyses were done on a per-lesion basis, ignoring any possible correlation that might exist between multiple lesions within a patient.

If three or more studies were present, pairs of sensitivity and specificity were jointly meta-analyzed using a bivariate random effects approach.16 This approach enabled the calculation

of summary estimates of sensitivity and specificity while dealing with sources of within- and between-study variation and any correlation that might exist between sensitivity and specificity. The within-study variation or precision by which sensitivity and specificity have been measured was directly modeled based on the binomial distribution. The NLMIXED procedure of SAS was used to fit these bivariate random models.

Results

Description of studies

A total number of 34 reports on NBI for colonic use were retrieved by the search strategy. Eighteen manuscripts were reviews, commentaries or case reports.[17-34] The remaining 16 studies were clinical evaluations of NBI, either concerning the detection of neoplasia (n=5)[35-39], detection and differentiation of polyps (n=1)[40] or concerning the differentiation of lesions only (n=10).[11-14, 41-46] Only one of those studies assessed the value of NBI for the detection of neoplasia in patients with longstanding ulcerative colitis[36], and two studies reported on differentiation in these patients.[44, 46] The characteristics of all clinical studies are represented in table 1 and the methodological quality (QUADAS scores) of the studies on differentiation is represented in table 2.

Detection

Three large randomized trials have been performed, which directly compared NBI to WLE concerning the detection of colorectal adenomas.[35, 37, 39] In the study by Inoue *et al*, 243 patients were assigned to undergo either NBI or WLE.[39] This was the only study that demonstrated a significantly improved adenoma detection rate by NBI versus WLE (mean number of adenomas per evaluated patient of 0.84 versus 0.55; p=0.046) (Table 3). When comparing the proportions of patients with at least one adenoma between NBI and WLE, no advantage for NBI could be demonstrated. In this study, however, an insufficient allocation method caused inadequate distribution of NBI procedures among all participating endoscopists. One endoscopist (who performed most of the colonoscopies) was significantly more often allocated to NBI when compared to all the others (Chi square test: p<0.001). Detected differences in this study may therefore be attributed to the experience of this single endoscopist as well as to the use of NBI.

On the contrary, Rex *et al*[35] and Adler *et al*[37] could not demonstrate an increased adenoma detection rate (both per-lesion and per-patient) by NBI in two large (434 and 401 subjects) randomized studies. These studies were well designed large trials with sufficient quality concerning allocation, patient selection and comparability of randomization groups; blinding of endoscopists for the procedures is not feasible in this kind of studies. In the study by Adler *et al*, an initial improved detection of patients with adenoma(s) was equalized in the later phase of the study when gaining more experience with NBI, thereby postulating a learning effect from NBI that resulted in improved detection with WLE.

Some differences existed between the 3 randomized studies. Rex *et al* used high definition monitors which may improve adenoma detection compared to standard monitors. In addition, differences in NBI-systems, inclusion criteria and experience of endoscopists between the three

studies may make pooling of the results less valid. The pooled results of the 3 randomized studies revealed a non-significant increase of patients with at least one adenoma (odds ratio 1.19; 95%-CI: 0.86-1.64) or total number of adenomas (OR 1.23; 95%-CI: 0.93-1.61) when NBI was used for detection (table 3).

In addition to the randomized trials, two cross-sectional back-to-back colonoscopy studies have been performed using WLE as primary detection technique during the first pass and additional NBI during the second pass.[38, 40] No randomization was done for the sequence of the detection techniques. In the study by East *et al*, patients with hereditary non polyposis colorectal cancer syndrome (including Lynch syndrome) were consecutively included, whereas patients undergoing colorectal cancer screening were included in the study by Rastogi *et al*. Since no randomization was done and NBI was always performed during the second pass, the results of NBI from those studies could not reliably be compared to the abovementioned randomized trials.

In the two back-to-back colonoscopy studies, the adenoma miss-rates of WLE were 40% (29/72) and 46% (21/46), respectively, when an additional inspection was done with NBI (table 3).[38, 40] When comparing these data to historical adenoma miss-rates of WLE from a systematic review (overall miss-rate of 22%; 95%-confidence interval 15% to 32%), both studies demonstrated higher miss-rates.6 This suggests NBI to have an additional yield of adenomas when compared to WLE alone. However, since other endoscopy systems (lower quality charge coupled device chips) were used in historical studies and adenoma miss-rates do not take into account the total number of adenomas detected, a formal conclusion cannot be drawn from these studies.

Only one study by Dekker *et al* reported on the use of NBI for the detection of neoplasia in patients with longstanding ulcerative colitis.[36] In this study, a first prototype NBI system was compared to standard resolution WLE (CF-140 or CF-160 endoscopes; Olympus Inc.). All included patients underwent 2 colonoscopies: one with NBI for targeted biopsies only, and one with WLE for targeted plus random biopsies. Those procedures were performed with a time period of at least 3 weeks between the two examinations and the order of the procedures was randomized. This pilot study did not contain a predefined sample size and therefore included only 42 patients. In addition, a first prototype NBI system was used, having less brightness (Evis CLV-U40, Olympus Inc.) compared to current systems. In this study, NBI did not lead to an increased detection of neoplasia. On the contrary, both diagnostic strategies (NBI with targeted biopsies *vs.* WLE with targeted plus random biopsies) did not detect 4 out of 12 patients with neoplasia. Therefore, the sensitivity of NBI for detecting a patient with neoplasia was only 67%.

Differentiation

Nine studies reported on the use of NBI for differentiating neoplastic from non-neoplastic colonic polyps.[11-14, 41-43, 45] All studies concerned post-hoc image evaluation studies, except for the study by Katagiri *et al*[45] in which instant diagnoses were made during ongoing endoscopy. Several classification systems were used for assessments with NBI, all encompassing either mucosal (pit pattern) or vascular pattern (vascular pattern intensity, brown hue, dense vessels, irregular vessels).

Quality assessments were made for all differentiation studies of colonic polyps based on the QUADAS checklist and are represented in table 2. For all evaluated polyps, final histopathology

was used as reference standard which was performed blinded (or was unclear for blinding) in all studies. Details of the histopathological evaluation procedure were not provided in three studies and objective information on the assessment with NBI was not provided in four and unclear in one study (e.g. assessment of 'brown hue' or 'dense vessels'). In addition, blinded evaluation of NBI (without knowledge of the reference standard) was not stated, and therefore scored as *unclear*, in four studies. None of the studies reported on uninterpretable test results.

The two studies by Hirata *et al* [13, 42] selected patients on a retrospective basis leading to a large proportion of included colorectal cancers (>30%), and the study by Katagiri *et al* [45] excluded lesions with unsuspicious vascular pattern in order to evaluate only for differentiation of low-grade and high-grade dysplastic polyps. Therefore, these 3 studies were excluded from the final pooled analysis. The 6 remaining manuscripts had a proper study design plus representative patient selection and were selected for random effects pooling.[11, 12, 14, 40, 41, 43]

In these 6 studies, a total of 358 neoplastic (adenomas) and 158 non-neoplastic lesions were differentiated by NBI with sensitivities, specificities and overall accuracies varying between 83-97%, 64-100% and 77-93% respectively.[11, 12, 14, 40, 41, 43] The bivariate random effects 'pooled' summary estimates of sensitivity, specificity and overall accuracy for NBI in the colon are presented in table 4. The sensitivity, specificity and overall accuracy were 92% (95%-CI: 89-94), 86% (80-91) and 89% (87-91) respectively; information on diagnostic accuracy for each individual study is represented in figure 1. Five of those studies provided figures of accuracy for chromoendoscopy as well. Corresponding sensitivity, specificity and overall accuracy of chromoendoscopy were 91% (83-96), 89% (83-93) and 91% (85-94) (table 4 and figure 1).

In addition to the abovementioned differentiation studies of colonic polyps, only two studies addressed the use of NBI for differentiation of lesions in patients with longstanding ulcerative colitis.[44, 46] In the study by Matsumoto *et al*, patients underwent white light colonoscopy for the detection of visible protruded lesions, which were subsequently inspected by NBI for mucosal classification (honeycomb appearance, villous or tortuous pattern). In addition, multiple non-suspicious flat areas were inspected with magnification NBI for mucosal classification as well. In this study, 296 colonic areas were evaluated with NBI (20 protruded lesions and 276 areas of non-suspicious flat mucosa). The sensitivity, specificity and overall accuracy of NBI for differentiating neoplasia from non-neoplastic mucosa were 80% (95%-CI: 38-96), 84.2% (80-88) and 84.1% (80-88) respectively.[44] These rather disappointing values of accuracy may be questioned, since only one pathologist evaluated all biopsy specimens, although a second pathologist should confirm the presence of neoplasia in case of ulcerative colitis according to international guidelines.[47] Furthermore, only 5 neoplastic areas were included in the analysis, making the sensitivity particularly unsure.

In the second study by Van den Broek *et al*, patients were randomized for WLE or autofluorescence imaging concerning the detection of lesions; once detected, all lesions were assessed with NBI by using the Kudo classification.[46] Blinded histopathology (confirmed by a second expert gastrointestinal pathologist) was used as reference standard and all NBI assessments were made during ongoing endoscopy. In this study 16 neoplastic lesions and 82 non-neoplastic lesions were included with a reported sensitivity, specificity and overall accuracy for NBI of 75% (51-90), 81 (71-88) and 80% (71-86). These figures are comparable to the study by Matsumoto *et al*, with a wide 95%-confidence interval of the sensitivity as well.

Inter- and intraobserver agreement

Four differentiation studies reported to some extent on interobserver agreement (expressed in kappa values), but none evaluated intraobserver agreement.[11, 12, 14, 43] In only one study, an accurate description was given on the methods of measuring agreement with subsequent kappa calculation.[14]

In the study by Su *et al*, a kappa value of 1.0 was reached for NBI by 2 assessors who scored for brownish vascular network among 110 colorectal polyps. Although brown vascular network appears a subjective outcome measure, this led to a perfect score on interobserver agreement.[11] Another remarkable result from this study was a kappa value of 0.981 for the assessment with conventional WLE, which was based on reddish polyp color and polyp size on the images. In the study by Chiu *et al*, a sub study on interobserver agreement was performed, utilizing only 10 images per diagnostic modality.[12] The overall kappa value was 0.86, however no results were provided on each modality (including NBI) separately. In the study by Tischendorf *et al* 200 polyps were assessed by 2 observers, who had a perfect agreement for NBI (corresponding to a kappa of 1.0) based on mucosal as well as vascular patterns.[43] Finally, East *et al* were the only authors who provided sufficient details on the methods of their interobserver study. The assessment of NBI images of 32 polyps by 2 observers led to a kappa value of 0.48 (95%-CI: 0.18-0.77) for Kudo pit pattern and 0.64 (95%-CI: 0.35-0.92) for vascular pattern intensity, which corresponds to a moderate to good agreement.

Discussion

Since the recognition of a relatively high prevalence of flat and depressed colonic lesions in western countries many efforts are being made for improved visualization of these subtle lesions, which harbor an increased risk of malignant progression.[48-52] Until now, chromoendoscopy appeared exclusively to be associated with improved detection of those flat and usually small adenomas, as shown in three large randomized trials.[53-55] In addition, chromoendoscopy has proven to increase the detection of neoplasia in patients with ulcerative colitis.[56-59] However, methodological inadequacies in a few of these studies tend to overestimate the value of chromoendoscopy.[32] Furthermore, since chromoendoscopy is associated with increased procedure time, higher costs and labor intensive examination, this technique has not been implemented in daily clinical practice.[60] The use of NBI, which is also named 'digital chromoendoscopy', might be a more convenient and cost-effective alternative for chromoendoscopy, as NBI highlights mucosal structures without the use of dyes and visualizes vascular patterns as well.[19]

Despite the theoretical comparability of NBI and chromoendoscopy, the results of this systematic review reveal that NBI does not definitely improve the detection of adenomas. Only one out of three large randomized studies demonstrated a significant increased detection of adenomas by NBI, although the methods of allocation raised concerns of bias in this positive study.[39] In another randomized study, all colonoscopies were performed by only one highly experienced endoscopist who had an extraordinary high adenoma detection rate for both NBI and WLE.[35] Moreover, the study by Adler *et al* revealed a significant increased adenoma detection only in the initial phase of the study, postulating a possible learning effect from the use

of NBI.[37] Preliminary results of additional randomized studies have already been published in abstract form and hopefully will expand the already published evidence which was described in this review.[61-66] Whether endoscopists with limited experience may benefit from NBI should be evaluated in studies among non-expert endoscopists in a general clinical setting.

Concerning the improved detection of neoplasia in patients with ulcerative colitis which has been demonstrated for chromoendoscopy, the only randomized study evaluating NBI for this purpose did not show an increased detection of patients with neoplasia by NBI.[36] However, this trial was an underpowered pilot study and made use of a first generation NBI system with technical inadequacies. Future studies in ulcerative colitis should focus on new generation NBI systems with high definition or high resolution imaging and should compare NBI versus chromoendoscopy, preferably in general clinical setting. Thus far, the use of NBI for surveillance of neoplasia in ulcerative colitis cannot be recommended.

Besides the issue of improved detection, NBI also has the potential of endoscopic differentiation of neoplastic and non-neoplastic lesions by means of either mucosal pattern or vascular details. As shown by this review, NBI (using either mucosal or vascular patterns) has a comparable high sensitivity and specificity to chromoendoscopy, which has already been used for many years. With a sensitivity of 92% and specificity of 86%, NBI appears to have the potential to be used in clinical practice for differentiation of innocent hyperplastic polyps and premalignant adenomas. However, for safe clinical use the sensitivity should approach to 100%, since leaving adenomas *in situ* (with current sensitivity this would happen in 8% of all cases) may be harmful for patients. Future research therefore should focus on assessing the sensitivity of NBI among small versus large polyps, on defining learning curves for NBI differentiation, on interobserver variation in NBI assessments and on validation of NBI in general practice with endoscopists lacking extensive experience with this technique. Another important topic for upcoming research is the diagnostic value of NBI for differentiation of hyperplastic polyps and (sessile) serrated adenomas, which may endoscopically appear similar but have different malignant potential.[67-71] The prevalence of serrated adenomas among the subgroup of patients under investigation may therefore determine whether NBI can be used for differentiation. Lastly, the use of NBI should be compared to other differentiation techniques, such as autofluorescence imaging or confocal endomicroscopy, which may further improve the diagnostic accuracy.

In conclusion, this systematic review evaluated all available evidence on the diagnostic value of NBI with respect to the *detection* of colonic neoplasia/adenomas as well as the *differentiation* between neoplastic and non-neoplastic colonic polyps. Narrow band imaging is a relatively new technique, which has extensively been studied in the last few years as it has become commercially available all over the world. Until now, NBI has failed to demonstrate an improved *detection* of neoplasia in the colon, and therefore its use in routine clinical practice will likely not improve the yield of neoplasia. The value of NBI for *differentiating* neoplastic from non-neoplastic colonic polyps has proven to be associated with high sensitivity and specificity in experienced hands. Results on differentiation with NBI seem comparable to results achieved with chromoendoscopy; however, future research should focus on defining learning curves, interobserver variation and validation in general practice.

>> **For figures 2-5; see page 135-136**

Reference List

1 van Sandick JW, van Lanschot JJ, Kuiken BW, Tytgat GN, Offerhaus GJ, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998;43:216-222.

2 Whiting JL, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JW. The long term results of endoscopic surveillance of premalignant gastric lesions. Gut 2002;50:378-381.

3 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, . Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.

4 Yalamarthi S, Witherspoon P, McCole D, Auld CD. Missed diagnoses in patients with upper gastrointestinal cancers. Endoscopy 2004;36:874-879.

5 Robertson DJ, Greenberg ER, Beach M, Sandler RS, Ahnen D, Haile RW, Burke CA, Snover DC, Bresalier RS, Keown-Eyssen G, Mandel JS, Bond JH, Van Stolk RU, Summers RW, Rothstein R, Church TR, Cole BF, Byers T, Mott L, Baron JA. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005;129:34-41.

6 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.

7 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006;130:1030-1038.

8 Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004;9:568-577.

9 Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38:76-81.

10 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.

11 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.

12 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.

13 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Evaluation of microvessels in colorectal tumors by narrow band imaging magnification. Gastrointest Endosc 2007;66:945-952.

14 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.

15 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:1-13.

16 Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982-990.
17 Anandasabapathy S. Endoscopic imaging: emerging optical techniques for the detection of colorectal neoplasia. Curr Opin Gastroenterol 2008;24:64-69.
18 Singh R, Kaye PV, Ragunath K. Distinction between neoplastic and non-neoplastic colorectal polyps utilizing narrow band imaging with magnification: A novel technique to increase the efficacy of colorectal cancer screening? Scand J Gastroenterol 2008;43:380-381.
19 Sano Y, Muto M, Tajiri H, Ohtsu A, Yoshida S. Optical/Digital chromoendoscopy during colonoscopy using narrow-band imaging system. Dig Endosc 2005;17:S43-S48.
20 Sano Y, Horimatsu T, Fu KI, Katagiri A, Muto M, Ishikawa H. Magnifying observation of microvascular architecture of colorectal lesions using a narrow-band imaging system. Digestive Endoscopy 2006;18:S44-S51.
21 Sano Y, Muto M, Yoshida S. Observation using narrow band imaging (NBI) system during colonoscopy. Gastroenterological Endoscopy 2007;49:220-228.
22 Kato S, Fujii T, Koba I, Sano Y, Fu KI, Parra-Blanco A, Tajiri H, Yoshida S, Rembacken B. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? Endoscopy 2001;33:306-310.
23 Mizuno H, Gono K, Takehana S, Nonami T, Nakamura K. Narrow band imaging technique. Techniques in Gastrointestinal Endoscopy 2003;5:78-81.
24 Lammersdorf K, Kiesslich R. Early diagnosis of colorectal cancer with newly available endoscopic techniques. Verdauungskrankheiten 2006;24:282-290.
25 Larghi AMP, Lecca PG, Costamagna G. High Resolution Narrow Band Imaging Endoscopy. Gut 2008.
26 Lecca PG, Larghi A. Narrow band imaging. Argomenti di Gastroenterologia Clinica 2006;19:5-8.
27 East JE, Guenther T, Kennedy RH, Saunders BP. Narrow band imaging avoids potential chromoendoscopy risks. Gut 2007;56:1168-1169.
28 Gross SA, Wallace MB. Hold on Picasso, narrow band imaging is here. Am J Gastroenterol 2006;101:2717-2718.
29 Atkinson RJ, Hurlstone DP. Narrow-band imaging: the next frontier in colonoscopy? Gastrointest Endosc 2007;66:317-319.
30 Cohen J. Adenoma detection using high definition endoscopy - Does narrow band imaging increase the yield? Commentary. Evidence-Based Gastroenterology 2007;8:79-80.
31 East JE, Saunders BP. Look, remove, and discard: can narrow-band imaging replace histopathology for small colorectal polyps? It is time to push the button! Gastrointest Endosc 2007;66:953-956.
32 van den Broek FJ, Fockens P, Dekker E. Review article: New developments in colonic imaging. Aliment Pharmacol Ther 2007;26 Suppl 2:91-99.
33 Tanaka S, Oka S, Hirata M, Yoshida S, Kaneko I, Chayama K. Pit pattern diagnosis for colorectal neoplasia using narrow band imaging magnification. Digestive Endoscopy 2006;18:S52-S56.
34 Fu K, Tsujinaka Y, Hamahata Y, Matsuo K, Tsutsumi O. Squamous metaplasia of the rectum associated with ulcerative colitis diagnosed using narrow-band imaging. Endoscopy 2008.
35 Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-47.

36 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, Van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.

37 Adler A, Pohl H, Papanikolaou IS, bou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rosch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? Gut 2008;57:59-64.

38 East JE, Suzuki N, Stavrinidis M, Guenther T, Thomas HJ, Saunders BP. Narrow band imaging for colonoscopic surveillance in hereditary non-polyposis colorectal cancer. Gut 2008;57:65-70.

39 Inoue T, Murano M, Murano N, Kuramoto T, Kawakami K, Abe Y, Morita E, Toshina K, Hoshiro H, Egashira Y, Umegaki E, Higuchi K. Comparative study of conventional colonoscopy and pan-colonic narrow-band imaging system in the detection of neoplastic colonic polyps: a randomized, controlled trial. J Gastroenterol 2008;43:45-50.

40 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2008;67:280-286.

41 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.

42 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.

43 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.

44 Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc 2007;66:957-965.

45 Katagiri A, Fu KI, Sano Y, Ikematsu H, Horimatsu T, Kaneko K, Muto M, Yoshida S. Narrow band imaging with magnifying colonoscopy as a diagnostic tool for predicting the histology of early colorectal neoplasia. Aliment Pharmacol Ther 2008.

46 van den Broek FJ, Fockens P, van eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.

47 Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:314-321.

48 Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? Endoscopy 1998;30:437-443.

49 Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211-1214.

50 Saitoh Y, Waxman I, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, Pasricha PJ. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120:1657-1665.
51 Tsuda S, Veress B, Toth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. Gut 2002;51:550-555.
52 Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-1035.
53 Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, Cardwell CR, Williams CB. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56:333-338.
54 Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376-380.
55 Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy 2006;38:444-448.
56 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.
57 Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53:256-260.
58 Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005;37:1186-1192.
59 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.
60 Johanson JF. Practicality of high-resolution chromoendoscopy during routine screening colonoscopy. Gastrointest Endosc 2006;63:829-830.
61 East JE, Suzuki N, Stavrinidis M, Palmer N, Guenther T, Saunders BP. Narrow band imaging improves adenoma detection in patients at high risk for adenomas: a randomised trial. Gastrointest Endosc 2007;65:AB95.
62 Kaltenbach TR, Friedland S, Soetikno RM. A new benchmark in the colorectal neoplasm miss rate during colonoscopy: results of a randomized controlled trial of wide angle view (170) colonoscopy comparing narrow band imaging and white light. Gastrointest Endosc 2007;65:AB127.
63 Shutian Z, Peng L, Zhonglin Y, Li Y, Ming J, Yongdong W, Xiaomei L, Yinglin N, Yongjun W, Hong Z. Detecting colorectal lesions at colonoscopy: a randomized con trolled comparison trial between conventional imaging, narrow band imaging and pancolonic indigo carmine and acetic acid dye. Gastrointest Endosc 2007;65:AB314.
64 Rodriguez-Luna H, Gilani N, Ramirez FC. The role of high definition narrow band imaging endoscopy in the screening of colorectal neoplasia: initial experience with 100 consecutive patients. Gastrointest Endosc 2007;65:AB349.

65 Repici A, Hervoso CM, Preatoni P, Gambaro C, Danese S, Omodei P, Barbera R, De Caro G, Comunale S, Stefanelli T, Malesci A. A prospective study comparison of narrow band imaging (NB() versus chromoendoscopy with indigo carmine (IC) versus white light (WL) colonoscopy in the detection of adenomatous colonic lesions. Gastrointest Endosc 2007;65:AB351.

66 Adler A, Yenerim T, Aschenbeck J, Mayr M, Aminalai A, Drossel R, Schröder A, Scheel M, Papanikolaou S, Wiedenmann B, Roesch T. Narrow Band Imaging Versus Conventional Colonoscopy for Screening Colonoscopy in a Private Practice Setting - A Large Prospective Randomized Trial. Gastrointest Endosc 2008;67:AB100-AB101.

67 Jaramillo E, Watanabe M, Rubio C, Slezak P. Small colorectal serrated adenomas: endoscopic findings. Endoscopy 1997;29:1-3.

68 Matsumoto T, Mizuno M, Shimizu M, Manabe T, Iida M, Fujishima M. Serrated adenoma of the colorectum: colonoscopic and histologic features. Gastrointest Endosc 1999;49:736-742.

69 Rubio CA, Jaramillo E. Flat serrated adenomas of the colorectal mucosa. Jpn J Cancer Res 1996;87:305-309.

70 Jass JR, Baker K, Zlobec I, Higuchi T, Barker M, Buchanan D, Young J. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.

71 Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. Am J Clin Pathol 2005;124:380-391.

Table 1: Characteristics of colon studies, subdivided into studies regarding the detection and the differentiation of abnormalities

Detection of adenomas / neoplasia by NBI								
author, year	**ref**	**study design**	**N**	**inclusion criteria**	**mean age/ male (%)**	**number and experience of endoscopists**	**inspection time (min.) WLE vs. NBI**	**number of false positives WLE vs. NBI†**
Rex 2007	35	RCT: NBI vs. WLE	434	- CRC screening (n=257) - Surveillance (n=167) - Other (n=10)	62.5 / 231 (53%)	1 highly experienced endoscopist	7.3 vs. 7.7	-
Adler 2007	37	RCT: NBI vs. WLE	401	- Surveillance (n=45) - Symptoms (n=226) - Other (n=130)	59.4 / 211 (53%)	7 endoscopists without previous experience with NBI	10.7 vs. 12.2	32 vs. 106
East 2007	38	Tandem design: WLE - NBI	62	- HNPCC (n=62)	46.0 / 24 (39%)	1 experienced endoscopist (including NBI) performed most colonoscopies (>90%)	6.6 vs. 7.0	33 vs. 31
Rastogi 2008	40	Tandem design: WLE - NBI	40	- CRC screening (n=40)	62.0 / 40 (100%)	1 experienced endoscopist with unknown experience with NBI	-	29 vs. 22
Inoue 2008	39	RCT: NBI vs. WLE	243	- Surveillance (n=193) - Symptoms (n=50)	62.0 / 150 (62%)	6 endoscopists with unknown experience, of whom 1 performed >60% of colonoscopies	8.5 vs. 8.8	12 vs. 24
Dekker 2007	36	RCT cross-over design: NBI vs. WLE	42	- Longstanding UC (pancolitis) (n=42)	50.0 / 31 (74%)	3 experienced endoscopists (first evaluation of NBI)	47 vs. 50	16 vs. 43
Differentiation based on NBI patterns								
author, year	**ref**	**study design**	**N**	**index test (NBI classifications used)**	**reference standard (histology)**	**mean age/ male (%)**	**number and experience of endoscopists (observer)**	
Rastogi 2008	40	image evaluation	40	fine capillary network, dark dots, light rounds, tubular or gyrus-like	- TA (n=29) - HP (n=22)	62.0 / 40 (100%)	1 experienced observer with unknown experience with NBI	
Machida 2004	41	selected patients: image evaluation	34	Kudo classification (type I-II for non-neoplastic mucosa; III-V for neoplasia)	- HGD (n=9) - LGD (n=25) - HP (n=9)	? / 22 (65%)	2 observers with unknown experience	
Su 2006	11	consecutive image evaluation	78	brownish vascular network for predicting neoplasia	- CRC (n=5) - TA (n=32) - TVA (n=13) - VA (n=20) - HP (n=40)	51.3 / 42 (54%)	2 experienced observers	

Chiu 2007	12	consecutive image evaluation	133	brown blob or dense vascular network for predicting neoplasia	- CRC (n=1) - VA (n=1) - TVA (n=4) - TA (n=134) - SA (n=1) - HP (n=35) - other (n=4)	54.6 / 75 (56%)	2 experienced observers
East 2007	14	image evaluation	20	Kudo classification and vascular pattern intensity (light, equal or dark compared to surroundings)	- TA (n=21) - HP (n=9) - Other (n=2)	? / ?	2 experienced observers
Hirata 2007	42	retrospective: unclear evaluation	99	Kudo classification	- CRC (n=48) - TA (n=84) - HP (n=16)	? / ?	Unclear, probably 1 endoscopist
Hirata 2 2007	13	retrospective: unclear evaluation	163	vessel thickness (3 categories) and vessel regularity (4 categories)	- CRC (n=60) - TA (n=109) - HP (n=20)	? / ?	2 highly experienced endoscopists
Tischendorf 2007	43	randomized image evaluation	99	Kudo classification as well as vascular pattern (fine capillary network or increased tortuous cork-screw type vessels)	- CRC (n=7) - VA (n=3) - TVA (n=35) - TA (n=78) - non neoplastic (n=77)	68.7 / 51 (52%)	2 observers with unclear experience
Katagiri 2008	45	consecutive real time evaluation	104	capillary pattern: honeycomb like or not	- CRC (n=21) - HGD (n=9) - LGD (n=104)	64.6 / 80 (77%)	1 endoscopist performing endoscopy, and 1 independent observer assessing polyps in real time (?)
Matsumoto 2007*	44	real time evaluation	46	honeycomb-like, tortuous or villous like pattern	- HGD (n=3) - LGD (n=2) - non neoplastic (n=291)	38.2 / 20 (43%)	1 experienced endoscopist
Van den Broek 2008*	46	real time evaluation	50	Kudo classification	- HGD (n=1) - LGD (n=15) - non neoplastic (n=82)	50.4 / 31 (62%)	3 experienced endoscopists

ref reference number, N number of included patients, NBI narrow band imaging, WLE white light endoscopy, RCT randomized controlled trial, CRC colorectal cancer, HNPCC hereditary non polyposis colorectal cancer, UC ulcerative colitis, HGD high grade dysplasia, LGD low grade dysplasia, VA villous adenoma, TVA tubulovillous adenoma, TA tubular adenoma, SA serrated adenoma, HP hyperplastic polyp, * studies in patients with longstanding ulcerative colitis, † number of non-neoplastic lesions removed

Table 2: Methodological quality of included studies on differentiation of colonic polyps [QUADAS items]

	Rastogi, 2008	Machida, 2004	Su, 2006	Chiu, 2007	East, 2007	Hirata, 2007	Hirata 2, 2007	Tischendorf, 2007	Katagiri, 2008
1. Patient spectrum	yes	yes	yes	yes	unclear	no	no	no	no
2. Selection criteria	yes	no	unclear	yes	no	no	no	no	yes
3. Reference standard	yes	yes	yes	yes	yes	yes	yes	yes	yes
4. Disease progression	yes	yes	yes	yes	yes	yes	yes	yes	yes
5. Partial verification	yes	yes	yes	yes	yes	yes	yes	yes	yes
6. Differential verification	yes	yes	yes	yes	yes	yes	yes	yes	yes
7. Incorporation	yes	yes	yes	yes	yes	yes	yes	yes	yes
8. Test details	unclear	yes	no	no	yes	no	no	yes	yes
9. Reference standard details	yes	yes	no	yes	no	yes	yes	no	yes
10. Test bias	yes	unclear	yes	unclear	yes	unclear	unclear	yes	yes
11. Review bias	yes	unclear	unclear	yes	yes	yes	yes	unclear	unclear
12. Clinical data	no	no	no	no	no	no	no	no	yes
13. Uninterpretable results	unclear	no	no	unclear	-	no	no	no	no
14. Withdrawals	unclear	no	yes	no	yes	no	no	no	yes

'yes' means good quality concerning the topic of interest, 'no' means poor quality, 'unclear' means unsure about quality

Table 3: Percentage of patients with at least 1 adenoma and mean number of adenomas per examined patient for NBI versus WLE (randomized controlled trials) and adenoma miss-rates (per patient and per adenoma) for WLE when an additional inspection was done by NBI (back-to-back colonoscopy studies)

Randomized controlled trials: NBI vs. WLE								
Author, Year	**N NBI**	**N WLE**	**Patients with adenoma detected by NBI (%)**	**Patients with adenoma detected by WLE (%)**	**Odds ratio (95%-CI) of NBI vs. WLE**	**N of adenomas detected by NBI (mean per patient)**	**N of adenomas detected by WLE (mean per patient)**	**Relative ratio (95%-CI) of means for NBI vs. WLE**
Rex, 2007	217	217	140 (65%)	145 (67%)	0.90 (0.61-1.34)	403 (1.86)	395 (1.82)	1.02 (0.89-1.17)
Adler, 2007	198	198	45 (23%)	33 (17%)	1.47 (0.89-2.42)	65 (0.33)	51 (0.26)	1.27 (0.88-1.84)
Inoue, 2008	122	121	51 (42%)	41 (34%)	1.40 (0.83-2.36)	103 (0.84)#	66 (0.55)#	1.55 (1.14-2.11)
Pooled results	537	536	236 (44%)	219 (41%)	1.19 (0.86-1.64)	571 (1.06)	512 (0.96)	1.23 (0.93-1.61)
Back-to-back colonoscopy studies: WLE followed by NBI								
Author, Year	**N WLE**	**N NBI**	**Patients with adenoma detected by WLE (%)**	**Added patients with adenoma by NBI (%)**	**Miss-rate of patients with adenoma**	**N of adenomas detected by WLE (mean per patient)**	**N of adenomas detected by NBI (mean per patient)**	**Adenoma miss-rate**
Rastogi, 2008*	40	40	-	-	-	43 (1.08)	29 (0.73)	29/72 (40%)
East, 2007*	62	62	17 (27%)	9 (15%)	17/26 (65%)†	25 (0.40)	21 (0.34)	21/46 (46%)

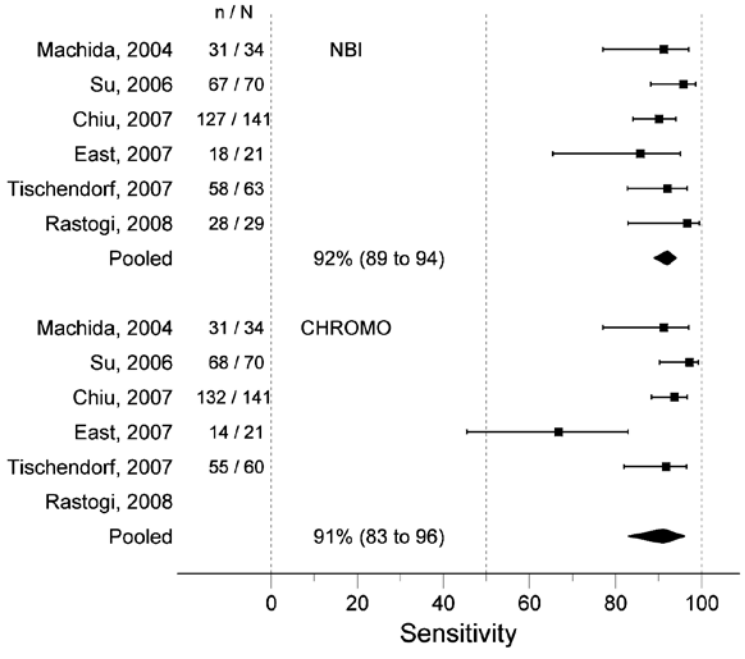
N number of subjects, WLE white light endoscopy (reference standard for detection), NBI narrow band imaging, *back-to-back colonoscopy studies: represented figures correspond for first inspection (reference) with WLE, # includes 2 invasive cancers, † some patients with missed adenomas already had adenomas detected by WLE

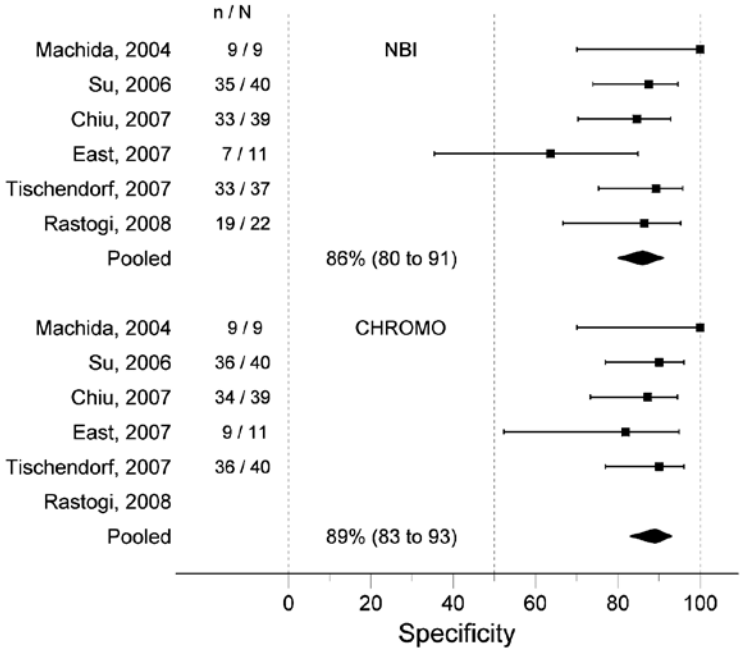
Table 4: Accuracy of the index tests (classification with NBI or chromoendoscopy) for the differentiation of neoplastic (adenoma) versus non-neoplastic colonic polyps: summary estimates of sensitivity, specificity and overall accuracy from a bivariate random effects model

Test	N of studies	N neoplastic lesions	N non-neoplastic lesions	Sensitivity (95% CI)	Specificity (95% CI)	Overall accuracy (95% CI)
NBI *	6	358	158	92% (89% to 94%)	86% (80% to 91%)	89% (87% to 91%)
Chromoendoscopy	5	326	139	91% (83% to 96%)	89% (83% to 93%)	91% (85 to 94%)

* pooled data of all classification systems with NBI (e.g. Kudo classification, vascular pattern intensity etc.)

Figure 1: Forrest plots of sensitivities and specificities concerning the differentiation (adenoma versus non-neoplastic polyp) by NBI and corresponding chromoendoscopy per individual colon study as well as the pooled results (obtained with bivariate random effects method).





CHAPTER 3

Valid and efficient study designs for the evaluation of new colonoscopic techniques: clinical and statistical considerations

Frank J.C. van den Broek
Evelien Dekker
Aeilko H. Zwinderman
Paul Fockens
Johannes B. Reitsma

Submitted

Introduction

Optical colonoscopy is considered the "gold standard" for the detection of premalignant lesions in the colon.[1] However, polyps are frequently overlooked by standard colonoscopy and polyp miss-rates are estimated to be as high as 26% for lesions £5mm.[2] In recent years, novel endoscopic imaging techniques have overwhelmed colonoscopic research in order to improve the *detection* of neoplastic lesions.[3] In addition, these new imaging techniques may also be able to *differentiate* neoplastic from non-neoplastic polyps, thereby enabling the endoscopist to leave non-neoplastic lesions *in situ* and making colonoscopy more efficient.[4, 5]

Several imaging techniques (e.g. chromoendoscopy, narrow band imaging) have extensively been evaluated for their ability to detect colonic polyps on one hand, and for their diagnostic accuracy in differentiating neoplastic from non-neoplastic polyps on the other hand.[6-15] Critical appraisal of these studies reveals remarkable differences in study design and statistical analysis, despite their similar objectives. The aim of this paper is to critically evaluate reported study designs, thereby focusing on validity and efficiency.

Regarding their ability to differentiate neoplastic from non-neoplastic polyps, new colonoscopic techniques can be compared using the classical design to evaluate diagnostic tests (i.e. comparing the index test result against a high quality reference standard, which is the histological examination of the polyp).[4, 5, 15-19] The design, reporting and evaluation of such differentiation studies can methodologically be guided by the Standards for Reporting of Diagnostic Accuracy (STARD) initiative and the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS).[20, 21]

Methodological papers about studies evaluating new colonoscopic techniques with respect to their capability to detect polyps are lacking and therefore the focus of our paper is on detection. The detection of polyps is a methodologically challenging subject due to the lack of a high quality reference standard against which the new technique can be compared, and due to the possibility of multiple polyps within one patient. A colonoscopic technique should ideally detect all colonic polyps that are present within one patient, and hence the test result cannot be defined as a single dichotomous variable as in the classical evaluation of a diagnostic test.

In the next section we describe and critically compare the three most commonly reported study designs and discuss their respective methodology, outcome measures, and statistical analyses. In the final section, we present a flowchart that provides methodological guidance to researchers planning a colonoscopic *detection* study and to readers for critical appraisal of such studies.

Study designs to evaluate colonoscopic techniques for detection of polyps

A Parallel randomized design

Acknowledging that a traditional accuracy study for the purpose of detection is not possible because an acceptable reference standard does not exist, an alternative is to use a study with a parallel-randomized design (figure 1). In this design, patients are randomized to receive either

examination with technique A or technique B. At the end of the study we directly compare the number of detected polyps (*per-lesion analysis*) or the proportion of patients with ≥1 polyp (per-patient analysis) between both arms.[8-11, 22-25]

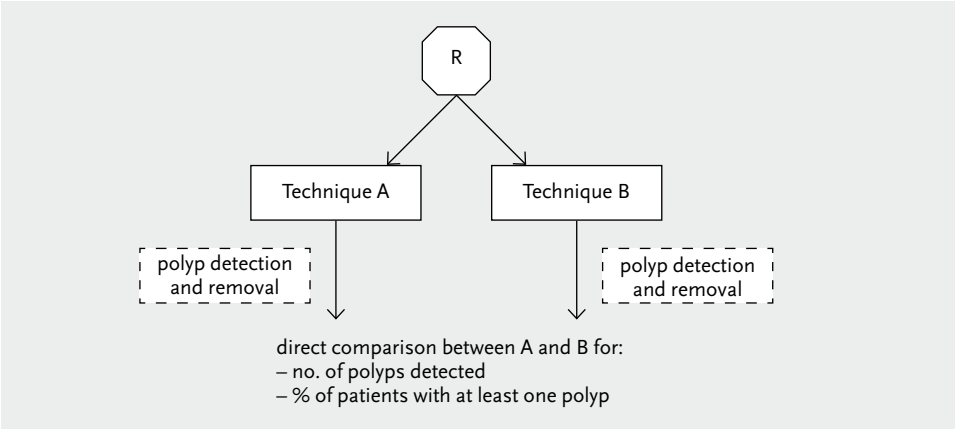


Figure 1: Parallel randomized study design comparing two colonoscopic techniques (A *vs.* B).

Validity and efficiency

Due to the randomization, the expected number of polyps or expected proportion of patients with ≥1 polyp will, on average, be the same in both arms of the study. Therefore, the results are unbiased, meaning that if such a trial would be repeated many times, the average result would be similar to the true effect. In a single study, however, differences in the number of polyps between the two arms can be expected just by chance. Such differences have a strong impact on the final results because the presence of more polyps directly means that more polyps can be detected. So any mismatch in the number of polyps at baseline has a direct and large effect on the results.

The analogy with an intervention trial would be an imbalance in a major risk factor between treatment groups. Researchers will try to avoid such an imbalance by either stratified randomization or minimization. These techniques may be used in diagnostic colonoscopy studies as well, as the number of polyps in patients at baseline may partially be predicted by the age of the patient, gender, and colonoscopy indication.[26, 27] However, the presence of polyps in patients is not fully understood, meaning that imbalances at baseline in the number of polyps cannot be avoided. This implies that results from one trial to another will vary just because of this random noise, and sample sizes need to be sufficient large to discover real differences in detection capability between techniques (see also results of our simulation study in the appendix). In addition, polyp detection rates may vary greatly between different endoscopists and between different examination times.[28-31]

Outcome measures and analysis

The results of the parallel, randomized design can be analyzed on a *per-polyp* basis or on a *per-patient* basis. The former has the advantage of more statistical power, since each polyp will generate information about the detection capability of a technique. Besides, the detection of each

individual polyp has clinical significance, as each polyp may be premalignant. In situation with multiple lesions there is the issue of correlation in detection within a patient. In general, correlation is ignored as the impact of patient factors on detection is considered limited.

This means that the *number of detected polyps per patient* should be used as primary outcome measure for comparison of the two techniques (with non-parametric Wilcoxon rank or Mann-Whitney U testing to detect a shift in distribution towards more polyps). Additionally, the *proportion of patients with ≥1 polyp* may be used as secondary outcome measure (Chi-square or Fisher's exact testing).

Example from literature

A parallel randomized study by Inoue *et al* can illustrate the reporting and analysis of this type of study design.[9] Patients planned for surveillance, screening or diagnostic colonoscopy were randomized to undergo either conventional colonoscopy (n=121) or narrow band imaging (n=122). The procedures were performed by one of six endoscopists who were allowed to select one out of two colonoscopes (PCF-240ZI or CF-H260AI, Olympus Inc., Tokyo, Japan) having different resolutions. The main outcome measure was the number of adenomas (e.g. mean number of adenomas per included patient), which resulted in 102 adenomas (0.84 per patient) for narrow band imaging *vs.* 65 (0.55 per patient) for conventional colonoscopy (Student's t-test; p=0.046).

Although patients were well balanced for age, gender, indication, and level of bowel preparation, and examination times were comparable between both randomization groups, it was not reported that one of the six endoscopists performed significantly (p<0.001; calculated from their results with Chi-square testing) more procedures with narrow band imaging in this study. Consequently, the difference in performance between the two techniques may be attributed to the experience of this single endoscopist. Stratification could have prevented this imbalance in endoscopists.

The authors used the Student's t-test was used for comparison but should be reserved for comparing normally distributed data. As the number of adenomas per patient varied greatly and most patients did not harbor adenomas at all, the adenoma distribution was skewed. Consequently, a non-parametric test would have been more appropriate and probably more powerful.

The main uncertainty remains whether the true number of polyps was equally distributed at baseline in this study. Substantial differences in the number of polyps can occur just by chance. These differences can be large in comparison to the expected differences in detection rate between the two techniques being evaluated. A relatively large difference at baseline will dominate the results of the study, basically making the study useless (uninformative). Our simulations show that to detect an absolute difference of 10% in detection rate (80 *vs.* 90%), the required sample size is around 2000 patients per group to achieve a power of 80% (see table 1, first row of results; or see appendix for further details). This is much higher than the number of patients required to detect a difference in a study where the proportion of patients with an event is 80 *vs.* 90%; a sample size of 200 per group would then be sufficient. Several adjustments in study design have been proposed to reduce the noise generated by an imbalance in the number of polyps at baseline.

B Sequential (back-to-back) design with fixed order

The most encountered attempt to increase the efficiency of a study comparing two colonoscopic techniques is using a sequential design with fixed order (i.e. back-to-back procedure). Technique A is applied first in all patients and any detected polyp is removed immediately. In a subsequent second examination, all patients are evaluated again but now with technique B (generally the more novel technique) to assess whether it can detect additional polyps, e.g. polyps missed by the first technique (see figure 2).[32-38]

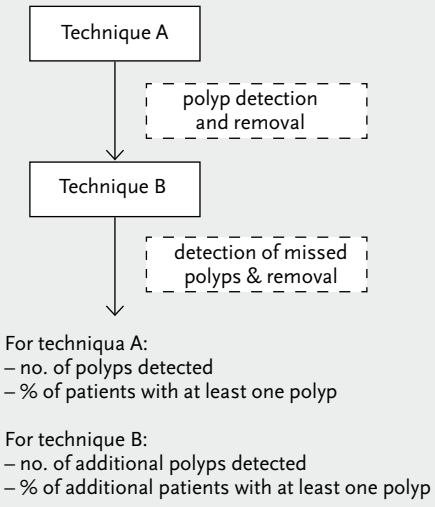


Figure 2: Sequential study design with fixed order: A colonoscopic examination with technique A is followed by a second examination with technique B. Polyps detected by technique A are removed immediately, as a result of which only missed polyps can be picked up by technique B.

Validity and efficiency

The potential for increased efficiency by this design lies within the fact that each patient is examined by both techniques.[39] However, this sequential design with fixed order is only informative if the underlying research question is whether the new technique should be added to the existing technique, i.e. the intended role of the new technique is that of an add-on test.[40] New techniques are valuable as add-on tests when they are capable of identifying additional polyps.

In case the underlying question is whether either technique A *or* B should be used for the detection of polyps (replacement question), this study design does not provide informative evidence. The reason is that it remains unknown what would be the performance of technique B with respect to polyps that have already been detected and removed by technique A. The assumption that all these polyps would have been identified by technique B as well is untenable, given the fact that polyp miss-rates up to 48% have been reported for standard colonoscopic techniques.[28] The bottom line is that for the decision whether to use either technique A or B for polyp detection, this study design is not providing the right evidence and should not be used.

In case the study objective is indeed that of an add-on diagnostic test (should we use technique B on top of technique A?), a study design with two arms using technique A first during both study arms and randomizing between technique A and B for the second examination would be a more informative design (A+A *vs.* A+B).

Outcome measures and analysis

When using this design, the correct outcome measure is the polyp miss-rate of technique A, given the fact that technique B is used during the second examination. This miss-rate is defined as the number of polyps detected during technique B, divided by the total number of polyps detected by A plus B (*per-lesion analysis*). Likewise, for a *per-patient analysis* the miss-rate is defined as the number of patients with ≥1 polyp during B, divided by the total number of patients with ≥1 polyp during either A and/or B. These proportions should only be described without comparative statistical tests.

A better alternative to answer the question whether technique B is really superior as an add-on test, is a design where the second round of examination is either by A or B, i.e. comparing A+A *vs.* A+B. The appropriate analysis would be the comparison of the two miss rates (proportions) using a Chi-square or Fisher's exact test.

Example from literature

Several studies may illustrate the problems in analyzing and reporting the results of this study design.[6, 34-37] East *et al* used this design in patients with hereditary non-polyposis colorectal cancer syndrome.[6] High definition endoscopy was used first (technique A) followed by narrow band imaging (technique B); polyps were removed instantaneously during technique A. The proportion of patients with ≥1 adenoma during technique A (17/62 pts) was compared to the same proportion during both A *and* B (26/62) using a statistical test for paired data (p=0.004; McNemar's test).

However, the data from such a design are not fully paired as the initial polyps detected by technique A have not been examined by technique B. It is therefore impossible for techniques A plus B to detect fewer lesions than technique A alone, meaning that the paired analysis is incorrect as it will always favor technique B. Most studies with this design have used the incorrect paired analysis.[6, 34-37] It is better to report the magnitude of the polyp miss-rate and possibly compare it with previously reported miss rates, as accurately done by Rastogi *et al*.[7] A systematic review of back-to-back colonoscopy studies has demonstrated an estimated overall polyp miss-rate of 21% (95%-confidence interval: 14-30%).[2] When comparing one's own study results to this systematic review, one has to be aware of the fact that miss-rates may vary greatly by level of experience[28-30], examination time[31], bowel preparation and by utilized technique.

C Cross-over (back-to-back) design with randomized order and direct removal

A more informative and efficient study design to compare the accuracy of two techniques to detect polyps is one in which patients undergo back-to-back examinations with both techniques, but the order in which they receive both techniques is determined by randomization (see figure 3). Polyps detected by the first technique (either A or B) are removed immediately, as a result of which only missed polyps can be picked up during the second examination.

Validity and efficiency

The layout of this design is similar to that of a crossover trial in intervention research comparing two treatments. The first part of this design (before cross-over) is equal to the parallel-randomized design. This also means that the same outcomes and analyses can be used for this part. The strength of this design is that it greatly increases the power to detect a difference in detection for two reasons. Firstly, the information from the second round can strengthen the results from the first round because it is likely that the technique with the better detection in the first round will also detect a larger proportion of initially missed polyps in the second round. This increases the difference in detected polyps between techniques. Secondly, because patients in each arm have been examined by both techniques, the total number of polyps detected (the denominator) is a reflection of the number polyps present at baseline. This means that the impact of differences in polyps at baseline is reduced, making this design more efficient. From our simulations it is clear that the increase in power is large, often reducing the number of patients required by a factor of 3 or more. The contribution of the second mechanism is more important, as even in the situation where there is no difference in detection between techniques in the second round, there is still a large increase in statistical power (see table 1).

Furthermore, this design enables the evaluation of the characteristics of the missed polyps (additional outcome measure), revealing which types of polyps are more difficult to detect for one technique compared to the other.

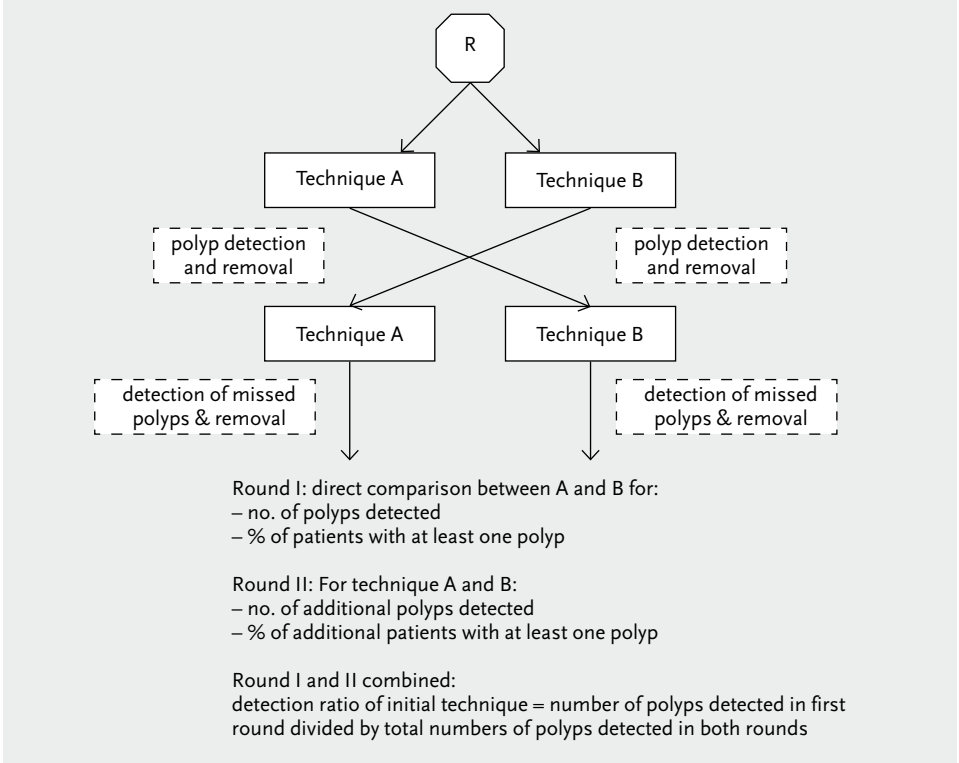


Figure 3: Crossover study design with randomized order and direct removal of polyps. The first of the back-to-back examinations is determined by randomization.

Outcome measures and analysis

Analogous to the 'sequential (back-to-back) design with fixed order', the primary outcome measure can be defined on a *per-polyp* or on a *per-patient* basis. The proportion of initially detected polyps (or its complement: the proportion of initially missed polyps can be compared between the randomization groups using the Chi-square or Fisher's exact test. Although these ratios are not true proportions from a statistical perspective, because the denominator is a number with uncertainty rather than a known number, the standard test for a difference in proportion (Chi-square test) performs well (see simulations).

Example from literature

We have previously used this randomized cross-over design to compare the detection of neoplasia between autofluorescence imaging and high resolution endoscopy among patients with ulcerative colitis.[41] Twenty-five patients were randomized to autofluorescence imaging first and high-resolution endoscopy second, whereas 25 other patients were allocated to high-resolution endoscopy first and autofluorescence imaging second. Lesions detected during the first techniques were immediately sampled or removed. The neoplasia miss-rates (proportion of neoplastic lesions missed during the first examinations) were compared between the two techniques by using Fisher's exact test for proportions.

D Cross-over design with randomized order and matching of polyps

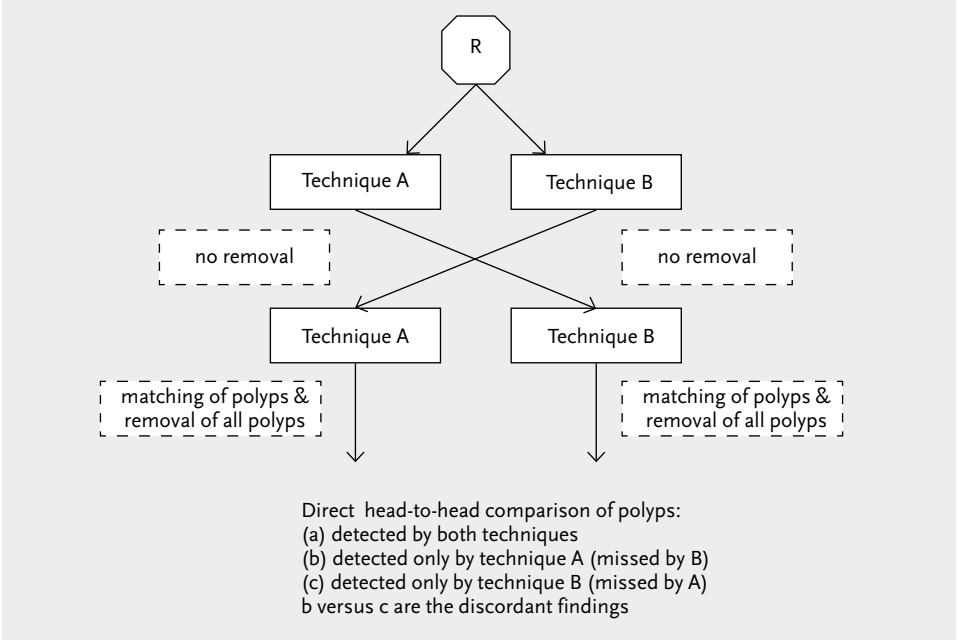


Figure 4: Cross-over study design with randomized order without direct removal of polyps. The first of the back-to-back examinations is determined by randomization. Polyps detected by the first technique (either A or B) are left in situ, as a result of which these polyps can be picked up during the second examination as well.

Potential additional increment of efficiency

This cross-over design with direct removal of all detected polyps after each stage is still not optimal from a methodological point of view. The strength of a true cross-over trial is that each patient can serve as his own control (paired analysis).[39] A key factor is therefore that patients are in similar health status at the start of the first and second part of the study. Thus, cross-over intervention trials are limited to chronic stable conditions where symptomatic treatments can be compared, e.g. patients are not cured. Furthermore, a period without any treatment is build after the first treatment, the so-called wash-out period, in order to bring patients back to their original health status. If this is feasible, the treatment effect in each part of the study can directly be compared within patients.

However, this situation does not arise in a cross-over colonoscopy study when polyps are removed during the first examination; patients then have a different number of polyps during the second examination. A further gain in efficiency would therefore be reached if removal of polyps could be postponed to after the second examination. This would allow a head-to-head comparison between the techniques for each polyp within a patient (figure 4). Our simulations show that such a true paired comparison has the greatest statistical power to detect a difference in detection (see simulation results).

A true paired comparison of detection requires several fundamental adjustments. First, two endoscopists are required: one performing technique A and another technique B. Second, they should be blinded for each other's findings. Third, polyps detected during technique A must be left *in situ*, providing an opportunity for detection (and removal) by technique B as well. Fourth, in order to perform a paired analysis, each individual polyp should be matched between the two successive examinations.

Several methods exist to match identical polyps between the procedures: (1) linking polyp size, distance from the anus, colonic location, and shape; (2) comparing photographs of each polyp; and (3) using an independent observer of both examinations to determine whether polyps can be matched. The most reliable method, however, would be to perform all three methods to match polyps between techniques A and B. This impractical methodology may cause resistance among patients, endoscopists and researchers.

Example from literature

This *paired* variant of the randomized cross-over design has been used only once.[42] This study compared standard colonoscopy to narrow band imaging for the detection of patients with neoplasia in ulcerative colitis. Two endoscopists blinded for each other's results performed either technique A or B in the same patient. The McNemar's test was used to compare the proportion of patients in which a neoplasia was detected. The exact information on individual lesions was not observed in a paired manner, preventing the possibility for a per-lesion analysis as well.

As uncertainty may still exist when matching individual lesions, one might prefer to compare only the total number of detected lesions within each patient using a paired Wilcoxon rank test.

Results of simulation study

The underlying research question in our simulations is to compare two colonoscopic techniques (A and B) and determine which one has the better detection capability. Across several clinical scenarios, we compared the three main study designs that have been used for such a study: the parallel randomized design (figure 1), the randomized cross-over design with (figure 3) and without direct removal of polyps (figure 4). Our focus was on difference in statistical power between the three designs. Detailed results of our simulations can be found in the appendix.

The final results of our simulations are summarized in table 1. Each scenario was repeated 1000 times across a range of sample sizes and we report the sample size that produced a significant result in about 80% (power) of the simulations. Scenarios differed in the number of polyps present, the absolute height and difference in detection capabilities. The simulation results indicate that the cross-over design has far greater power to identify differences in detection than the parallel design. In many scenarios, the randomized design requires 10 to 15 times more patients than the cross-over design with direct removal to reach the same statistical power of 80%. Even further reductions in sample size can be achieved if matching of individual polyps (i.e. a true paired analysis) would be possible.

In the three scenarios where there was no differences in detection capability, the frequency of significant results (type I error = finding a significant result when in reality there is none) were close to the expected nominal value of 5% (see Table). This was true for all three designs.

Recommendations for research

We have outlined the various advantages and disadvantages of commonly encountered designs in studies evaluating the detection capability of new colonoscopic techniques. Researchers have to balance these against each other to select the most adequate study design. Factors which have to be taken into account are validity, statistical power (efficiency), possibility to perform back-to-back examinations, and feasibility to match lesions in a cross-over design.

With respect to *validity*, the sequential design with fixed order should be abandoned in case the research question is that of a replacement question (should we use either technique A or B for the detection of polyps?). Only in case the objective is that of an add-on diagnostic test (should we use technique B on top of technique A?), this design provides useful information. In that case however, a study design where technique A is applied first in all patients and then patients are randomized for additional examination either by A again or technique B is more informative. Only then the additional value of technique B on top of A can be compared to the strategy in which technique A is used twice. Nevertheless, as in colonoscopic research the objective is that of a replacement question, a parallel randomized design or a randomized cross-over design should be selected.

Table 1: Summary table showing total sample sizes required to achieve 80% power for the three main designs applied in studies evaluating the detection capability of colonoscopic techniques. Scenarios differed in the number of polyps present, the underlying size and difference in detection capabilities.

Mean number polyps	P1_A	P2_B	P1_B	P2_A	Parallel randomized		Cross-over with direct removal		Cross-over with matching	
1	0.85	0.80	0.95	0.70	3980		280		125	
2	0.85	0.80	0.95	0.70	2400		145		70	
2	0.85	0.7	0.95	0.70	2400*		180		70*	
1	0.75	0.60	0.90	0.50	1500		230		98	
1	0.75	0.60	0.95	0.50	930		130		50	
Scenarios with no difference in detection					**% significant studies**		**% significant studies**		**% significant studies**	
					SS=200	**SS=800**	**SS=200**	**SS=800**	**SS=200**	**SS=800**
1	0.85	0.70	0.85	0.70	5.2%	5.5%	5.6%	5.2%	3.9%	4.6%
2	0.85	0.70	0.85	0.70	5.9%	4.1%	6.1%	5.5%	6.5%	5.7%

P1_A sensitivity of technique A as first examination;
P1_B sensitivity of technique B as first examination
P2_A conditional sensitivity of technique A as second examination after technique B;
P2_B conditional sensitivity of technique B as second examination after technique A
* same sample size as row before as conditional sensitivities are not used in these designs

With respect to efficiency (or statistical power), there is the general issue that an analysis at the level of lesions is more powerful than an analysis at the level of patients. Besides, each polyp has clinical significance as each polyp may be premalignant and should therefore be detected. The power of the parallel-randomized design to detect differences in detection capability is very limited. The main reason is that differences in the number of polyps at baseline, although by chance, have a large impact on the results. Even with relatively large sample sizes, differences in the number of polyps are possible that will dominate the results. It means that only very large parallel-randomized studies have appropriate power. The crossover design with randomized order is much more powerful and should be considered more often. The main reason for the increase in power is that using the total number of detected polyps during both examinations as the denominator reduces the impact of any imbalance in the number of polyps at baseline. Back-to-back procedures may however be repellant and impractical for patients and endoscopists, but researchers need to be more aware of the low power of the parallel design

The randomized crossover design with matching of polyps would be even more *efficient*, as a true paired analysis increases the statistical power even further. However, such a design would require two endoscopists and a time-consuming, technical challenging approach to match lesions. Despite extensive precautionary measures, there may still be a risk of incorrect matching of lesions. Lastly, some patients who will have polyps detected by the first examination that are subsequently missed by the second examination need a third colonoscopy to remove these potential harmful polyps.

In figure 5 a flow chart is presented that guides researchers in selecting the most appropriate study design for the evaluation of a new colonoscopic technique with respect to its ability to detect polyps.

Except for proper selection of study design, researchers have to be aware of several other possible factors, which may interfere with the outcome measures. One of those factor is the quality of bowel preparation, which can be measured quantitatively by using different classification schemes.[43, 44] Polyp detection rates may be higher in case the colon is perfectly prepared; however, this factor will be balanced by randomization. Another important factor is the experience of the endoscopist. Polyp detection rates or miss-rates may vary greatly between endoscopists.[28-30] Therefore, the experience of the endoscopist should preferably be stated in terms of polyp detection rates or miss-rates; in case of absence of these quality indicators, the number of endoscopies performed in the past should be stated. A third possible factor is examination time, which has shown to be associated with polyp detection rates as well.[31] Longer inspection times are associated with higher polyp detection rates. Lastly, some patient characteristics are associated with a higher prevalence of polyps, such as gender, age, race or indication of colonoscopy (e.g. polyposis patients).[26, 27] In case differences are found between two colonoscopic techniques, these ought not to be attributed to abovementioned confounding factors. Therefore, these factors have to be balanced between the two techniques by randomization or their impact should be examined at the analysis stage.

Summary

In summary, when evaluating new colonoscopic techniques with respect to their ability to differentiate neoplastic from non-neoplastic polyps a classical diagnostic accuracy study can be used by using histopathology of the removed polyps as reference standard. As no high quality reference standard exists for the evaluation of new colonoscopic techniques with respect to their ability to *detect* polyps, we critically evaluated the most commonly used study designs. The randomized parallel design has been frequently used and, although is free from bias, its power turns out to be disappointingly low. Researchers should carefully consider whether the cross-over design can be used instead. This design has far greater power, but will be more cumbersome for patients, endoscopists, and researchers. Outcome measures (e.g. polyp detection rates) should be properly defined, as well as the use of appropriate statistical tests.

Finally, reporting of possible confounders for the outcome measures (i.e. gender, age, race, indication of colonoscopy, experience of endoscopists, degree of bowel preparation, examination time, and type of endoscope used) are obligatory in detection studies. Detected differences in outcome measures may not be attributed to these confounders and should be balanced either through randomization or by having a strict protocol.

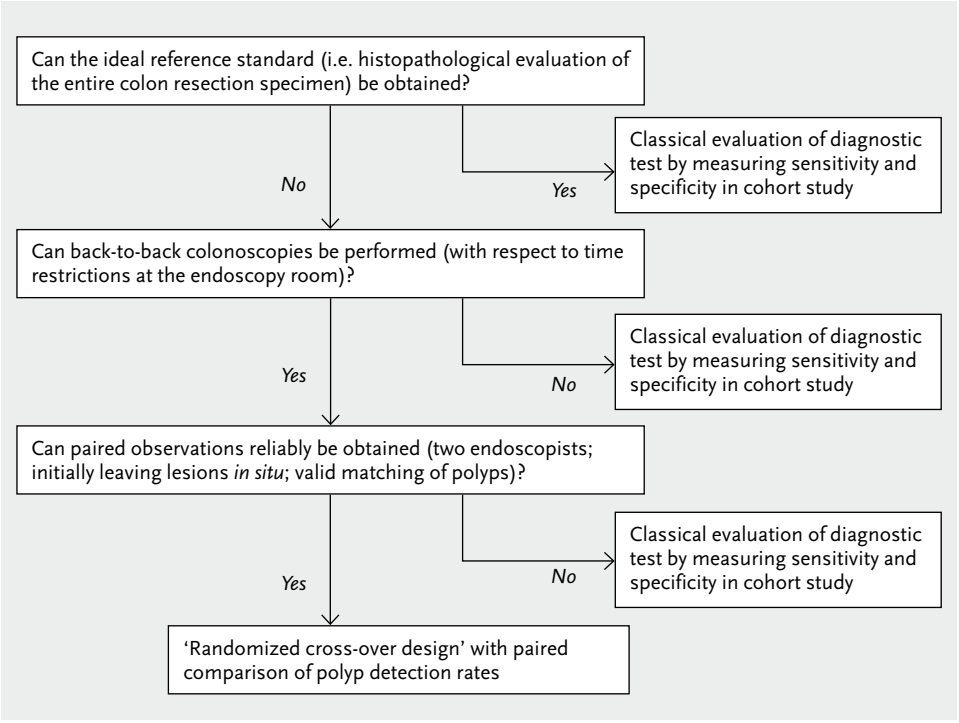


Figure 5: Guidance for researchers for selection of study design. Designs are listed in order of efficiency with the most efficient designs at the top.

APPENDIX: Detailed results of simulation study

The underlying research question in our simulations is to compare two colonoscopic techniques (A and B) and determine which one has the better detection capability. In a series of simulations we compared the three main study designs that have been used for such a study: the parallel randomized design (figure 1), the randomized cross-over design with (figure 3) and without direct removal (figures 4). Our focus was on difference in statistical power between the three designs across a range of clinical situations.

In our simulations we varied the following parameters: total sample size; the true number of polyps within each patient coming from a negative binomial distribution (characterized by the mean number of polyps and a overdispersion parameter); detection capability of technique A when applied first (sensitivity of A = p1_A); detection capability of technique B when applied first (sensitivity of B = p1_B); detection capability of technique A in the second round to find additional polyps missed by technique B (conditional sensitivity of A = p2_A); the detection capability of technique B at the second examination to find additional polyps missed by technique A (conditional sensitivity of B = p2_B).

To explain our simulations in more detail, we will illustrate the first scenario in table A by showing the intermediate results from a single study based on this scenario. We will use a study with total sample size of 200 meaning that in the parallel design 100 patients will be randomized to examination by technique A and 100 patients by the new technique B. The detection capability of technique A (representing conventional colonoscopy) is assumed to be 85%, which is 1 minus the reported miss-rate of at least 15%.[2] The new technique has a better detection capability at 95%. In our simulations, we replicated such a study with these parameters 1000 times and we calculated how many times the three designs would produce a statistically significant result, i.e. the power of such a study. To actually generate detected polyps in patients we need to simulate the true, but unobserved number of polyps within each patient. To do this, we used the negative binomial distribution. This type of distribution is closely related to the Poisson distribution and is characterized by the mean number of polyps and an overdispersion parameter to account for the fact that the number of patients with no polyps and the number of patients with many polyps is often higher than expected under the Poisson distribution. In the basic scenario the parameters of the negative binomial distribution were chosen such that the observed mean number of polyps would be 1 and that in 50% of the patients no polyp would be identified with conventional colonoscopy. Such numbers are often reported in the literature.[45]

# of polyps	Technique A (N=100)	Technique B (N=100)
0	49	46
1	27	28
2	16	12
3	5	14
4 or more	3	0
Total polyps detected	86	94
Mean number per patient	0.86	0.94
P-value	0.59	

Table A: Observed distribution of the number of polyps in a single simulation study with the parallel randomized design

Total sample size=200; mean number of true polyps=1
Sensitivity of technique A=85% and for B=95%

The true number of all polyps (detected + undetected) among patients will never be observed (unless at autopsy), but after applying a specific detection rate we obtain an observed number of polyps in our simulations. In table A the distribution of detected polyps within patients is shown for the two randomized groups after they have been examined with two techniques that differ in their detection capability (technique A 85% *vs.* technique B 95%. In the analysis we compare the observed number of polyps in both arms of the trial. The non-parametric Wilcoxon statistic can be used to test whether the distribution has shifted towards more detected polyps in the group examined with the new technique. Our single study produces a non-significant p-value of 0.59. This is a typical value for the parallel-randomized design in this scenario because with a total sample size of 200 the parallel design has a power of only 10%. To achieve a power of 80%, the total sample size needs to be as high as 4,000 (see first row of table 1 in manuscript).

In the crossover design with removal of polyps, patients will be examined by the other technique to see whether any additional polyps can be detected. In our simulation study the number of missed polyps is known and we can simulate whether these will be detected in the second round using the conditional detection capabilities of technique A and B. The conditional (i.e. as observed in the second round) sensitivity of technique A (70% in first scenario) and B (80%) was assumed to be lower than their corresponding sensitivities in the first round as missed polyps are probably more difficult to detect. The results of the same single study are presented in table B. In the paired design with removal we can calculate for each strategy the ratio of the number of polyps detected in the first round by the total number of detected polyps in both rounds. A higher proportion indicates that the initial technique has better detection capabilities. A chi-square test can be used to test for a difference in the two proportions. This crossover design with the same sample size, but examining patients twice, now produces a significant result with a p-value of 0.015. To obtain a power of 80% for this design requires a sample size of only 280.

Single study	Strategy I: A first, B second	Strategy II: B first, A second	P-value
True number of polyps present	102	101	
Detected polyps in first round	86	94	0.59
Truly missed in first round	16	7	
Detected in second round	12	3	
True number of polyps missed by both techniques	4	4	
Ratio: polyps first round / polyps first + second round	86/(86+12)=88%	94/(94+3)=97%	0.015

Table B: Number of detected polyps per strategy in the cross-over design with direct removal

In the crossover design without initial removal, both techniques are applied in the same patient and for each detected polyp we observe whether it was detected by only one technique (thus missed by the other) or detected by both techniques. The results of the 200 patients can be summarized in the following 2*2 table: The difference in detection capability manifests itself in the number of discordant results in this case 35 versus 14. These numbers can be analyzed by the McNemar test for paired observations, leading to a p-value of 0.0027. Because this is now a true paired analysis on each detected polyp, it increases the power even further. To achieve 80% power with this design using the same scenario now only requires 125 patients (see table 1 in the manuscript).

		Technique B		
		Detected	Undetected	
Technique A	Detected	153	14	167
	Not detected	35	1 (not observed)	
		188		P=0.0027

Table C: Number of polyps detected by only one or both techniques in the cross-over design with matching of lesions

The final results of all our simulations are summarized in table 1 of the manuscript. Each scenario was repeated 1000 times across a range of sample sizes and we report the sample size that produced a significant result in about 80% of the simulations. In many scenarios, the randomized parallel design requires 10 to 15 times more patients to reach the same statistical power of 80% than the cross-over design with direct removal Even further reductions in sample size can be achieved if matching of individual polyps (i.e. a true paired analysis) is possible.

In the final three scenarios there were no differences in detection capability between the two techniques. In these simulations we report the number of significant results when using a total sample size of 200 and 800. In these simulations the frequency of significant results (type I error = finding a significant result when in reality there is none) were close to the expected nominal value of 5% (see final table). This was true for all three designs.

Reference List

1 Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, Smith RA, Lieberman DA, Burt RW, Levin TR, Bond JH, Brooks D, Byers T, Hyman N, Kirk L, Thorson A, Simmang C, Johnson D, Rex DK. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology 2006;130:1872-1885.

2 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.

3 van den Broek FJ, Fockens P, Dekker E. Review article: New developments in colonic imaging. Aliment Pharmacol Ther 2007;26 Suppl 2:91-99.

4 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.

5 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.

6 East JE, Suzuki N, Stavrinidis M, Guenther T, Thomas HJ, Saunders BP. Narrow band imaging for colonoscopic surveillance in hereditary non-polyposis colorectal cancer. Gut 2008;57:65-70.

7 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2008;67:280-286.

8 Aschenbeck J, Adler A, Yenerim T, Mayr M, Aminalai A, Drossel R, Schroder A, Scheel M, Wiedenmann B, Rosch T. Narrow-Band Versus White-Light HDTV Endoscopic Imaging for Screening Colonoscopy: A Prospective Randomized Trial. Gastroenterology 2008.

9 Inoue T, Murano M, Murano N, Kuramoto T, Kawakami K, Abe Y, Morita E, Toshina K, Hoshiro H, Egashira Y, Umegaki E, Higuchi K. Comparative study of conventional colonoscopy and pancolonic narrow-band imaging system in the detection of neoplastic colonic polyps: a randomized, controlled trial. J Gastroenterol 2008;43:45-50.

10 Adler A, Pohl H, Papanikolaou IS, bou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rosch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? Gut 2008;57:59-64.

11 Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-47.

12 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.

13 Sikka S, Ringold DA, Jonnalagadda S, Banerjee B. Comparison of white light and narrow band high definition images in predicting colon polyp histology, using standard colonoscopes without optical magnification. Endoscopy 2008.

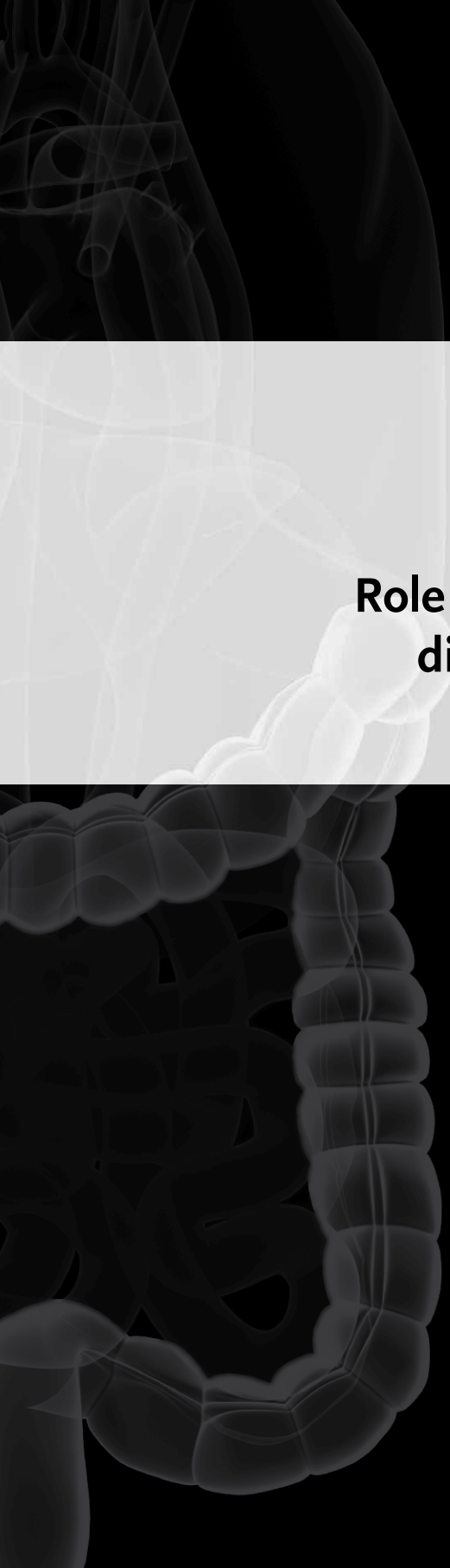
14 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.
15 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.
16 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.
17 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.
18 Katagiri A, Fu KI, Sano Y, Ikematsu H, Horimatsu T, Kaneko K, Muto M, Yoshida S. Narrow band imaging with magnifying colonoscopy as a diagnostic tool for predicting the histology of early colorectal neoplasia. Aliment Pharmacol Ther 2008.
19 McCallum AL, Jenkins JT, Gillen D, Molloy RG. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. Gastrointest Endosc 2008.
20 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ 2003;326:41-44.
21 Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:1-13.
22 Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, Cardwell CR, Williams CB. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56:333-338.
23 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.
24 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.
25 Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376-380.
26 Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, Nowacki MP, Butruk E. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl
27 Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570-1595.

28 Rex DK, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-28.
29 Atkin W, Rogers P, Cardwell C, Cook C, Cuzick J, Wardle J, Edwards R. Wide variation in adenoma detection rates at screening flexible sigmoidoscopy. Gastroenterology 2004;126:1247-1256.
30 Chen SC, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. Am J Gastroenterol 2007;102:856-861.
31 Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533-2541.
32 Kiesslich R, von BM, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001;33:1001-1006.
33 Stergiou N, Frenz MB, Menke D, Riphaus A, Wehrmann T. Reduction of miss rates of colonic adenomas by zoom chromoendoscopy. Int J Colorectal Dis 2006;21:560-565.
34 Lecomte T, Cellier C, Meatchi T, Barbier JP, Cugnenc PH, Jian R, Laurent-Puig P, Landi B. Chromoendoscopic colonoscopy for detecting preneoplastic lesions in hereditary nonpolyposis colorectal cancer syndrome. Clin Gastroenterol Hepatol 2005;3:897-902.
35 Hurlstone DP, Karajeh M, Cross SS, McAlindon ME, Brown S, Hunter MD, Sanders DS. The role of high-magnification-chromoscopic colonoscopy in hereditary nonpolyposis colorectal cancer screening: a prospective "back-to-back" endoscopic study. Am J Gastroenterol 2005;100:2167-2173.
36 Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53:256-260.
37 Marion JF, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. Am J Gastroenterol 2008;103:2342-2349.
38 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2008;67:280-286.
39 Irwig L, Bossuyt P, Glasziou P, Gatsonis C, Lijmer J. Designing studies to ensure that estimates of test accuracy are transferable. BMJ 2002;324:669-671.
40 Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ 2006;332:1089-1092.
41 van den Broek FJ, Fockens P, van ES, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008.
42 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.
43 Rostom A, Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. Gastrointest Endosc 2004;59:482-486.

44 Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc 2009;69:620-625.

45 van den Broek FJ, Reitsma JB, Curvers WL, Fockens P, Dekker E. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon (with videos). Gastrointest Endosc 2009;69:124-135.

PART II



Role of endoscopic imaging in diagnosis of colonic polyps

CHAPTER 4

Clinical evaluation of endoscopic tri-modal imaging for the detection and differentiation of colonic polyps

Frank J.C. van den Broek
Paul Fockens
Susanne van Eeden
Mohammed A. Kara
James C.H. Hardwick
Johannes B. Reitsma
Evelien Dekker

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ABSTRACT

Background & aims: Endoscopic tri-modal imaging (ETMI) incorporates high-resolution endoscopy (HRE) and autofluorescence imaging (AFI) for adenoma detection, and narrow band imaging (NBI) for differentiation of adenomas from non-neoplastic polyps. The aim of this study was to compare AFI with HRE for adenoma detection and to assess the diagnostic accuracy of NBI for differentiation of polyps. This was a randomized trial of tandem colonoscopies. The study was performed at the Academic Medical Centre in Amsterdam.

Methods: One hundred patients underwent colonoscopy with ETMI. Each colonic segment was examined twice for polyps, once with HRE and once with AFI, in random order per patient. All detected polyps were assessed with NBI for pit pattern and with AFI for color, and subsequently removed. Histopathology served as the gold standard for diagnosis. The main outcome measures of this study were adenoma miss-rates of AFI and HRE; and diagnostic accuracy of NBI and AFI for differentiating adenomas from non-neoplastic polyps.

Results: Among 50 patients examined with AFI first, 32 adenomas were initially detected. Subsequent inspection with HRE identified 8 additional adenomas. Among 50 patients examined with HRE first, 35 adenomas were initially detected. Successive AFI yielded 14 additional adenomas. The adenoma miss-rates of AFI and HRE therefore were 20% and 29% respectively (p=0.351). The sensitivity, specificity and overall accuracy of NBI for differentiation were 90%, 70% and 79% respectively; corresponding figures for AFI were 99%, 35% and 63%.

Conclusion: The overall adenoma miss-rate was 25%; AFI did not significantly reduce the adenoma miss-rate compared to HRE. Both NBI and AFI had a disappointing diagnostic accuracy for polyp differentiation, although AFI had a high sensitivity.

Trialregister.nl Identifier: ISRCTN76121851

Introduction

Colorectal cancer (CRC) is one of the most common cancers in western countries.[1, 2] Genetic alterations in the mucosa lead to the formation of adenomas, that take a varying time span to progress into CRC.[3] This time span provides an opportunity for detection and removal of adenomas by colonoscopy, thereby preventing their progression into CRC.[4] Periodic removal of all adenomas is estimated to reduce the CRC incidence by 76-90%.[5] Recent reports demonstrated that patients under close colonoscopic surveillance still develop CRC.[6] This may be explained by either rapid progression of adenomas, or by the fact that colonoscopy is not infallible for the detection of adenomas.[7, 8] A systematic review of back-to-back colonoscopies demonstrated that 15-32% of adenomas were overlooked.[9] Furthermore, flat and depressed adenomas were long thought to be rare in western countries until colonoscopies were performed in conjunction with Japanese endoscopists and advanced techniques, demonstrating that 7-40% of adenomas in the western world were of the flat and depressed type as well.[10-14]

Advanced endoscopic techniques may improve the yield of adenomas and optimize the potential for CRC prevention. In addition, endoscopic differentiation of neoplastic and non-neoplastic polyps would further improve the efficacy of colonoscopy, since adenomas should be removed and non-neoplastic lesions may be left *in situ*. Only chromoendoscopy (CE) has shown to improve both the detection of adenomas, as well as the differentiation of polyps.[15-20] However, CE is labour-intensive, time-consuming and operator-dependent. Furthermore, it is impossible to switch back and forth between the conventional and CE image. As a result, the implementation of CE in western countries has fallen short.

Narrow band imaging (NBI) is a new endoscopic technique, utilizing spectral characteristics of the endoscopic light to enhance mucosal patterns and capillaries without dyes.[21, 22] Concerning the detection of adenomas, NBI has failed to demonstrate an increased yield compared to high resolution endoscopy (HRE) in two randomized studies.[23, 24] For the differentiation of neoplastic from non-neoplastic lesions, however, NBI has an accuracy comparable to CE.[25-31]

Autofluorescence imaging (AFI) is another novel technique which might improve the detection of adenomas.[32] During AFI, blue light is used for illumination of the mucosa, which leads to fluorescent light emission of colonic tissue.[33] Differences in fluorescence spectra between adenomas and normal mucosa are translated into a real-time pseudo color image. The use of AFI has demonstrated an improved yield of neoplasia in patients under surveillance for Barrett's esophagus or ulcerative colitis.[34-37]

Endoscopic tri-modal imaging (ETMI) integrates AFI, NBI and HRE into one system.[36, 37] For the purpose of this system, AFI functions as a red flag detection technique, whereas NBI serves for differentiation. The aims of this randomized trial of tandem colonoscopies with ETMI were (1) to compare AFI with HRE for adenoma detection, and (2) to determine the diagnostic accuracy of NBI for polyp differentiation.

Patients and Methods

Patients

Patients scheduled for colonoscopy in the Academic Medical Centre Amsterdam were screened for participation. Inclusion criteria were a personal history of adenomas or CRC, or positive family history for CRC (one first-degree family member fulfilling one of the revised Bethesda criteria).[38] Exclusion criteria were age <18 years, polyposis syndromes, inflammatory bowel disease, severe coagulopathy and insufficient bowel preparation. Eligible patients were invited for this study for which informed consent was necessary. This study was approved by the medical ethical committee of our institution.

Endoscopic equipment

Colonoscopies were performed with the ETMI system (Olympus Inc., Tokyo, Japan). The light source (XCLV-260HP) provides sequential red-green-blue illumination and contains two rotating filters: one for HRE and one for NBI. The band pass ranges of green and blue light in the NBI filter have been narrowed to 530-550nm and 390-445nm, respectively. In addition, the intensity of blue light is increased. Since blue light penetrates the mucosa superficially and is absorbed by hemoglobin, this setting allows for enhancement of mucosal and capillary details.

A high-resolution colonoscope (XCF-H240FZL, magnification 100x) was used, containing two charge coupled devices (CCDs): one for HRE/NBI and one for AFI. For AFI, blue light (390-470nm) is used for excitation and green light (540-560nm) for reflection. A barrier filter allows passage of light to the CCD with wavelengths between 500-630nm only, consisting of autofluorescence emission and green reflectance which are integrated into a real-time pseudo color AFI image. During AFI, normal mucosa appears green while adenomas are purple (Figure 1).

A high-resolution monitor was used for all procedures and the endoscopists could easily switch between the three imaging modes by pressing a button on the endoscope.

Colonoscopy and randomization

Patients were prepared with 4 liters of polyethylene glycol solution (Kleanprep; Norgine GmbH, Marburg, Germany) and underwent colonoscopy under conscious sedation with midazolam and/or fentanyl. The colonoscope was advanced to the cecum using HRE, and cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve. Upon reaching the cecum, the level of bowel preparation was determined as good (100% mucosa visibility), moderate (90-100%) or poor (<90%) after extensive cleansing and aspiration of liquid stools. Patients with persisting poor bowel preparation were excluded.

After introduction, each colonic segment (ascending, transverse, descending, recto-sigmoid) was inspected twice during withdrawal: once with AFI and once with HRE by the same endoscopist. Randomization determined which technique was used first for the detection of polyps. Allocation was done by opening opaque sealed envelopes (containing a note with 'AFI' or 'HRE') by a research fellow after reaching the cecum and confirmation of sufficient bowel preparation.

All procedures were performed by 3 colonoscopists (>2,500 standard and >30 ETMI colono-

scopies) who were instructed to perform meticulous inspection and equal examination times for both detection techniques. In a random set of 15 patients, examination times for both techniques were recorded by using two stopwatches which were started at the cecum and stopped during cleansing, taking biopsies, and finally at extubation. The entire procedural time (including time of introduction, cleansing, and polypectomies) was recorded for all patients.

The size (estimated by an 8mm biopsy forceps) and location (colon segment and distance to anus) of detected lesions were recorded, as well as lesion type according to the Paris classification.[39] Furthermore, each lesion was scored for color (green, ambiguous, purple) on AFI (Figure 2); as well as for Kudo pit pattern on NBI using optical magnification; and subsequently removed for histopathological evaluation.[40] Lesions detected during the first inspection were removed immediately; therefore, the second inspection could only add lesions, which were missed by the first inspection.

Histopathology

Resection specimens were routinely evaluated by a general pathologist; afterwards, all polyps were re-examined by an expert gastrointestinal pathologist who was only aware of the location and size of the lesions, but blinded for AFI and NBI findings. In case disagreement existed between the general and expert pathologist, the expert pathologist was made aware of the discrepancy to make a final diagnosis. All lesions were classified according to the revised Vienna criteria. Advanced adenomas were defined as adenomas with villous histology, high-grade intraepithelial neoplasia or size ≥1cm.[41] Polyps diagnosed as sessile serrated adenoma (SSA) were primarily regarded as non-adenomatous for analysis. However, since SSAs may be considered premalignant as well, findings on this subgroup of polyps were described separately.[42]

Outcome measures

The primary outcome measure for comparing AFI and HRE with respect to adenoma *detection* was the number of initially missed adenomas. Concerning polyp *differentiation*, the primary outcome measure was the amount of agreement between the Kudo classification by NBI and final histopathology.

Secondary outcomes were miss-rates of patients with adenomas and characteristics of missed lesions. The diagnostic accuracy of AFI-color for differentiation was calculated as well.

Statistics

Continuous variables with normal or skewed distribution were summarized by mean ± standard deviation or median ± interquartile range. Means and medians were compared with the student's t-test and Wilcoxon test respectively, and proportions were compared with the chi-square test.

The *adenoma miss-rate* was defined as number of adenomas detected during the second inspection only, divided by the total number of detected adenomas (during the first and second inspection). The *miss-rate of patients with adenomas* was defined as number of patients with at least one adenoma detected during the second inspection, divided by the total number of patients with adenomas.

The sensitivity and specificity of NBI for differentiating adenomas from non-neoplastic polyps were assessed by linking Kudo classification to histopathology, which was used as gold standard diagnosis. Kudo type I-II was considered non-neoplastic and Kudo type III-V as adenomatous. For the sensitivity and specificity of AFI-color, purple and ambiguous AFI-colors were regarded as adenomatous and green as non-neoplastic (Figure 2). The accuracies of the Kudo classification by NBI and the color by AFI were compared with McNemar's test for paired data.

Finally, logistic regression analysis was performed to estimate the effect size, expressed in odds ratio and 95% confidence interval (95% CI), of clinicopathological characteristics of lesions on adenoma miss-rates.

Sample size

In a systematic review of back-to-back colonoscopies the adenoma miss-rate was 22%. We aimed for a 3-fold reduction in adenoma miss-rate for AFI, which resulted in a sample size of 90 adenomas (α-error 0.05 and β-error 0.2). Since the prevalence of adenomas ranges between 0.3-2.0 per patient, we estimated that including 100 patients would be sufficient.

Results

Patient characteristics

Between June 2005 and March 2007 a total of 109 patients gave informed consent; 6 patients were excluded because of poor bowel preparation and 3 because of technically difficult and painful colonoscopy (Figure 3). The mean age of the remaining 100 patients (43 male) was 52 (±14) years and the cecal intubation rate was 100%. Fifty patients underwent tandem colonoscopy with a first inspection in the AFI-mode; the remaining 50 patients were examined with HRE first. No adverse events occurred. Table 1 demonstrates patient characteristics and quality of bowel preparation among the randomization groups. The mean inspection time during AFI was equal to HRE (paired data: 8.1 versus 7.9 minutes; p=0.784).

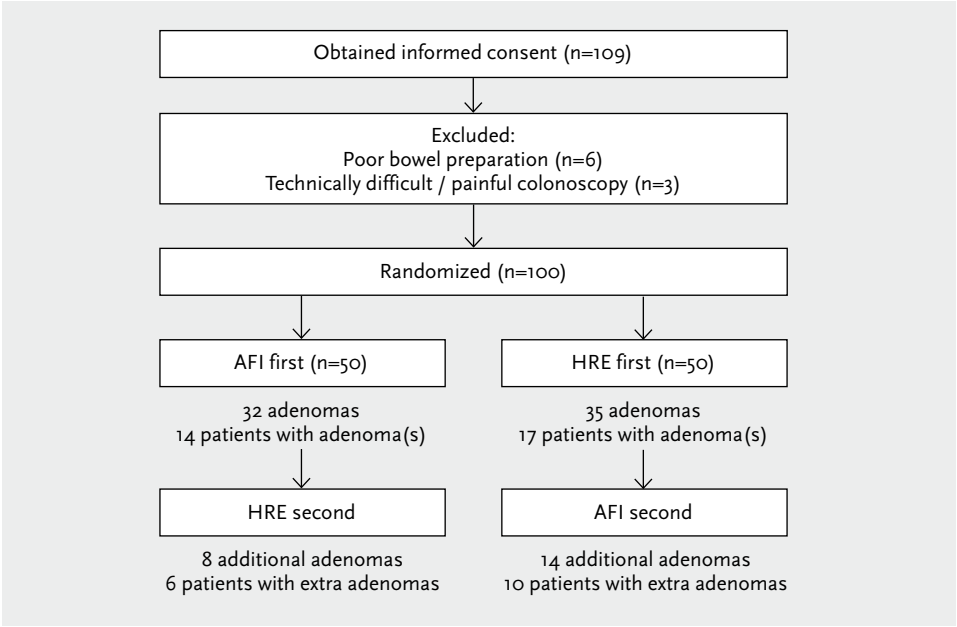

Figure 3: Flow chart of patients during the study, including the number of detected adenomas and the number of patients with at least one adenoma after AFI and HRE inspection during tandem colonoscopy.

	Randomization		p-value
	AFI first (n=50)	HRE first (n=50)	
Male n (%)	25 (50%)	18 (36%)	0.157
Mean age - yrs (SD)	50 (15)	54 (13)	0.274
Median interval to previous endoscopy - yrs (IQR)	2.0 (0.4-2.4)	2.0 (1.3-2.6)	0.362
Indication for colonoscopy n (%) - History of neoplasia - HNPCC *Genetic mutation positive* *Amsterdam criteria positive* - Family history of CRC	 13 (26%) 25 (50%) 12 (24%) 13 (26%) 12 (24%)	 13 (26%) 25 (50%) 11 (22%) 14 (28%) 12 (24%)	1.0
Good colon preparation n (%) Excellent colon preparation n (%)	32 (64%) 18 (36%)	32 (64%) 18 (36%)	1.0
Entire procedural time – min (SD)	55 (26)	47 (19)	0.102

Table 1: Patient characteristics among patients assigned to AFI and HRE as first inspection technique (IQR, interquartile range)

Miss-rates of adenomas and patients with adenomas

Group randomized to AFI first: Among the 50 patients assigned to inspection with AFI first, 32 adenomas were found in 13 patients (26%) with AFI. Of these adenomas, 8 were found to be advanced within 5 patients (10%). The mean adenoma detection rate per patient for AFI was 0.64 (32/50) (95% CI: 0.50-0.76). The second examination with HRE yielded 8 additional adenomas (0 advanced) in 6 patients (Figure 3). One patient (6.7%) only had adenomas during second HRE inspection. The *adenoma miss-rate* of AFI was 20% (8/40); the *miss-rate of patients with adenomas* was 40% (6/15).

In this group randomized to AFI first, 9 SSAs were detected by AFI and 5 additional SSAs by HRE. When considering SSAs to be adenomas as well, the overall adenoma miss-rate of AFI was 24% (13/54).

Group randomized to HRE first: Among those 50 patients, the first inspection with HRE yielded 35 adenomas among 17 patients, corresponding to a mean adenoma detection rate per patient of 0.70 (35/50) (95% CI: 0.56-0.81). Of these adenomas, 6 were advanced within 5 patients (10%). Subsequent AFI identified 14 additional adenomas (0 advanced) in 10 patients (Figure 3). Two patients (5.3%) only had adenomas during second AFI inspection. The a*denoma miss-rate* of HRE was 29% (14/49), which was not significantly different from AFI (p=0.351). The HRE *miss-rate of patients with adenomas* was 53% (10/19) (compared to AFI: p=0.464).

In this group, 11 SSAs were initially detected by HRE and 3 additional SSAs by AFI. When considering SSAs to be adenomas as well, the overall adenoma miss-rate of HRE was 27% (17/63).

Diagnostic accuracy of NBI and AFI

A total of 208 polyps (89 adenomas; 28 SSAs; 46 hyperplastic; 37 normal; 1 juvenile; and 7 inflammatory) were detected by either AFI or HRE and subsequently classified with NBI for Kudo pit pattern. The endoscopist was not able to recognize a pit pattern in 2 polyps (1 adenoma). When compared to final histopathology, the sensitivity, specificity and overall accuracy of the pit pattern diagnosis by NBI were 89.8%, 70.3% and 78.6% respectively (Table 2). The negative and positive predictive values were 90.2% and 69.3%.

Additionally, all lesions were assessed by AFI for color: 87 were purple, 81 ambiguous, and 42 were green. The sensitivity, specificity and overall accuracy of AFI-color were 98.9%, 35.3% and 62.5% respectively. The negative and positive predictive values were 97.7% and 53.3%. Although the sensitivity of AFI was significantly higher than NBI (p=0.021), it was accompanied by much lower specificity. Therefore the overall diagnostic accuracy of AFI was even lower than NBI (p<0.001).

While performing this study, we found the combined use of NBI and AFI to be useful for achieving a high diagnostic accuracy for differentiation. The following algorithm, combining information obtained by NBI and AFI, was subsequently evaluated for accuracy: all AFI-purple lesions as well as AFI-ambiguous lesions with Kudo III-V (NBI) were regarded as adenomas, whereas AFI-green lesions and AFI-ambiguous polyps with Kudo I-II were considered non-neoplastic. This algorithm had a sensitivity, specificity and accuracy of 97.7%, 73.7% and 84.0%; the negative and positive predictive values were 97.8% and 73.5%. The overall accuracy of the

algorithm was higher than AFI alone (p<0.001) and showed a trend for superiority compared to NBI alone (p=0.064). In fact, the algorithm was able to retain the high sensitivity of AFI, without loss of specificity.

Of all polyps, 28 (14%) were SSAs which revealed Kudo type I-II in 21/28 (75%) and green color on AFI in 19/28 (68%). If these SSAs were considered to be adenomas, the sensitivity and specificity of NBI would only be 74.1% and 68.9%; corresponding figures for AFI would be 82.9% and 25.3%; and figures for the algorithm would be 77.6% and 70.0%.

Clinicopathological differences between detected and missed polyps

In total, 152 polyps have been detected during the first and 56 (27%) during the second inspection. Of these polyps 15 (7.2%) were ≥10mm, 127 (61%) were located proximal to the splenic flexure, and 84 (39%) were macroscopically flat. Size, location and macroscopic appearance did not differ between polyps detected by either AFI or HRE. The median size of polyps identified during the first inspection was 3mm (interquartile range 2-5; range 1-50) compared to 2mm (interquartile range 2-4; range 1-10) during the second inspection (p=0.096). Size was the only factor negatively associated with polyp miss-rate (odds ratio 0.89; 95% CI: 0.78-1.01).

Adenomas (n=89) had a median size of 3mm (interquartile range 2-5; range 1-50); 68 (76%) were located proximal to the splenic flexure and 34 (38%) were flat. Large adenomas were less likely to be missed than small ones (odds ratio 0.82; 95% CI: 0.6-1.1). Eight adenomas (9.0%) were ≥10mm, none of which were detected during the second inspection. Location and macroscopic appearance of adenomas were not associated with the miss-rate.

		Final histopathology		
		Adenoma	Non-neoplastic	
NBI Classification	Kudo type III-V	79	35	114 PPV 69.3%
	Kudo type I-II	9	83	92 NPV 90.2%
		88 Sensitivity 89.8%	118 Specificity 70.3%	206

Table 2: Correlation of the Kudo classification assessed by using NBI and the actual histopathology after evaluation by the blinded pathologist

PPV, positive predictive value; *NPV*, negative predictive value

Discussion

Since adenoma miss-rates may cause interval cancers in patients undergoing periodic colonoscopy, great efforts are being made to reduce miss-rates by good quality colonoscopy and advanced imaging techniques.[8] Chromoendoscopy has shown to improve both the *detection* and *differentiation* of colonic polyps.[15-20] However, advanced imaging techniques like AFI and NBI are easier to use and may be more cost-effective as they involve only a push on a button instead of the application of dyes to enhance contrast of colonic polyps.

The present randomized study reports on the use of ETMI for both the detection and differentiation of colonic polyps. With respect to *detection*, the adenoma miss-rate of AFI was 20% versus 29% by HRE, a difference that was not statistically significant (p=0.351). Mainly small adenomas (median 2mm) were missed during the first examination, as a result of which the impact on cancer prevention may be questioned and likely will be minor. All advanced adenomas were already detected by the first inspection. Previous research has shown that chromoendoscopy increases the detection of small adenomas as well, however long-term data on cancer reduction by removal of small adenomas are currently lacking.[15-18] Therefore, a clinically significant improvement in adenoma miss-rate cannot be defined at this moment.

When comparing our data to a systematic review of back-to-back colonoscopies, the adenoma miss-rates for both AFI and HRE lie within the reported 95%-confidence interval of 15-32%, despite using high resolution technology in our study.[9] By contrast, two recent studies reported adenoma miss-rates for HRE of 40-46% when a second examination was performed with NBI, suggesting this technique to be superior to HRE.[31, 43] Studies using CE as second examination technique have shown miss-rates as high as 79%.[44-47] Unfortunately, in all those studies the advanced imaging technique was only used during the second pass, omitting an assessment of the miss-rate for the advanced imaging technique itself. Conversely, the randomized design of the present study enabled an assessment of the miss-rate not only for HRE, but for AFI as well. Furthermore, we carefully instructed the 3 endoscopists to spend equal examination time to both HRE and AFI in order to avoid favorable results of one technique due to the intensity of examination rather than the nature of the examination.

In addition to miss-rates, adenoma detection rates (mean number of adenomas per patient) can also function as quality indicator for colonoscopy.[48, 49] The increased adenoma miss-rate of 46% due to an additional inspection by NBI in the study by East *et al* was accompanied by an adenoma detection rate during the first inspection of only 0.40.[43] Lecomte *et al* reported an adenoma miss-rate of 79% when a second inspection was done with CE; however, the initial adenoma detection rate was only 0.09 in that study.[47] Consequently, a low yield of adenomas during the first inspection leaves more lesions to be detected by the second examination. The first inspection with HRE and AFI in the present study however yielded 0.70 and 0.64 adenomas per patient already. Therefore, we conclude that HRE and AFI are both equally effective in detecting adenomas.

Despite successful randomization, one may argue that our results can not be generalized to the regular population undergoing surveillance as a rather large part of our patients had genetically proven HNPCC, which is associated with proximally located adenomas.[50] However, the frequency of proximal adenomas among these patients was comparable to non-HNPCC patients (results not shown). In addition, we did not find differences in AFI and NBI appearance among adenomas in HNPCC or non-HNPCC patients.

Concerning the *differentiation* between adenomas and non-neoplastic polyps, recent studies have shown that CE and NBI are comparable for this purpose.[25-31] The reported accuracies for differentiation varied from 77-99%. A major drawback of these studies was that only still images were assessed afterwards, which may have introduced selection bias of images with obvious pit patterns only. This selection bias is clearly demonstrated in one study with a reported accuracy of 99%, in which a high proportion (32%) of invasive cancers was included.[28]

In the present study, pit patterns were assessed prospectively during real time imaging instead of analyzing selected images afterwards. Therefore, the results of NBI in the present study will better reflect the true clinical value of this technique. The sensitivity, specificity and accuracy of the Kudo classification by NBI were 89.8%, 70.3% and 78.6% respectively. These slightly disappointing figures may be explained by the fact that pit patterns are more difficult to visualize when polyps do not lie perpendicular to the endoscopic view or are located just behind a mucosal fold; these lesions were however included in the analysis. In addition, one might argue that in previous studies NBI has been evaluated for vascular pattern instead of Kudo pit pattern, which may have affected the diagnostic accuracy. However, East *et al* demonstrated that the accuracy of the pit pattern by NBI or CE was comparable to the vascular pattern by NBI.[29]

The already disappointing accuracy of NBI in this study would further decline when SSAs were considered as adenomas as well; 75% of all SSAs had a Kudo type I-II on NBI. This would lead to a sensitivity and specificity of only 74.1% and 68.9%. In all previous studies reporting on accuracy of NBI, only 1 out of 753 (0.1%) lesions was a SSA[25-31, 51], whereas 28 out of 208 polyps (13%) were SSAs in the present study. The large differences in prevalence of SSAs between studies may reflect the difficulty which pathologists experience when differentiating these lesions from hyperplastic polyps.[52] Lesions classified as hyperplastic polyps by others may in fact be diagnosed as SSA by pathologists with special interest and experience in these lesions.[53] Therefore, the prevalence and presumed relevance of SSAs will influence the usefulness of NBI for polyp differentiation in clinical practice.

Autofluorescence may be used for differentiation of polyps as well, although the diagnostic accuracy has only been assessed for fiberoptic systems. The first studies used fluorescence spectroscopy for which a probe was placed gently on the colonic tissue and violet or blue light was used for excitation.[54-56] Emitted tissue fluorescence was translated into a spectroscopic signal for differentiation with sensitivities of 85-98% and specificities of 91-95%.[54-56] However, those studies were performed in selected polyps and macroscopically normal mucosa only. Subsequently, a real-time fiberoptic fluorescence imaging system was developed, which was able to differentiate adenomas from non-neoplastic polyps based on color with sensitivities of 83-91% and specificities of 81-100%.[57-60] Again, only selected polyps and macroscopically normal mucosa were studied, except for the study by McCallum *et al* that demonstrated the lowest diagnostic accuracy. Furthermore, the system was not feasible for surveillance of larger areas due to low resolution and low color contrast.

The present study reports on the use of video endoscopic AFI for the differentiation of polyps. Autofluorescence imaging had a higher sensitivity compared to NBI (99% versus 90%), however at the price of a lower specificity (35% versus 70%). Therefore, a negative AFI-test (green color) will better exclude the presence of adenomatous tissue but at the expense of removing more non-neoplastic lesions. When including SSAs as adenomas again, AFI had a sensitivity of only 83% since most SSAs were green on AFI.

Interestingly, an algorithm which combined information from AFI and NBI was able to make use of the high sensitivity of AFI and the high specificity of NBI together. In this algorithm, all AFI-purple as well as all AFI-ambiguous lesions with Kudo type III-V on NBI were considered suspicious for adenoma; whereas AFI-green and AFI-ambiguous lesions with Kudo type I-II on NBI were considered non-suspicious. The sensitivity of the algorithm was 98%, which

proved significantly higher than NBI; the specificity of the algorithm was slightly higher than NBI (74% *vs.* 70%). In our opinion, high sensitivity is more important than high specificity since adenomas are premalignant and should accurately be excluded to leave only non-neoplastic lesions *in situ*. The achieved sensitivity of 98% (and corresponding negative predictive value of 98%) by the algorithm would clinically be acceptable for its use in daily practice; especially for small adenomas since a false negative rate of 2% for these lesions would be acceptable. Therefore, AFI can play an important role in the differentiation of colonic polyps. Since the combined use of AFI and NBI was experienced for the first time during this study, the algorithm needs formal validation and evaluation of interobserver agreement in future research.

In conclusion, the present study again demonstrates that adenomas are regularly being missed by colonoscopy, and that an additional inspection with either AFI or HRE increases the yield of adenomas. The overall adenoma miss-rate was 25%; and the use of AFI for *detection* did not significantly reduce the adenoma miss-rate when compared to HRE (20% *vs.* 29%; p=0.351). Concerning the *differentiation* of adenomas from non-neoplastic polyps, AFI had a higher sensitivity than NBI but at the expense of a low specificity. The combined use of AFI and NBI in an algorithm had both high sensitivity (98%) and high specificity (74%), and therefore needs further prospective evaluation and validation.

>> **For figures 1 and 2; see page 136**

Reference List

1 Wilmink AB. Overview of the epidemiology of colorectal cancer. Dis Colon Rectum 1997;40:483-493.

2 Potter JD. Colorectal cancer: molecules and populations. J Natl Cancer Inst 1999;91:916-932.

3 Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525-532.

4 Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson D, Kirk L, Litin S, Simmang C. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003;124:544-560.

5 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, . Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.

6 Robertson DJ, Greenberg ER, Beach M, Sandler RS, Ahnen D, Haile RW, Burke CA, Snover DC, Bresalier RS, Keown-Eyssen G, Mandel JS, Bond JH, Van Stolk RU, Summers RW, Rothstein R, Church TR, Cole BF, Byers T, Mott L, Baron JA. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology 2005;129:34-41.

7 Matsumoto T, Iida M, Kuwano Y, Tada S, Yao T, Fujishima M. Small nonpolypoid neoplastic lesions of the colon: endoscopic features with emphasis on their progression. Gastrointest Endosc 1995;41:135-140.

8 Rex DK. Maximizing detection of adenomas and cancers during colonoscopy. Am J Gastroenterol 2006;101:2866-2877.

9 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.

10 Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? Endoscopy 1998;30:437-443.

11 Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211-1214.

12 Saitoh Y, Waxman I, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, Pasricha PJ. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120:1657-1665.

13 Tsuda S, Veress B, Toth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. Gut 2002;51:550-555.

14 Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-1035.

15 Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, Cardwell CR, Williams CB. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56:333-338.

16 Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376-380.
17 Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy 2006;38:444-448.
18 Le Rhun M., Coron E, Parlier D, Nguyen JM, Canard JM, Alamdari A, Sautereau D, Chaussade S, Galmiche JP. High resolution colonoscopy with chromoscopy versus standard colonoscopy for the detection of colonic neoplasia: a randomized study. Clin Gastroenterol Hepatol 2006;4:349-354.
19 Kato S, Fujii T, Koba I, Sano Y, Fu KI, Parra-Blanco A, Tajiri H, Yoshida S, Rembacken B. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? Endoscopy 2001;33:306-310.
20 Fu KI, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T, Okuno T, Yoshida S, Fujimori T. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. Endoscopy 2004;36:1089-1093.
21 Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004;9:568-577.
22 Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38:76-81.
23 Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-47.
24 Adler A, Pohl H, Papanikolaou IS, bou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rosch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? Gut 2008;57:59-64.
25 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.
26 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.
27 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.
28 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.
29 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.

30 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.
31 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2008;67:280-286.
32 van den Broek FJ, Fockens P, Dekker E. Review article: New developments in colonic imaging. Aliment Pharmacol Ther 2007;26 Suppl 2:91-99.
33 DaCosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. Curr Opin Gastroenterol 2005;21:70-79.
34 Kara MA, Peters FP, ten Kate FJ, Van Deventer SJ, Fockens P, Bergman JJ. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc 2005;61:679-685.
35 Kara MA, Peters FP, Fockens P, ten Kate FJ, Bergman JJ. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointest Endosc 2006;64:176-185.
36 Curvers WL, Singh R, Song LM, Wolfsen HC, Ragunath K, Wang K, Wallace MB, Fockens P, Bergman JJ. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 2008;57:167-172.
37 van den Broek FJ, Fockens P, van eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.
38 Umar A, Boland CR, Terdiman JP, Syngal S, de la CA, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.
39 Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570-578.
40 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.
41 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255.
42 Jass JR, Baker K, Zlobec I, Higuchi T, Barker M, Buchanan D, Young J. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.
43 East JE, Suzuki N, Stavrinidis M, Guenther T, Thomas HJ, Saunders BP. Narrow band imaging for colonoscopic surveillance in hereditary non-polyposis colorectal cancer. Gut 2008;57:65-70.

44 Stergiou N, Frenz MB, Menke D, Riphaus A, Wehrmann T. Reduction of miss rates of colonic adenomas by zoom chromoendoscopy. Int J Colorectal Dis 2006;21:560-565.
45 Hurlstone DP, Karajeh M, Cross SS, McAlindon ME, Brown S, Hunter MD, Sanders DS. The role of high-magnification-chromoscopic colonoscopy in hereditary nonpolyposis colorectal cancer screening: a prospective "back-to-back" endoscopic study. Am J Gastroenterol 2005;100:2167-2173.
46 Kiesslich R, von BM, Hahn M, Hermann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001;33:1001-1006.
47 Lecomte T, Cellier C, Meatchi T, Barbier JP, Cugnenc PH, Jian R, Laurent-Puig P, Landi B. Chromoendoscopic colonoscopy for detecting preneoplastic lesions in hereditary nonpolyposis colorectal cancer syndrome. Clin Gastroenterol Hepatol 2005;3:897-902.
48 Rex DK. Quality in colonoscopy: cecal intubation first, then what? Am J Gastroenterol 2006;101:732-734.
49 Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, Kirk LM, Litlin S, Lieberman DA, Waye JD, Church J, Marshall JB, Riddell RH. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002;97:1296-1308.
50 Rijcken FE, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. Gut 2002;50:382-386.
51 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Evaluation of microvessels in colorectal tumors by narrow band imaging magnification. Gastrointest Endosc 2007;66:945-952.
52 Farris AB, Misdraji J, Srivastava A, Muzikansky A, Deshpande V, Lauwers GY, Mino-Kenudson M. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol 2008;32:30-35.
53 Sandmeier D, Seelentag W, Bouzourene H. Serrated polyps of the colorectum: is sessile serrated adenoma distinguishable from hyperplastic polyp in a daily practice? Virchows Arch 2007;450:613-618.
54 Cothren RM, Sivak MV, Jr., Van DJ, Petras RE, Fitzmaurice M, Crawford JM, Wu J, Brennan JF, Rava RP, Manoharan R, Feld MS. Detection of dysplasia at colonoscopy using laser-induced fluorescence: a blinded study. Gastrointest Endosc 1996;44:168-176.
55 Mycek MA, Schomacker KT, Nishioka NS. Colonic polyp differentiation using time-resolved autofluorescence spectroscopy. Gastrointest Endosc 1998;48:390-394.
56 Mayinger B, Jordan M, Horner P, Gerlach C, Muehldorfer S, Bittorf BR, Matzel KE, Hohenberger W, Hahn EG, Guenther K. Endoscopic light-induced autofluorescence spectroscopy for the diagnosis of colorectal cancer and adenoma. J Photochem Photobiol B 2003;70:13-20.
57 Wang TD, Crawford JM, Feld MS, Wang Y, Itzkan I, Van DJ. In vivo identification of colonic dysplasia using fluorescence endoscopic imaging. Gastrointest Endosc 1999;49:447-455.
58 Brand S, Stepp H, Ochsenkuhn T, Baumgartner R, Baretton G, Holl J, von RC, Paumgartner G, Sackmann M. Detection of colonic dysplasia by light-induced fluorescence endoscopy: a pilot study. Int J Colorectal Dis 1999;14:63-68.

59 Haringsma J, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, Watanabe H, Sato N, Marcon N, Wilson BC, Cline RW. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53:642-650.

60 McCallum AL, Jenkins JT, Gillen D, Molloy RG. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. Gastrointest Endosc 2008.

CHAPTER 5

Combining autofluorescence imaging and narrow band imaging for the differentiation of adenomas from non-neoplastic colonic polyps among experienced and non-experienced endoscopist

Frank J.C. van den Broek
Ellert J. van Soest
Anton H. Naber
Arnoud H.A.M. van Oijen
Rosalie Ch. Mallant-Hent
Clarisse J.M. Böhmer
Pieter Scholten
Pieter C.F. Stokkers
Willem A. Marsman
Elisabeth M.H. Mathus-Vliegen
Wouter L. Curvers
Jacques J.G.H.M. Bergman
Susanne van Eeden
James C.H. Hardwick
Paul Fockens
Johannes B. Reitsma
Evelien Dekker

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ABSTRACT

Background: Endoscopic tri-modal imaging incorporates high-resolution white light endoscopy (HR-WLE), narrow band imaging (NBI) and autofluorescence imaging (AFI). Combining these advanced techniques may improve endoscopic differentiation between adenomas and non-neoplastic polyps.
Aim: Assessment of interobserver variability and accuracy of HR-WLE, NBI and AFI for polyp differentiation; and evaluation of the combined use of AFI and NBI.
Methods: First, still images of 50 polyps (22 adenomas; median 3mm) were randomly displayed to 3 experienced and 4 non-experienced endoscopists. All HR-WLE- and NBI-images were scored for Kudo classification and AFI-images for color. Secondly, the combined AFI- and NBI-images were assessed using a newly developed algorithm by 6 additional non-experienced endoscopists.
Outcome: Interobserver agreement and diagnostic accuracy using histopathology as reference standard.
Results: Experienced endoscopists had better interobserver agreement for NBI (κ=0.77) than for AFI (κ=0.33), whereas non-experienced endoscopists had better agreement for AFI (κ=0.58) than for NBI (κ=0.33). The accuracies of HR-WLE, NBI and AFI among experienced endoscopists were 65, 70 and 74% respectively. Figures among non-experienced endoscopists were 57, 63 and 77%. The algorithm was associated with a significantly higher accuracy of 85% among all observers ($p<0.023$). These figures were confirmed in the second evaluation study.
Conclusions: Non-experienced endoscopists have better interobserver agreement and accuracy for AFI than for HR-WLE or NBI, indicating that AFI is easier to use for polyp differentiation in non-experienced setting. The newly developed algorithm, combining information of AFI and NBI together, had the highest accuracy and obtained equal results between experienced and non-experienced endoscopists.

Introduction

Colonoscopic detection and removal of adenomas prevents the development of colorectal cancer and is therefore the aim of screening and surveillance colonoscopy.[1-3] All colonoscopically detected polyps are removed with an accompanying risk of perforation or bleeding of 0.04-1.1% and 0.48-8.6% respectively.[4-7] However, 45-61% of all resected polyps are non-neoplastic polyps.[8, 9] Removal of these lesions leads to unnecessary risks, higher pathology costs and an increased workload for endoscopists/pathologists.

Several endoscopic techniques may provide real-time differentiation of neoplastic from non-neoplastic polyps, enabling the endoscopist to decide whether lesions should be resected (adenomas) or left *in situ* (non-neoplastic polyps).[10] Chromoendoscopy makes use of dye-spraying in order to elucidate the mucosal pattern of polyps.[11] This technique allows differentiation of neoplastic and non-neoplastic polyps by applying the Kudo classification, with a sensitivity and specificity of 91% and 89% respectively.[12-16] Narrow band imaging (NBI) is a novel imaging technique that uses optical filters to highlight mucosal as well as vascular details.[17] The sensitivity and specificity of NBI for polyp differentiation are comparable to chromoendoscopy.[12-16] In all previous studies, however, the diagnostic accuracy was determined among endoscopists with extensive experience in the assessment of mucosal and vascular patterns.[12-16]

Autofluorescence imaging (AFI) is another method that can be used for polyp differentiation. During AFI, the mucosa is illuminated by short wavelength light which induces the tissue to emit autofluorescent light of longer wavelength.[18] As the composition of emitted autofluorescent light varies between adenomas and non-neoplastic polyps, it can be used for differentiation.[19, 20] McCallum *et al* recently evaluated light-induced fluorescence endoscopy which yielded a sensitivity of 85% and specificity of 81%.[21] However, the technology used in that study was based on a fiber-optic system which resulted in low quality imaging and a highly variable level of background fluorescence across patients. Video AFI may deal with some of these drawbacks as this technology produces high quality imaging, but video AFI has not yet been evaluated for the differentiation of colonic polyps.

Recently, AFI and NBI have been incorporated into one video endoscopic system, together with high resolution white light endoscopy (HR-WLE). This system, named 'endoscopic tri-modal imaging', has been evaluated in patients with Barrett's esophagus and ulcerative colitis, but may aid in the differentiation of colonic polyps as well.[22, 23]

The aims of this image evaluation study were to determine (1) the interobserver variation in polyp assessments by AFI, NBI and the combined use of AFI plus NBI; and (2) the diagnostic accuracy of these techniques for polyp differentiation among endoscopists with and without experience in advanced imaging techniques. In addition, (3) an attempt was made to develop an algorithm for the combined use of AFI plus NBI that yields a higher diagnostic accuracy than either AFI or NBI alone.

Patients & methods

Patients

All images of polyps evaluated in this study were derived from our image database that includes data from 107 patients (48 male; mean age 52 ± 14 years) who underwent surveillance colonoscopy for a personal history of adenomas/cancer (n=59) or positive family history of colorectal cancer (n=48). All colonoscopies were performed under conscious sedation by one of three experienced endoscopists (ED, PF, and JCH). These procedures have been approved by the medical ethical committee of our institution and informed consent was obtained from all patients prior to the colonoscopy.

Endoscopic equipment and methods of imaging

The specifications of the equipment used for all colonoscopies were described elsewhere.[23] In short, the 'endoscopic tri-modal imaging' system (Lucera, Olympus Inc., Tokyo, Japan) provides HR-WLE, NBI and AFI based on sequential red-green-blue illumination.[17] A high-resolution colonoscope (XCF-H240FZL) was used for all procedures. For NBI, narrowed bands of blue (390-445 nm) and green (530-550 nm) light were used. During AFI, blue (390-470 nm) and green light (540-560 nm) were used for illumination, whereas autofluorescent and reflected light of 500-630 nm were collected. Switching between the imaging modes was done by pressing a button on the endoscope.

During all colonoscopies, several overview and zoomed (maximally 100x) images were taken of all detected polyps by HR-WLE, NBI and AFI in order to achieve high quality images at the discretion of the endoscopist; these were stored as bitmap (.bmp) files. In general, images with HR-WLE and NBI were taken under higher magnification than images with AFI, although no fixed protocol was used. After images were taken, all polyps were removed for histological evaluation. All images were entered in a database and linked to corresponding patient and polyp data, including polyp size (estimated by an open biopsy forceps), shape (Paris classification[24]), colonic location and histopathology.

Selection of images for this study

A research fellow hand-searched the database to select the best images obtained with each technique (HR-WLE, NBI and AFI), based on highest quality regarding sharp motionless images with the most perpendicular view of the polyp and proper bowel cleansing. All images were matched for the same polyp. Fifty out of 274 available polyps were selected, in order to obtain a set of images that is feasible to assess within 2 hours. Just after this selection process, it was checked whether the distribution of adenomatous and non-neoplastic polyps represented the known distribution with 45-61% of all polyps being non-neoplastic.[8, 9]

Without any form of post processing (except from removing patient name or chart number from the image), one HR-WLE-image, one NBI-image and one AFI-image of the 50 chosen polyps were incorporated into a slideshow (Microsoft PowerPoint 2003; Microsoft Inc, Redmond, WA). All images had the same size and resolution.

Image evaluation study I

Classification schemes

All polyps on HR-WLE and NBI were scored for Kudo pit pattern and all polyps on AFI-images were assessed for color. The Kudo classification consists of 6 categories and we stratified AFI-color into 3 (see Figures 1 and 2).[11] Kudo type I-II and green AFI-color were considered to be non-neoplastic, whereas Kudo type III-V and ambiguous/purple AFI-color were considered to be adenomatous.

Assessors

Initially, the slideshow was presented separately to 3 experienced (ED, PF, and JCH) and 4 non-experienced endoscopists (PCS, WAM, EMM and WLC) from the same university hospital. Experienced endoscopists each had performed at least 30 colonoscopies with AFI and 50 colonoscopies with NBI. Non-experienced endoscopists had no previous experience with NBI or AFI in the colon.

Systematic training session

Before starting the image evaluation process, a short systematic training was provided to each endoscopist personally regarding the Kudo classification and assessment of color by AFI. This training included 7 NBI-images demonstrating the different types of pit patterns and 6 AFI-images demonstrating the different colors.

Hereafter, the HR-WLE, NBI and AFI-images of 10 polyps (4 non-neoplastic and 6 adenomas) were assessed by each endoscopist as a learning set, giving the single observer feedback immediately after scoring each image. The images used for this training were not included in the final image evaluation process. The systematic training was provided to the experienced endoscopists as well.

First image evaluation process

After the systematic training session, the endoscopists independently assessed all images of the 50 included colonic polyps (Figure 3). First, 50 HR-WLE-images were scored on whether the image quality was sufficient to visualize the pit pattern and assessed for Kudo classification (I-V). Secondly, 50 corresponding NBI-images were scored on image quality and assessed for Kudo classification. The endoscopists were instructed a priori to assess the Kudo classification irrespective of polyp size, color and shape. In case no pit pattern could be identified on either HR-WLE or NBI, the observer had to diagnose the polyp as adenomatous or non-neoplastic based on his personal endoscopic experience (considering the polyp size, color and shape). Subsequently, 50 AFI-images were assessed for image quality and polyp color. Finally, the HR-WLE, NBI and AFI-images from the same polyp were displayed simultaneously. Again the same scores were given for image quality, Kudo classification and polyp color. During the entire image evaluation process, images were displayed in a random order per technique. The endoscopists were blinded for histopathology and were unaware of the personal history of patients.

Image evaluation study II

New classification scheme

After finishing the first image evaluation process, an attempt was made to generate an algorithm from the initial results by combining the information provided by AFI and NBI together. The following algorithm, that was associated with the highest diagnostic accuracy for discriminating adenomas from non-neoplastic polyps, was derived from the first image evaluation process: all AFI purple polyps as well as all AFI ambiguous polyps with Kudo type III-V were considered to be adenomas; whereas all AFI green polyps as well as AFI ambiguous polyps with Kudo type I-II were considered to be non-neoplastic.

Assessors

Six additional endoscopists (EJvS, AHN, AHvO, RCM, CJB, and PS) from 5 non-university hospitals were included for the second image evaluation process incorporating the algorithm. These endoscopists had no previous experience with NBI and AFI in the colon.

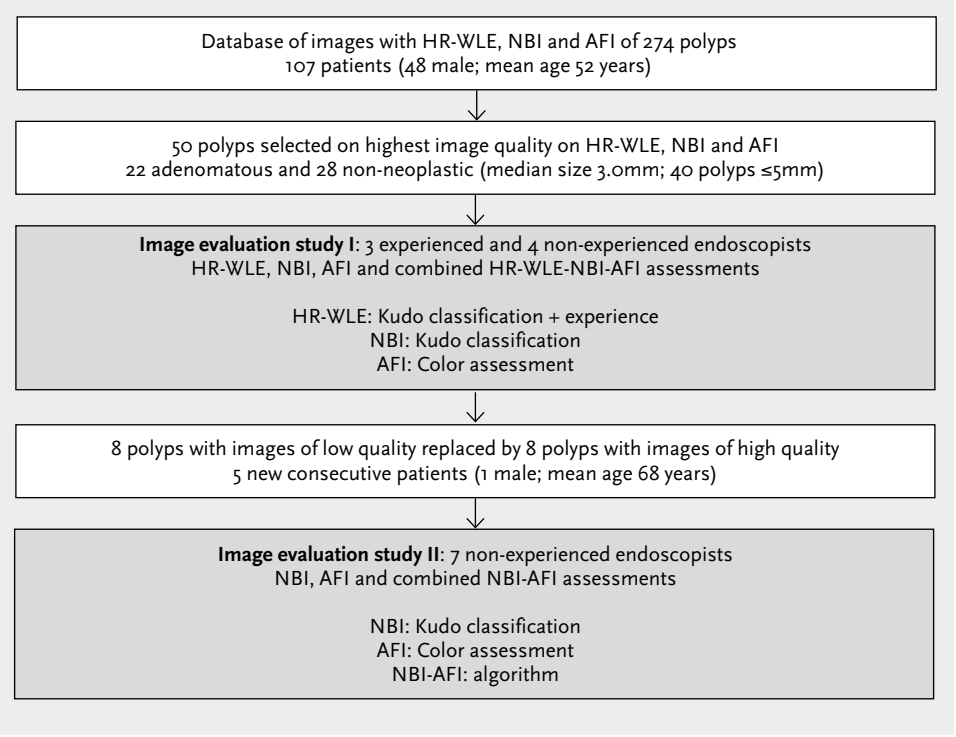

Figure 3: Study design demonstrating the order of image selection process, image evaluation study I and image evaluation study II.

Second image evaluation process

Images of 8 polyps from the first image evaluation process were scored as having insufficient quality on NBI and AFI by at least two of the initial seven assessors (see results section). Therefore, for the second image evaluation process these were replaced by higher quality NBI- and AFI-images of new polyps (with equal histopathology). These new images were derived from five consecutive patients (1 male; mean age 68±11 years) who underwent colonoscopy for a history of adenomas.

The 6 additional endoscopists assessed the images after the same systematic training session as described above. This time, the HR-WLE images were left out, as these did not add relevant information to NBI and AFI for polyp differentiation (see results). Again NBI-images were scored for Kudo classification and AFI-images for color. When displaying the AFI- and NBI-images simultaneously, however, the endoscopists were instructed a-priori to use the new algorithm. In addition, during all assessments (NBI, AFI and algorithm), the observers were asked to score their level of certainty with respect to their assessment (not sure at all, moderately sure, absolutely sure).

Reference standard

The histopathology of all resected polyps served as reference standard and was provided by an experienced gastrointestinal pathologist (SvE), who was blinded for the endoscopic appearance on the advanced imaging techniques. A sessile serrated adenoma (SSA) was diagnosed when a polyp demonstrated histological serration resembling a hyperplastic polyp, but with architectural crypt distortion and abnormal proliferation at the base of the crypts without or with minimal epithelial neoplastic changes.[25] A SSA was primarily considered to be non-adenomatous, however, as SSAs may be considered premalignant as well, findings with respect to the diagnostic accuracy on this subgroup of polyps were described separately.[26]

Statistical analysis

The interobserver agreement was expressed by the percentage of full agreement among *all* observers as well as by an overall kappa statistic with 95%-confidence interval (95-CI).[27] Whether a lesion was considered to be adenomatous or non-neoplastic by each imaging technique was used to evaluate interobserver agreement. The interpretation of κ-values was done according to Landis and Koch.[28] Because of the correlated nature of our data when comparing kappa's between different groups of raters (experts *vs.* non-experts or between different techniques), we used bootstrapping techniques (k=2000 bootstrap samples) to obtain p-values for differences in kappa's.

For calculating the diagnostic accuracy of the Kudo classification and AFI-color, 2x2 tables were constructed to compare each imaging technique (plus the algorithm) with histopathology. The outcome parameters were sensitivity, specificity and overall accuracy of each technique. The diagnostic accuracies between the several techniques were compared in the following manner: each correct (true positive or true negative) score of an observer counted as +1 point; each incorrect score counted as 0 points. The sum of all scores was compared between each technique by the paired Wilcoxon signed ranks test. This statistical procedure was used in order to prevent too optimistic significance levels only by using multiple observers.

Results

Image evaluation study I

Patients and polyps

The images used during the first image evaluation were derived from 32 patients (17 male; mean age 59±12 years) who underwent colonoscopy for a history of neoplasia (n=24) or family history of colorectal cancer (n=8). The mean polyp size was 5.5 mm (median 3.0; IQR 2.0-5.0); 18 (36%) were flat (Paris IIa/IIb); and 33 (66%) were located proximal to the splenic flexure. The histopathology of these polyps was adenomatous in 22 (44%) and non-neoplastic in 28 (56%) lesions. Forty polyps were £5mm and five were ≥10mm. Of the non-neoplastic lesions, 13 (46%) were diagnosed as SSAs.

Image quality

During the first image evaluation process, all 7 observers fully agreed that HR-WLE-images of only 6 polyps (12%) were sufficient to visualize the Kudo pit pattern; whereas all observers fully agreed that HR-WLE-images were *in*sufficient for 18 polyps (36%).

There was full agreement by all observers that NBI-image quality was sufficient for 31 polyps (62%). Five or less of the seven observers fully agreed that the NBI-image quality was sufficient for 8 polyps (16%). Only 2 non-experienced endoscopists did not assess all NBI-images due to too low quality.

With respect to AFI-image quality, all observers fully agreed on 37 polyps (74%) to be sufficient. Five or less of them agreed that the AFI-image quality was sufficient for 3 polyps (6%). One non-experienced endoscopist did not assess one AFI-image due to too low quality.

Interobserver variability

The interobserver agreement among 3 experienced endoscopists in their assessment of pit pattern on HR-WLE was 'fair' (κ=0.34; 95-CI: 0.15-0.53), on NBI 'substantial' (κ=0.77; 0.59-0.95); and for AFI-color this was 'fair' (κ=0.33; 0.13-0.53). Interobserver agreement among 4 non-experienced endoscopists on the same images was 'moderate' for HR-WLE (κ=0.44; 0.29-0.58), 'fair' for NBI (κ=0.33; 0.16-0.50; compared to experts, p<0.001), and 'moderate' for AFI (κ=0.58; 0.45-0.72; compared to experts p=0.002).

The combined presentation of the HR-WLE, NBI- and AFI-images together had a minor positive effect on the interobserver agreement (Table 1).

	Experienced endoscopists (n=3)		Non-experienced endoscopists (n=4)	
	Percentage full agreement	κ-value	Percentage full agreement	κ-value
HR-WLE	28	0.34 (0.11-0.57)	58	0.47 (0.29-0.65)
NBI	84	0.77 (0.59-0.95)	44	0.33 (0.16-0.50)
AFI	56	0.33 (0.13-0.53)	62	0.58 (0.45-0.72)
NBI (+AFI)	68	0.57 (0.41-0.73)	56	0.52 (0.40-0.64)
AFI (+NBI)	58	0.32 (0.10-0.54)	68	0.64 (0.52-0.76)

Table 1: Results of image evaluation study I among 3 experienced and 4 non-experienced endoscopists: Percentages of full agreement between all observers and corresponding kappa-values (95%-confidence interval) with respect to the endoscopic diagnosis (i.e. adenoma or non-neoplastic polyp) for each imaging technique. In delineated cells, the best interobserver agreements are highlighted.

NBI, narrow band imaging; AFI, autofluorescence imaging; HR-WLE, high resolution white light endoscopy; NBI (+AFI), assessment of NBI image when combined with HR-WLE and AFI image; AFI (+NBI), assessment of AFI image when combined with HR-WLE and NBI image.

Diagnostic accuracy

Among the 3 experienced endoscopists only, the sensitivity, specificity and overall accuracy of HR-WLE respectively were 62%, 67% and 65%. Corresponding figures for NBI were 88%, 56% and 70%; AFI yielded figures of 97%, 56% and 74% (overall accuracy compared to HRE, p=0.177; to NBI, p=0.545).

Among non-experienced endoscopists the sensitivity, specificity and overall accuracy of HR-WLE were 53%, 60% and 57% respectively. Corresponding figures for NBI were 86%, 46% and 63% (accuracy compared to HR-WLE, p<0.001); figures for AFI were 92%, 65% and 77% (accuracy compared to HR-WLE, p<0.001; to NBI, p=0.016).

The simultaneous presentation of HR-WLE-, AFI- and NBI-images significantly (p<0.05) increased the specificity (Table 2). In order to discover the optimal diagnostic accuracy by 'endoscopic tri-modal imaging', which implies the combined availability of AFI and NBI, we examined the following algorithm: all AFI purple polyps as well as all AFI ambiguous polyps with Kudo type III-V were considered to be adenomatous; whereas all AFI green polyps as well as AFI ambiguous polyps with Kudo type I-II were considered non-neoplastic. This algorithm yielded a sensitivity, specificity and overall accuracy of 86%, 83% and 85% among experienced endoscopist (accuracy compared to NBI alone, p=0.004; to AFI alone, p=0.02); and 85%, 85% and 85% among non-experienced endoscopists (compared to NBI alone, p<0.001; to AFI alone, p=0.064).

	Experienced endoscopists (n = 3 observers; n = 50 polyps)			Non-experienced endoscopists (n = 4 observers; n = 50 polyps)		
	Sens	Spec	Acc	Sens	Spec	Acc
HR-WLE	62	67	65	53	60	57
NBI	88	56	70	86	46	63
AFI	97	56	74	92	65	77
NBI (+AFI)	88	79†	83	86	67†	76
AFI (+NBI)	97	49	70	92	76††	83
Algorithm	86	83	85	85	85	85

Table 2: Results of image evaluation study I: Sensitivity, specificity and overall diagnostic accuracy (in %) of each imaging technique for the differentiation between adenomas and non-neoplastic polyps, by using histopathology as reference standard diagnosis. In delineated cells, the best sensitivity, specificity and accuracy are highlighted.
Algorithm: all AFI purple polyps as well as all AFI ambiguous polyps with Kudo type III-V were considered to be adenomatous; whereas all AFI green polyps as well as AFI ambiguous polyps with Kudo type I-II were considered non-neoplastic
† $p<0.01$ †† $p<0.05$ compared to specificity of AFI and NBI alone

NBI, narrow band imaging; AFI, autofluorescence imaging; HR-WLE, high resolution white light endoscopy; NBI (+AFI), assessment of NBI image when combined with HR-WLE and AFI image; AFI (+NBI), assessment of AFI image when combined with HR-WLE and NBI image; Sens sensitivity; Spec specificity; Acc accuracy.

Image evaluation study II

Interobserver variability
Interobserver agreement among 6 non-experienced endoscopists in the second image evaluation was 'moderate' for NBI (κ=0.49; 0.39-0.59), 'moderate' for AFI (κ=0.52; 0.39-0.65), and 'moderate' for the algorithm (κ=0.53; 0.45-0.62; when compared between the techniques, p>0.590).

Diagnostic accuracy
The sensitivity, specificity and accuracy of NBI were 90%, 55% and 70% (Table 3); corresponding figures for AFI were 98%, 49% and 71% (p=0.773). The algorithm yielded corresponding figures of 96%, 69% and 80% (accuracy compared to AFI alone; p=0.04, to NBI alone; p=0.007).

When including the "level of certainty of the endoscopic diagnosis" according to each observer (Table 4), the diagnostic accuracy significantly improved with increasing level of certainty. The observers were absolutely sure on their diagnosis on 28% of NBI assessments, 49% of AFI assessments and 32% of assessments with the algorithm.

	Interobserver agreement		Diagnostic accuracy		
	Full agreement (%)	κ-value (95%-CI)	Sens	Spec	Acc
NBI	40	0.49 (0.39-0.59)	90	55	70
AFI	46	0.52 (0.39-0.65)	98	49	71
Algorithm AFI + NBI	46	0.53 (0.45-0.62)	96	69	80

Table 3: Results of image evaluation study II among 6 non-experienced endoscopists from 5 non-university hospitals: (1) Percentages of full agreement between all 6 observers and corresponding kappa-values (95%-confidence intervals) with respect to the endoscopic diagnosis, adenoma or non-neoplastic polyp. (2) Sensitivity, specificity and overall accuracy (in %) for the differentiation between adenoma and non-neoplastic polyp, with final histopathology as reference standard. In delineated cells, the best results concerning interobserver agreement and diagnostic accuracy are highlighted

NBI, narrow band imaging; AFI, autofluorescence imaging; Sens sensitivity; Spec specificity; Acc accuracy.

Sessile serrated adenomas

Polyps diagnosed by the pathologist as SSAs had a non-suspicious pit pattern (type I-II) on NBI in 55 out of 78 assessments (71%); had a green AFI-color in 31 assessments (40%); and 52 assessments (67%) were unsuspicious by the algorithm (Figure 4). Compared to hyperplastic polyps, SSAs more often had an unsuspicious pit pattern on NBI (35% *vs.* 71%; p<0.001), although AFI color was more often suspicious (37% *vs.* 60%; p=0.006). By using the algorithm, 23% of hyperplastic polyps were unsuspicious *vs.* 33% of the SSAs (p=0.199). When these SSAs would have been considered as adenomatous in the analysis of our results, the overall accuracy of NBI, AFI and the algorithm would have been only 60%, 76% and 72% respectively.

	Sensitivity			p	Specificity			p
	Not sure	*Moderate sure*	*100% sure*		*Not sure*	*Moderate sure*	*100% sure*	
NBI	63	90	97	0.023	45	47	76	0.003
AFI	100	94	100	0.089	33	29	78	<0.001
Algorithm AFI + NBI	100	96	94	0.711	10	62	94	<0.001

Table 4: Results of image evaluation study II: Sensitivity and specificity (in %) of each imaging technique for the differentiation between adenomas and non-neoplastic polyps, subdivided for the level of certainty of each assessment (not sure at all, moderately sure, or absolutely sure).

NBI, narrow band imaging; AFI, autofluorescence imaging; p, p-value Fisher's exact test.

Discussion

Several image evaluation studies have focused on NBI and chromoendoscopy for the differentiation of adenomas from non-neoplastic polyps, demonstrating comparable results for both techniques.[12-16, 29-32] Some of those studies investigated the accuracy of white light endoscopy as well and demonstrated that it was inferior to advanced techniques; results that were confirmed by the present study.[13, 14] None of the published series however evaluated the combined use of AFI and NBI, which are both available in 'endoscopic tri-modal imaging'.[22, 23] Results from previous research with this system suggested that the combined use of AFI and NBI may be highly accurate for differentiating neoplastic from non-neoplastic mucosa.[23] Another limitation of previous studies on this topic is that the diagnostic accuracy was assessed only for endoscopists with extensive experience in advanced imaging. The learning curve of NBI and chromoendoscopy may be short, but this has never been evaluated.

To our knowledge, the present study is the first to report on the combined use of AFI and NBI, not only among experienced endoscopists but among non-experienced endoscopists as well. Our first finding was that experienced endoscopists had better interobserver agreement for NBI (κ=0.77) than AFI (κ=0.33; p<0.001), although with a comparable diagnostic accuracy (70% *vs.* 74% respectively). Conversely, non-experienced endoscopists from the same university hospital had better interobserver agreement for AFI (κ=0.58) than for NBI (κ=0.33; p=0.035), as well as a higher accuracy with AFI (77%) compared to NBI (63%; p=0.016). These findings suggest that AFI-color is easier to assess for endoscopists without experience than the somewhat more sophisticated Kudo classification. When gaining experience with NBI, however, the interobserver agreement will likely increase, as demonstrated by the experienced endoscopists in this study and by expert Japanese endoscopists when using chromoendoscopy in a previous study.[33]

A more remarkable finding was that the simultaneous presentation of AFI- and NBI-images increased the interobserver agreement among non-experienced endoscopists, and significantly improved the specificities of both NBI and AFI. This finding suggested that combining the information obtained by each technique, synergistically improves their value with respect to differentiation. Therefore, an algorithm that combined the information obtained by both techniques was evaluated to investigate its effect on the accuracy. In this algorithm, all AFI-purple polyps were considered adenomatous, whereas all AFI-green lesions were considered non-neoplastic. When AFI-color was ambiguous, however, the Kudo classification by NBI was used to determine whether the polyp was considered adenomatous (type III-V) or non-neoplastic (I-II). For both experienced and non-experienced endoscopists this algorithm led to a significantly increased overall accuracy (85%) when compared to AFI alone (74-77%) or NBI alone (63-70%). This increased accuracy by the algorithm was confirmed in the second image evaluation study among 6 non-experienced endoscopists from 5 non-university hospitals, who were instructed a-priori to use the algorithm.

Real-time polyp differentiation will make colonoscopy more efficient by reducing the workload of the endoscopist, reducing pathology costs and reducing complications by resection of non-neoplastic lesions. However, these savings in workload and costs should *not* be accompanied

by a higher risk of leaving premalignant adenomas *in situ*. Therefore, the sensitivity for differentiation should preferably approach 100%, with an accompanying acceptable specificity. A systematic review on NBI demonstrated that this technique was associated with a sensitivity of 91% among experienced endoscopists.[34] This level of sensitivity means that 9% of all adenomas were not correctly recognized and were felt to be safe to be left *in situ*; a figure that instinctively should be lower. One has to bear in mind however, that almost all of these studies have been performed with monochromatic chip endoscopes using the sequential red-green-blue illumination system (Lucera, Olympus Inc.) which may be associated with different diagnostic accuracies when compared to NBI systems based on a color chip (Excera, Olympus Inc.).[17] Data comparing these two systems are however lacking. The present study demonstrated that AFI led to a higher sensitivity (92-98%); however with an accompanying lower specificity (49-65%) than NBI. When deliberately using the algorithm in the second image evaluation process, the high sensitivity of AFI could be maintained (96%) together with an acceptable specificity (69%). Moreover, the algorithm was easy to teach to non-experienced endoscopists, who only received a training of 17 example polyps and then already had a 'moderate' interobserver agreement (κ = 0.53).

Furthermore, we assessed the value of the "level of certainty about the endoscopic diagnosis" with respect to its effect on the diagnostic accuracy. The reason for this additional analysis is that endoscopists are unlikely to be willing to make a decision (remove or leave *in situ*), based on an uncertain diagnosis with NBI or AFI and hence still would take a diagnostic biopsy first. Polyps diagnosed with "absolute certainty", had sensitivities of NBI and AFI that approached 100% (97-100) with corresponding specificities of 76-78%. The algorithm then had a sensitivity and specificity of both 94%. The main drawback of introducing this "level of certainty" is that only 28-49% of all assessments were done with absolute certainty. However, as this was an image evaluation study, this figure may be much higher in clinical practice.

The results of this study all point to the fact that combining AFI and NBI improves the overall diagnostic accuracy and obtains comparable results between experienced and non-experienced endoscopists after a short training session already. However, Two limitations of this study must be mentioned. It might be questioned whether our results can be generalized to daily practice, as all images were obtained in a tertiary referral center and a selection was made of images with high quality only. It may be possible that in real-time some polyps are difficult to visualize as they are located behind mucosal folds which precludes obtaining high quality images. These polyps have possibly been excluded by the selection process. Ideally, analyzing consecutive patients including all detected lesions would better reflect true clinical practice.

Furthermore, the accuracy of NBI alone obtained in this study appears relatively low when compared to literature. Several reasons may explain this difference. First, in some studies about a third of all included lesions were cancers; one can imagine that discriminating cancers from non-neoplastic lesions is easier and hence can be done with higher accuracy.[29, 30] Second, Western endoscopists appear to have lower accuracies than Japanese endoscopists, as demonstrated by figures provided by East and Rogart *et al*, that are better comparable to our figures.[15, 35] Lastly, our prevalence of SSAs (having an indistinct appearance) was much higher when compared to other studies. However, it seems improbable that either the image selection process (based on techni-

cally sharp and motionless images with perpendicular view of the polyp only) or the relatively low accuracy of NBI alone would have altered the complementary effect of AFI and NBI in an algorithm that was demonstrated by this study.

The last remark that should be made is that the existence of SSAs is increasingly recognized and these polyps appear to be associated with an increased risk of malignant transformation as well.[26] These SSAs endoscopically appear as hyperplastic polyps, and there is no discriminating Kudo-type or AFI-color for these polyps. The algorithm resulted in an unsuspicious endoscopic appearance in 67% of these polyps, leading to an overall accuracy of only 72% when considering these SSAs as adenomatous as well. However, the impact and importance of these polyps on the negative predictive value of AFI and NBI in general practice will depend on the actual prevalence of these lesions and their ability to progress into invasive cancer. As all polyps in this study were derived from a tertiary referral centre, the prevalence of SSAs was high (26%) when compared to the general population, in which the prevalence is estimated to be only 1-7%.[36-38] In addition, the true prevalence is difficult to assess as pathologists experience difficulties in achieving consensus on the diagnosis of hyperplastic polyps or SSAs.[39, 40]

In conclusion, this study demonstrates that with respect to the differentiation of adenomas from non-neoplastic polyps, non-experienced endoscopists have a better interobserver agreement and diagnostic accuracy when using AFI instead of NBI. The use of AFI therefore seems easier and more practicable in non-experienced setting. Furthermore, the combined availability of AFI and NBI in one endoscopic system increased the diagnostic accuracy significantly. As AFI and NBI are techniques that only involve a push on a button instead of the application of dyes, they are easy to use and can differentiate polyps in only a few seconds. In fact, the combined use of AFI and NBI in an algorithm by non-experienced endoscopists was accompanied by a diagnostic accuracy that was comparable to experienced endoscopists. Our new developed algorithm however needs formal validation in a prospective study of consecutive patients, preferably in general setting, which has already been initiated in order to assess the true clinical value of 'endoscopic tri-modal imaging' on the efficiency of colonoscopies.

>> For figures 1, 2 and 4; see page 137-138

Reference List

1 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, . Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.

2 Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, Smith RA, Lieberman DA, Burt RW, Levin TR, Bond JH, Brooks D, Byers T, Hyman N, Kirk L, Thorson A, Simmang C, Johnson D, Rex DK. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology 2006;130:1872-1885.

3 Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, Burt RW, Byers T, Fletcher RH, Hyman N, Johnson D, Kirk L, Lieberman DA, Levin TR, O'Brien MJ, Simmang C, Thorson AG, Winawer SJ. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-167.

4 Levin TR, Zhao W, Conell C, Seeff LC, Manninen DL, Shapiro JA, Schulman J. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145:880-886.

5 Heldwein W, Dollhopf M, Rosch T, Meining A, Schmidtsdorff G, Hasford J, Hermanek P, Burlefinger R, Birkner B, Schmitt W. The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. Endoscopy 2005;37:1116-1122.

6 Su MY, Hsu CM, Lin CJ, Ho YP, Chiu CT, Chen PC, Lien JM, Wu CS, Tung SY. Endoscopic treatment of colorectal neoplasms: a simple and safe procedure to lower the incidence of colorectal cancers. Dig Dis Sci 2008;53:1297-1302.

7 Consolo P, Luigiano C, Strangio G, Scaffidi MG, Giacobbe G, Di GG, Zirilli A, Familiari L. Efficacy, risk factors and complications of endoscopic polypectomy: Ten year experience at a single center. World J Gastroenterol 2008;14:2364-2369.

8 Soetikno RM, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-1035.

9 Heresbach D, Barrioz T, Lapalus MG, Coumaros D, Bauret P, Potier P, Sautereau D, Boustiere C, Grimaud JC, Barthelemy C, See J, Serraj I, D'Halluin PN, Branger B, Ponchon T. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008;40:284-290.

10 DaCosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. Curr Opin Gastroenterol 2005;21:70-79.

11 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.

12 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.

13 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.

14 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.
15 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.
16 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.
17 Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38:76-81.
18 DaCosta RS, Andersson H, Wilson BC. Molecular fluorescence excitation-emission matrices relevant to tissue spectroscopy. Photochem Photobiol 2003;78:384-392.
19 Wang TD, Crawford JM, Feld MS, Wang Y, Itzkan I, Van DJ. In vivo identification of colonic dysplasia using fluorescence endoscopic imaging. Gastrointest Endosc 1999;49:447-455.
20 Mycek MA, Schomacker KT, Nishioka NS. Colonic polyp differentiation using time-resolved autofluorescence spectroscopy. Gastrointest Endosc 1998;48:390-394.
21 McCallum AL, Jenkins JT, Gillen D, Molloy RG. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. Gastrointest Endosc 2008;68:283-290.
22 Curvers WL, Singh R, Song LM, Wolfsen HC, Ragunath K, Wang K, Wallace MB, Fockens P, Bergman JJ. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 2008;57:167-172.
23 van den Broek FJ, Fockens P, van Eeden S., Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.
24 Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570-578.
25 Torlakovic EE, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, Snover DC. Sessile serrated adenoma (SSA) *vs.* traditional serrated adenoma (TSA). Am J Surg Pathol 2008;32:21-29.
26 Jass JR, Baker K, Zlobec I, Higuchi T, Barker M, Buchanan D, Young J. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.
27 Chmura KH, Periyakoil VS, Noda A. Kappa coefficients in medical research. Stat Med 2002;21:2109-2129.
28 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
29 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.

30 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Evaluation of microvessels in colorectal tumors by narrow band imaging magnification. Gastrointest Endosc 2007;66:945-952.
31 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2008;67:280-286.
32 Sikka S, Ringold DA, Jonnalagadda S, Banerjee B. Comparison of white light and narrow band high definition images in predicting colon polyp histology, using standard colonoscopes without optical magnification. Endoscopy 2008;40:818-822.
33 Huang Q, Fukami N, Kashida H, Takeuchi T, Kogure E, Kurahashi T, Stahl E, Kudo Y, Kimata H, Kudo SE. Interobserver and intra-observer consistency in the endoscopic assessment of colonic pit patterns. Gastrointest Endosc 2004;60:520-526.
34 van den Broek FJ, Reitsma JB, Curvers WL, Fockens P, Dekker E. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon (with videos). Gastrointest Endosc 2009;69:124-135.
35 Rogart JN, Jain D, Siddiqui UD, Oren T, Lim J, Jamidar P, Aslanian H. Narrow-band imaging without high magnification to differentiate polyps during real-time colonoscopy: improvement with experience. Gastrointest Endosc 2008;68:1136-1145.
36 Matsumoto T, Mizuno M, Shimizu M, Manabe T, Iida M, Fujishima M. Serrated adenoma of the colorectum: colonoscopic and histologic features. Gastrointest Endosc 1999;49:736-742.
37 Matsumoto T, Mizuno M, Shimizu M, Manabe T, Iida M. Clinicopathological features of serrated adenoma of the colorectum: comparison with traditional adenoma. J Clin Pathol 1999;52:513-516.
38 Jaramillo E, Watanabe M, Slezak P, Rubio C. Flat neoplastic lesions of the colon and rectum detected by high-resolution video endoscopy and chromoscopy. Gastrointest Endosc 1995;42:114-122.
39 Farris AB, Misdraji J, Srivastava A, Muzikansky A, Deshpande V, Lauwers GY, Mino-Kenudson M. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol 2008;32:30-35.
40 Sandmeier D, Seelentag W, Bouzourene H. Serrated polyps of the colorectum: is sessile serrated adenoma distinguishable from hyperplastic polyp in a daily practice? Virchows Arch 2007;450:613-618.

CHAPTER 6

Hyperplastic polyposis syndrome: a pilot study for the differentiation of polyps using high resolution endoscopy, autofluorescence imaging and narrow-band imaging

Karam S. Boparai
Frank J.C. van den Broek
Susanne van Eeden
Paul Fockens
Evelien Dekker

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ABSTRACT

Background: Endoscopic differentiation and removal of potentially premalignant sessile serrated adenomas (SSAs) may be an important step in preventing colorectal cancer (CRC) development in hyperplastic polyposis syndrome (HPS).
Objective: To assess the value of high resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow-band imaging (NBI) for differentiating polyps in HPS.
Design: A prospective polyp series.
Setting: Single tertiary referral center.
Patients and Interventions: 7 patients with HPS underwent colonoscopy using endoscopic trimodal imaging (ETMI), which incorporates HRE, AFI and NBI in one system. All detected polyps were analysed with AFI for colour and with NBI for Kudo pit pattern and vascular pattern intensity (VPI).
Main outcome measurements: The accuracy, sensitivity and specificity of AFI and NBI in differentiating detected polyps were determined by using histology as a gold standard.
Results: A total of 19 hyperplastic polyps (HPs), 32 SSAs and 15 adenomas were detected. For differentiating SSAs from HPs, AFI-colour, Kudo pit pattern and VPI resulted in a diagnostic accuracy of 55%, 55% and 52% respectively. For differentiating adenomas from HPs, this was 65%, 94% and 90% respectively. Macroscopically, the combination of size ≥3mm and proximal location resulted in the highest accuracy (76%) for differentiating SSAs from HPs.
Limitations: Small sample size.
Conclusion: Endoscopic differentiation between HPs and SSAs using ETMI proved unsatisfactory. Differentiation of adenomas from HPs was well possible with NBI but not with AFI.

Introduction

Hyperplastic polyposis syndrome (HPS) is a recently recognised condition characterised by the presence of multiple (>30) hyperplastic polyps (HPs) spread throughout the colon and has frequently been linked with colorectal cancer (CRC).[1-4] Besides multiple HPs, serrated adenomas are frequently seen in HPS as well. [1-8] In fact, the co-existence of sessile serrated adenomas (SSAs) has been considered by some as a characterizing feature of this condition.[9]

Molecular research in SSAs strongly suggests that these polyps are precursor lesions which may lead to CRC.[10-13] Accordingly, authorities recommend that SSAs should be endoscopically managed like conventional adenomas.[14] In this respect, endoscopic differentiation of SSAs from HPs and removal of SSAs may be an important step in preventing cancer development in HPS. However, HPs and SSAs, being both often small in size and sessile/flat in shape, are similar in appearance and therefore difficult to distinguish from each other when using standard endoscopy (figure 1).[15-18]

Novel endoscopic imaging techniques may aid in the differentiation of conventional adenomas and HPs with high accuracy.[19-22] Autofluorescence imaging (AFI) facilitates differentiation of adenomas from non-adenomatous polyps based on different fluorescence emission spectra.[23-25] The use of AFI in differentiating polyps in HPS patients has not been described before. Narrow band imaging (NBI) utilizes short wavelength visible light to provide improved details of the mucosal pit pattern and microvasculature. Pit pattern analysis by applying the Kudo classification has shown to be a reliable approach for distinguishing adenomas from non-adenomatous polyps and has also been used to describe serrated adenomas.[26-31] However, at the times of these studies the diagnosis SSA was not yet in practice and Kudo pit patterns for serrated adenomas varied considerably from II to as high as IV.[27, 28] In addition, the assessment of microvasculature and vascular pattern intensity (VPI) with NBI is believed to be a relatively easy method for differentiating adenomas from non-adenomatous polyps, but has not been evaluated in HPS.[20, 29, 30, 32-34]

The aim of this study was to assess the diagnostic accuracy of high resolution endoscopy (HRE), AFI and NBI for the differentiation of polyps in patients with HPS.

Patients and methods

Study population

This study was conducted at the Academic Medical Centre Amsterdam and was approved by the local medical ethics committee. Consecutive patients with HPS were invited to participate when fulfilling the criteria for HPS in accordance with the World Health Organisation (WHO): (1) at least five histologically confirmed HPs proximal to the sigmoid colon, of which two are greater than 10mm in diameter, or (2) more than 30 HPs distributed throughout the colon.[35] Patients <18 years or patients with severe coagulopathy or insufficient bowel cleansing were excluded from this study.

Endoscopic equipment

All procedures were performed with the endoscopic tri-modal imaging (ETMI) system, which integrates HRE, AFI and NBI into one unit (XCV-260 HP, Olympus Inc., Tokyo, Japan). The endoscope (XCF-H240FZL) is equipped with a movable lens for optical magnification (up to 100x) and two high quality charge coupled devices: one for HRE/NBI and one for AFI. The light source used in this system (XCLV-260HP) was of the type "sequential RGB-illumination". The ETMI specifications have previously been described in detail.[36, 37] During colonoscopy, the endoscopist could easily switch between the three imaging modalities by pressing a button on the shaft of the endoscope. A high resolution monitor was used for all procedures.

Colonoscopy procedure

Patients were prepared with 4-6 L polyethylene glycol solution (Kleanprep; Norgine GmbH, Marburg, Germany) and underwent colonoscopy under conscious sedation with midazolam and/or fentanyl. The colonoscope was advanced until cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve. Upon reaching the cecum, the level of bowel preparation was determined as good (100% of the mucosa visible), moderate (90-100%) or poor (<90%) after rinsing and suctioning.

During withdrawal of the endoscope, HRE was used to detect colonic polyps. All detected polyps were assessed for size (open biopsy forceps: 8mm), shape (Paris classification) and location.[38] Subsequently, each polyp was assessed with AFI for polyp colour: green, ambiguous or purple. Purple and ambiguous colours were considered suspicious for adenoma and green was considered non-suspicious for adenoma. Hereafter, the Kudo pit pattern (I-V) was assessed with NBI.[31] Kudo pit pattern III-V were considered suspicious for adenoma, while pit pattern I-II were non-suspicious. Still images (BMP-format) with all modalities were acquired after which the polyp was resected and harvested for histopathology.

All procedures and instant assessments with AFI and NBI were performed by one experienced endoscopist (ED), who has performed >2,500 colonoscopies and >50 ETMI colonoscopies.

In addition, representative NBI images of all detected lesions were later assessed for vascular pattern intensity (VPI) as described by East *et al.*[20] For this purpose, all sharp high-quality images were displayed in a random order to the same endoscopist who was blinded for final histopathology. Images were directly displayed on a personal computer in standard format (3.2 x 2.4 inch; 200 pixels/inch) without any post-processing. The VPI was scored as lighter (weak), the same (normal) or darker than (strong) the surrounding mucosa. Strong VPI was considered suspicious for adenoma, whereas weak/normal VPI was considered non-suspicious.

Reference standard

All polyp specimens were blindly evaluated by a gastrointestinal pathologist (SvE). Lesions were classified as HP, SSA, traditional serrated adenoma (TSA), mixed polyp or conventional adenoma based on the morphological features on H&E staining which was used as reference standard.[13, 14, 39]

Statistical analysis

SSAs were regarded as adenomatous polyps, owing to their premalignant potential.[10-14] Consequently, it was examined whether these polyps were suspicious on AFI (ambiguous/purple) and/or NBI-VPI (strong). In addition, NBI pit patterns of SSAs were expected to be comparable to HPs (Kudo II) as these polyps are described to be microscopically difficult to distinguish from each other.[14, 18, 40, 40] TSAs, mixed polyps and conventional adenomas were expected to be suspicious on AFI and NBI as these polyps harbour neoplastic changes of the epithelium.

The sensitivity, specificity, and diagnostic accuracy plus 95%-confidence interval (95%-CI, using the Wilson procedure without correction for continuity) for differentiating SSAs, TSAs, mixed polyps and conventional adenomas (i.e. adenomatous group) from HPs were determined for each modality by comparing the endoscopic diagnosis to final histopathology, which served as reference standard. Lesions histologically diagnosed as normal mucosa were excluded from the analysis. The size, location and shape of all lesions were summarized and compared between the different polyps using the Chi-Square test, Fisher's exact test, Kruskal-Wallis test or Mann-Whitney U test when appropriate. To make statistical comparisons and to calculate the 95%-CI, it is necessary to assume that results for individual polyps constitute statistically independent observations, even when there may have been more than one polyp assessed in individual patients. A p-value less than 0.05 from a single test was considered statistically significant, but it is recognized that there was multiple testing of outcome data arising from individual polyps. Examining the nominal p-values in light of correction for multiple testing using the method of correction of Bonferroni, it is suggested that only those nominal p-values less than 0.01 will retain significance after correction. The uncorrected p-values are presented with the warning that p-values between 0.01 and 0.05 should be considered as provisional. For reporting the results of this study, the STARD guidelines were used.[41]

Results

From January 2005 to July 2006, 7 patients (5 male) who met the criteria for HPS, underwent colonoscopy with ETMI. The median age of all patients was 55.8 (range 54-71) years. At colonoscopy all patients had good to moderate bowel preparation. A total of 66 polyps (19 HPs, 32 SSAs and 15 tubular adenomas) were detected as well as 10 additional lesions displaying normal mucosa on histology (excluded from the analysis). Macroscopic polyp characteristics are summarized in table 1. Overall, SSAs were larger than HPs ($p<0.001$, Mann-Whitney U test) and adenomas ($p<0.001$, Mann-Whitney U test). There was no significant difference in size between HPs and adenomas.

Concerning the differentiation of SSAs from HPs, the odds ratio for predicting a polyp to be SSA was 2.3 (95%-CI: 1.2-4.4) for size (per mm increase), 4.9 (1.3-18.0) for flat shape and 3.9 (1.1-14.7) for proximal location. The combination of size ≥3mm and proximal location yielded the largest differential value ($p<0.0001$) between SSAs (21/32: 66%) and HPs (1/19: 5%) with a corresponding odds ratio of 34.4 (4.0-292). The sensitivity and specificity of this combination for differentiating SSAs from HPs would be 66% (95%-CI: 48-80%) and 95% (75-99%) respectively. The overall diagnostic accuracy would be 76% (62-87%).

Autofluorescence imaging

With AFI, 10/19 (53%) HPs displayed a green colour versus 14/32 (44%) SSAs and 3/15 (20%) adenomas (p=0.142). The sensitivity, specificity and diagnostic accuracy of AFI for discriminating SSAs from HPs based on colour were 56% (95%-CI: 39-72%), 53% (32-73%) and 55% (41-68%) respectively. Differentiation with AFI between adenomas and HPs had a sensitivity, specificity and accuracy of 80% (55-93%), 53% (32-73%) and 65% (48-79%).

Polyp characteristics	All polyps (n=66)	HP (n=19)	SSA (n=32)	Adenoma (n=15)	P-value
Median size mm (interquartile range)	2 (2-5)	2 (1-2)	3 (2-8)	2 (1-3)	0.001*
Location					0.013**
Proximal colon	51 (77%)	11 (58%)	27 (84%)	13 (87%)	
Distal colon	6 (9%)	1 (5%)	3 (9%)	2 (13%)	
Rectum	9 (14%)	7 (37%)	2 (7%)	0 (0%)	
Shape					0.048**
0-Ip	0	0	0	0	
0-Is	18 (38%)	9 (47%)	5 (16%)	4 (27%)	
0-II	48 (62%)	10 (53%)	27 (84%)	11 (73%)	

Table 1: Clinicopathological characteristics of all detected polyps in 7 patients with hyperplastic polyposis syndrome.
Proximal colon = cecum, ascending and transverse colon; distal colon = descending colon and sigmoid colon. *Kruskal-Wallis test (only SSAs differed significantly from HPs and adenomas on additional testing with the Mann-Whitney U test). **Pearson Chi-Square test. Note that Bonferroni correction for multiple testing removes statistical significance except where p<0.01 in this table.

Narrow band imaging

The sensitivity, specificity and diagnostic accuracy of the Kudo classification with NBI for differentiation of SSAs from HPs were 28% (95%-CI: 16-33%), 100% (83-100%) and 55% (41-68%). For differentiating adenomas from HPs, the obtained sensitivity, specificity and diagnostic accuracy were 87% (81-98%), 100% (83-100%) and 94% (62-96%) (table 2). During the subsequent NBI image evaluation, the VPI was assessed for 14 HPs, 28 SSAs and 15 adenomas. Images of the other detected polyps could not be included for analysis because VPI assessment was not possible (e.g. blurry images). The sensitivity, specificity and diagnostic accuracy of VPI for differentiating SSAs from HPs, were 36% (21-54%), 86% (6-96%) and 52% (38-67%) respectively. When adenomas were compared with HPs the sensitivity, specificity and diagnostic accuracy were 93% (74-96%), 86% (60-96%) and 90% (70-98%).

NBI	HP (n=19)	SSA (n=32)	Adenoma (n=15)	P-value
Pit pattern				<0.0001*
Kudo I-II	19 (100%)	23 (72%)	2 (13%)	
Kudo III-V	0	9 (28%)	13 (87%)	
NBI	**HP (n=14)**	**SSA (n=28)**	**Adenoma (n=15)**	**P-value**
VPI				<0.0001*
Weak/normal	12 (86%)	18(64%)	1 (7%)	
Strong	2 (14%)	10 (36%)	14 (93%)	

Table 2: Kudo pit pattern classification and vascular pattern intensity (VPI) assessment of all detected polyps with NBI.
*p-value for adenomas compared to HPs and SSAs.

Table 3 lists the sensitivities, specificities and diagnostic accuracies of the different endoscopic modalities for the grouped differentiation of both high-risk SSAs and conventional adenomas from low-risk HPs.

	SSA/adenoma vs. HP		
	AFI	NBI-pit pattern	NBI-VPI
Sensitivity (95%-CI)	30/47: 64% (50-76%)	22/47: 47% (33-61%)	24/43: 56% (41-70%)
Specificity (95%-CI)	10/19: 53% (32-73%)	19/19: 100% (83-100%)	12/14: 86% (60-96%)
Diagnostic accuracy (95%-CI)	40/66: 61% (49-72%)	41/66:62% (50-73%)	36/57: 63% (50-74%)

Table 3: Sensitivity, specificity and diagnostic accuracy of all endoscopic modalities for differentiating sessile serrated adenomas and conventional adenomas (high risk) from hyperplastic polyps (low risk) in patients with hyperplastic polyposis syndrome.

Discussion

In the present study, SSAs were significantly larger and more often proximally located than HPs but the latter finding has its nominal significance removed by Bonferroni correction for multiple testing of data. This is in concordance with recent comparative studies, in which sporadic SSAs were also found to be larger than sporadic HPs and preferentially located in the right colon whereas HPs were more often found distally.[12, 18, 42] Interestingly, in our study the combination of size ≥3mm (median size of SSAs) and proximal location, showed a highly significant difference between SSAs and HPs but with a corresponding diagnostic accuracy of only 76%.

This pilot study demonstrated that the diagnostic accuracy of AFI was unsatisfactory for differentiating SSAs from HPs (accuracy 55%). The presence of epithelial dysplasia and hypervascularisation within adenomatous polyps are considered to be responsible for their different

fluorescence emission spectra when compared to non-adenomatous polyps and hence lead to a different colour on AFI.[24, 43] Although epithelial dysplasia has occasionally been described in advanced SSAs progressing to carcinomas [44], SSAs generally lack these histopathological features as confirmed by the present study (figure 2). Therefore, as expected a-priori, AFI appeared insufficient to distinguish HPs from SSAs. Furthermore, the diagnostic accuracy of AFI for differentiating adenomas from HPs was also insufficient (65%). This is in accordance with a previous study evaluating AFI for differentiation of neoplastic and non-neoplastic lesions in the colon, in which a similar diagnostic accuracy (68%) was obtained.[45]

Kudo pit pattern analysis with NBI demonstrated an equally insufficient diagnostic accuracy for differentiation of SSAs from HPs as AFI (55%). SSAs are microscopically defined as polyps with irregular crypts displaying dilatation, branching and exaggerated serration, especially at the base of the crypts. However, despite these defined crypt characteristics, microscopic differentiation of SSAs from HPs remains difficult.[14, 18, 40, 42] NBI pit pattern analysis, which describes the orifices of crypts, showed similar (Kudo II) phenotypes in HPs and SSAs, confirming that crypt characteristics of these polyps are not only microscopically but also endoscopically difficult to use for differentiation purposes (figure 3). As HPs and SSAs mainly differ in histological anatomy at the base of the crypts, it was therefore expected a-priori that the pit pattern of these polyps, which is assessed at the luminal site of the crypts, was comparable. Differentiation of adenomas from HPs however was very well possible with NBI (accuracy 94%). This corresponds with previous studies in which the diagnostic accuracy of NBI for differentiation of adenomas from non-neoplastic polyps ranged from 77-99%.[19-21, 29, 30, 32, 33, 46]

Previous use of VPI in sporadic polyps suggested that this method has a comparable diagnostic accuracy in differentiating adenomas from non-adenomatous polyps as pit pattern analysis.[20, 29, 46] Based on the principle of increased vascularization, adenomatous polyps would have a stronger VPI and thus have a darker colour when viewed with NBI.[19, 20, 29, 30, 32-34, 46] Owing to the presumed premalignant potential of SSAs, we examined whether a darker colour due to hypervascularization could be observed in these polyps. Overall only 10/28 (36%) of SSAs displayed a darker colour than the surrounding mucosa, resulting consequently in a low diagnostic accuracy and insufficient differential value (figure 4). NBI-VPI analysis did however show a similarly high diagnostic accuracy as NBI-pit pattern for differentiating adenomas from HPs. These high diagnostic accuracies observed with NBI (pit-pattern and VPI) are interesting considering that the median size of all polyps in this study was only 2mm. This corresponds with results from previous studies evaluating NBI for differentiating diminutive (<10mm) polyps.[20, 47-49]

This study was performed in HPS patients in a tertiary referral center by a single endoscopist specialized in HPS. This could explain the diminutive size of polyps detected in these patients as they undergo annual surveillance endoscopies with removal of most polyps, leaving only small ones *in situ*. However, typical HPs seldom exceed 5mm in size and in a recent prospective study of unselected consecutive patients undergoing colonoscopy, 83% of detected SSAs were ≤10mm and 36% were ≤5mm.[12, 50-55] These findings suggest that the predominant polyps in HPS, i.e. HPs and SSAs, are typically small. Nevertheless, HPS is associated with a significantly increased risk of developing CRC.[5] Also in our personal (unpublished) experience of annual HPS surveillance, intra-mucosal carcinomas have been detected in serrated polyps as small as 4mm.

Therefore, unlike in the general population, diminutive polyps should be considered clinically relevant in HPS.

A possible limitation of this study is that only HPS patients were selected for endoscopic differentiation of polyps using ETMI. Thus, our results for differentiating polyps can not by default be extrapolated to polyps in non-HPS patients, as these are not necessarily identical. Furthermore, one may question the generalizability of this pilot study since the sample size of SSAs was relatively small. However, as the accuracies of AFI, NBI-pit pattern and NBI-VPI were all far from acceptable (52-55%) in differentiating SSAs from HPs, and the upper limit of the 95%-confidence interval of these accuracies was 68% at best, a larger sample size is unlikely to alter the conclusion of this pilot study. Moreover, during real-time polyp assessment, AFI was used first after which an assessment with NBI was performed. This may cause AFI-colour to influence the subsequent NBI assessment and thus cause bias. However, when differentiating adenomas from HPs, NBI results were markedly better than prior AFI results, suggesting that bias due to the order of assessment was minimal. Finally, in this study diminutive lesions displaying normal mucosa on histology (n=10) were excluded from analysis. When these lesions were grouped with HPs at additional analysis, diagnostic accuracies for the different endoscopic modalities remained largely unchanged with a maximum difference of 5% (range: 1-5%).

In summary, the diagnostic accuracy of AFI, NBI-pit pattern and NBI-VPI proved unsatisfactory for differentiating SSAs from HPs in patients with HPS. Differentiation of conventional adenomas from HPs was well possible using both NBI-pit pattern and NBI-VPI. Proximal colonic location combined with a size ≥ 3mm proved to be the most valuable for differentiating SSAs from HPs. Nevertheless, the diagnostic accuracy of this combination appears still too low for clinical use (76%).

>> **For figures 1-4; see page 138-139**

Reference List

1 Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. Dis Colon Rectum 2004;47:2101-2104.

2 Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol 2001;25:177-184.

3 Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. Endoscopy 2006;38:266-270.

4 Rashid A, Houlihan PS, Booker S, Petersen GM, Giardiello FM, Hamilton SR. Phenotypic and molecular characteristics of hyperplastic polyposis. Gastroenterology 2000;119:323-332.

5 Carvajal-Carmona L, Howarth K, Lockett M, Polanco-Echeverry G, Volikos E, Gorman M, Barclay E, Martin L, Jones A, Saunders B, Guenther T, Donaldson A, Paterson J, Frayling I, Novelli M, Phillips R, Thomas H, Silver A, Atkin W, Tomlinson I. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. J Pathol 2007;212:378-385.

6 Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, Brown G, Winship I, Barker M, Buchanan D, Cowie S, Nasioulas S, du SD, Young J, Leggett B, Jass J, Macrae F. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30-39.

7 Ferrandez A, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol 2004;99:2012-2018.

8 Lage P, Cravo M, Sousa R, Chaves P, Salazar M, Fonseca R, Claro I, Suspiro A, Rodrigues P, Raposo H, Fidalgo P, Nobre-Leitao C. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. Am J Gastroenterol 2004;99:1779-1784.

9 Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;110:748-755.

10 Kambara T, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, Barker MA, Arnold S, McGivern A, Matsubara N, Tanaka N, Higuchi T, Young J, Jass JR, Leggett BA. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut 2004;53:1137-1144.

11 Minoo P, Baker K, Goswami R, Chong G, Foulkes WD, Ruszkiewicz AR, Barker M, Buchanan D, Young J, Jass JR. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. Gut 2006;55:1467-1474.

12 Spring KJ, Zhao ZZ, Karamatic R, Walsh MD, Whitehall VL, Pike T, Simms LA, Young J, James M, Montgomery GW, Appleyard M, Hewett D, Togashi K, Jass JR, Leggett BA. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology 2006;131:1400-1407.

13 Jass JR, Baker K, Zlobec I, Higuchi T, Barker M, Buchanan D, Young J. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.

14 Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. Am J Clin Pathol 2005;124:380-391.

15 Jaramillo E, Watanabe M, Rubio C, Slezak P. Small colorectal serrated adenomas: endoscopic findings. Endoscopy 1997;29:1-3.
16 Matsumoto T, Mizuno M, Shimizu M, Manabe T, Iida M, Fujishima M. Serrated adenoma of the colorectum: colonoscopic and histologic features. Gastrointest Endosc 1999;49:736-742.
17 Rubio CA, Jaramillo E. Flat serrated adenomas of the colorectal mucosa. Jpn J Cancer Res 1996;87:305-309.
18 Sandmeier D, Seelentag W, Bouzourene H. Serrated polyps of the colorectum: is sessile serrated adenoma distinguishable from hyperplastic polyp in a daily practice? Virchows Arch 2007;450:613-618.
19 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.
20 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.
21 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65:988-995.
22 McCallum AL, Jenkins JT, Gillen D, Molloy RG. Evaluation of autofluorescence colonoscopy for the detection and diagnosis of colonic polyps. Gastrointest Endosc 2008;68:283-290.
23 DaCosta RS, Andersson H, Cirocco M, Marcon NE, Wilson BC. Autofluorescence characterisation of isolated whole crypts and primary cultured human epithelial cells from normal, hyperplastic, and adenomatous colonic mucosa. J Clin Pathol 2005;58:766-774.
24 Haringsma J, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, Watanabe H, Sato N, Marcon N, Wilson BC, Cline RW. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53:642-650.
25 Wang TD, Van DJ, Crawford JM, Preisinger EA, Wang Y, Feld MS. Fluorescence endoscopic imaging of human colonic adenomas. Gastroenterology 1996;111:1182-1191.
26 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.
27 Morita T, Tamura S, Miyazaki J, Higashidani Y, Onishi S. Evaluation of endoscopic and histopathological features of serrated adenoma of the colon. Endoscopy 2001;33:761-765.
28 Oka S, Tanaka S, Hiyama T, Ito M, Kitadai Y, Yoshihara M, Haruma K, Chayama K. Clinicopathologic and endoscopic features of colorectal serrated adenoma: differences between polypoid and superficial types. Gastrointest Endosc 2004;59:213-219.
29 Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy 2007;39:1092-1096.
30 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.
31 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.

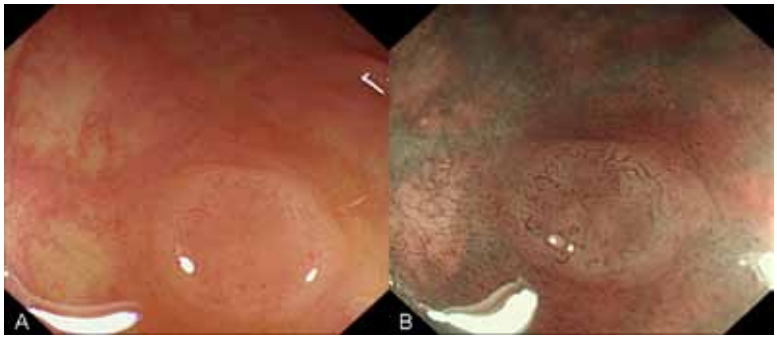
32 Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Evaluation of microvessels in colorectal tumors by narrow band imaging magnification. Gastrointest Endosc 2007;66:945-952.
33 Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, Sharma P. Narrow-band imaging colonoscopy-a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc 2007.
34 Konerding MA, Fait E, Gaumann A. 3D microvascular architecture of pre-cancerous lesions and invasive carcinomas of the colon. Br J Cancer 2001;84:1354-1362.
35 Burt RW, Jass J. Hyperplastic polyposis. In: Hamilton SR and Aaltonen LA, eds. World Health Organisation Classification of Tumours Pathology and Genetics. Berlin: Springer-Verlag, 2000:135-136.
36 Curvers WL, Singh R, Song LM, Wolfsen HC, Ragunath K, Wang K, Wallace MB, Fockens P, Bergman JJ. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 2008;57:167-172.
37 van den Broek FJ, Fockens P, van ES, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. Gut 2008;57:1083-1089.
38 Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570-578.
39 Hamilton SR, Vogelstein B, Kudo S, et al. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of the Digestive System. Lyon, France: IARC Press, 2000:104-119.
40 Farris AB, Misdraji J, Srivastava A, Muzikansky A, Deshpande V, Lauwers GY, Mino-Kenudson M. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol 2008;32:30-35.
41 Simel DL, Rennie D, Bossuyt PM. The STARD statement for reporting diagnostic accuracy studies: application to the history and physical examination. J Gen Intern Med 2008;23:768-774.
42 Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol 2003;27:65-81.
43 Georgakoudi I, Jacobson BC, Van DJ, Backman V, Wallace MB, Muller MG, Zhang Q, Badizadegan K, Sun D, Thomas GA, Perelman LT, Feld MS. Fluorescence, reflectance, and light-scattering spectroscopy for evaluating dysplasia in patients with Barrett's esophagus. Gastroenterology 2001;120:1620-1629.
44 Goldstein NS. Small colonic microsatellite unstable adenocarcinomas and high-grade epithelial dysplasias in sessile serrated adenoma polypectomy specimens: a study of eight cases. Am J Clin Pathol 2006;125:132-145.
45 F.J.C.van den Broek, Curvers WL, Hardwick JC, Fockens P, Dekker E. Interobserver variability and accuracy of colonic pit patterns by narrow band imaging and the additional value of autofluorescence characteristics. 65 ed. Gastrointestinal Endoscopy: 2007:AB349.

46 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.
47 East JE, Suzuki N, Bassett P, Stavrinidis M, Thomas HJ, Guenther T, Tekkis PP, Saunders BP. Narrow band imaging with magnification for the characterization of small and diminutive colonic polyps: pit pattern and vascular pattern intensity. Endoscopy 2008;40:811-817.
48 Rogart JN, Jain D, Siddiqui UD, Oren T, Lim J, Jamidar P, Aslanian H. Narrow-band imaging without high magnification to differentiate polyps during real-time colonoscopy: improvement with experience. Gastrointest Endosc 2008;68:1136-1145.
49 Sano Y, Ikematsu H, Fu KI, Emura F, Katagiri A, Horimatsu T, Kaneko K, Soetikno R, Yoshida S. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. Gastrointest Endosc 2008.
50 DiSario JA, Foutch PG, Mai HD, Pardy K, Manne RK. Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. Am J Gastroenterol 1991;86:941-945.
51 Estrada RG, Spjut HJ. Hyperplastic polyps of the large bowel. Am J Surg Pathol 1980;4:127-133.
52 Hayashi T, Yatani R, Apostol J, Stemmermann GN. Pathogenesis of hyperplastic polyps of the colon: a hypothesis based on ultrastructure and in vitro cell kinetics. Gastroenterology 1974;66:347-356.
53 Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Results of screening colonoscopy among persons 40 to 49 years of age. N Engl J Med 2002;346:1781-1785.
54 Johnson DA, Gurney MS, Volpe RJ, Jones DM, VanNess MM, Chobanian SJ, Avalos JC, Buck JL, Kooyman G, Cattau EL, Jr. A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. Am J Gastroenterol 1990;85:969-974.
55 Lieberman DA, Prindiville S, Weiss DG, Willett W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 2003;290:2959-2967.

Colour images

CHAPTER 2

Figure 2.2



Tubular adenoma during high resolution white light endoscopy (A) and narrow band imaging (B). During narrow band imaging the mucosal and vascular pattern are more clearly delineated demonstrating an increased vascular pattern intensity and Kudo pit pattern IIIS.

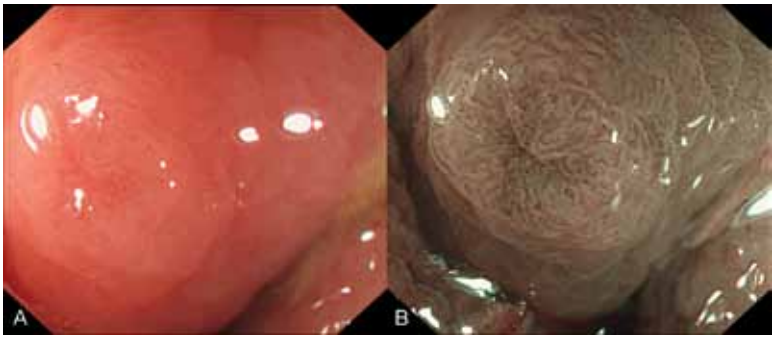
Figure 2.3

Hyperplastic polyp during high resolution white light endoscopy (A), overview narrow band imaging (B) and zoomed narrow band imaging (C). During narrow band imaging a light vascular intensity pattern and Kudo pit pattern type II (slightly darkened dots) is seen.

Figure 2.4

Tubulovillous adenoma during high resolution white light endoscopy (A), overview narrow band imaging (B) and zoomed narrow band imaging (C). With narrow band imaging the lesions becomes dark (vascular intensity pattern increased) and a Kudo pit pattern type IIIL (no or minimally branching elongated pits) is seen.

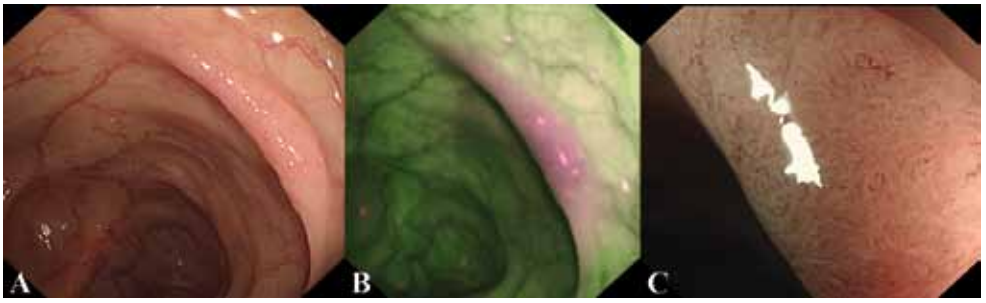
Figure 2.5



Lesion with low grade intraepithelial neoplasia in a patient with longstanding ulcerative colitis during high resolution white light endoscopy (A) and narrow band imaging (B). On image B the lesion is more clearly demarcated with increased contrast of vessels and mucosal morphology.

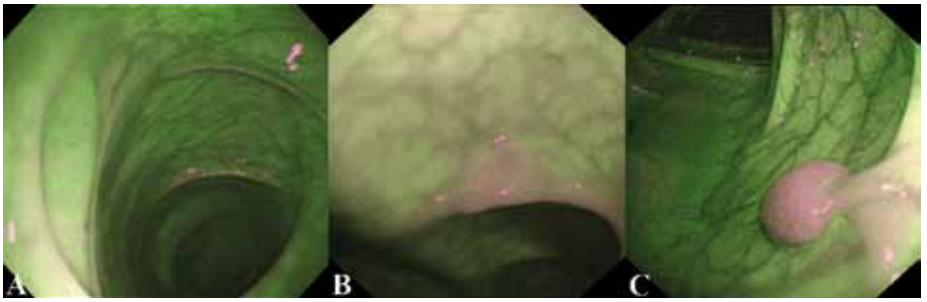
CHAPTER 4

Figure 4.1



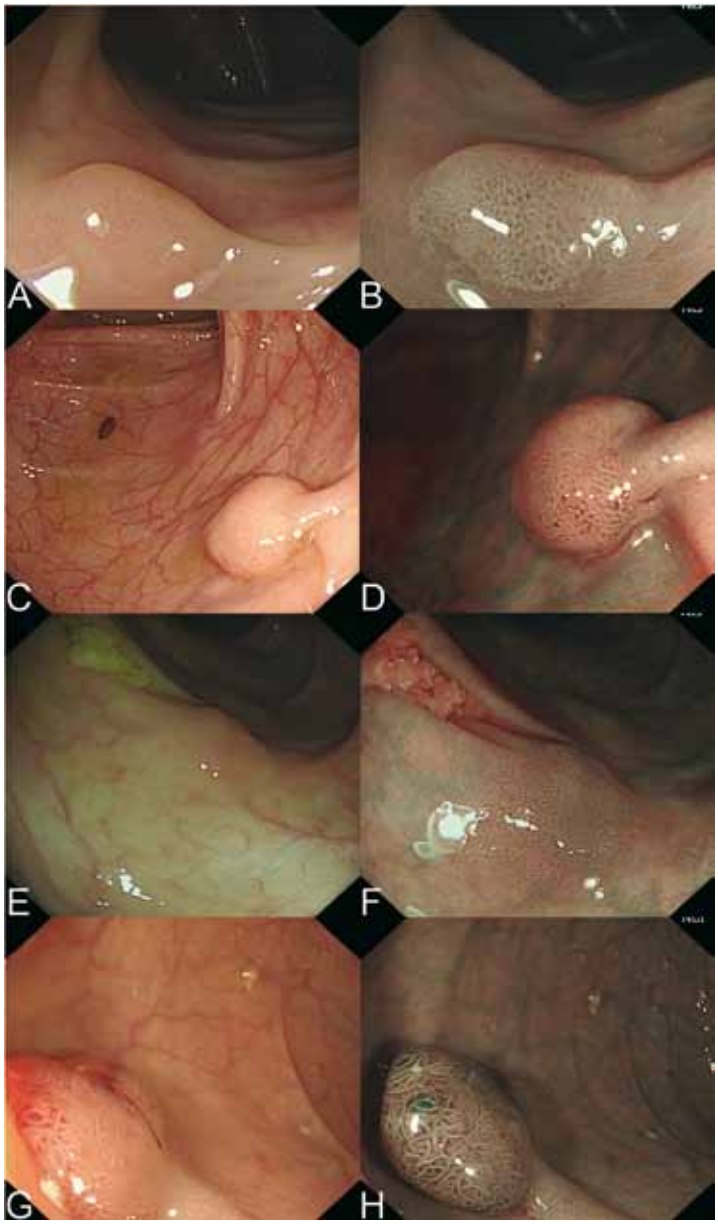
(A) High-resolution white light endoscopy, (B) autofluorescence imaging (AFI) and (C) narrow band imaging (NBI). On AFI, adenomas become purple while normal colonic mucosa appears green; on NBI a Kudo pit pattern type IIIL is seen.

Figure 4.2



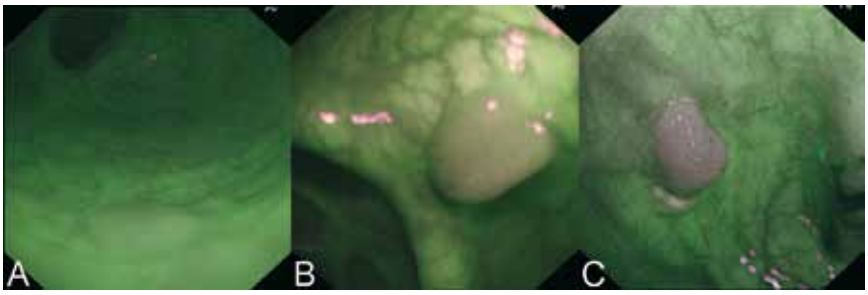
(A) Green color, (B) ambiguous color and (C) purple color during autofluorescence imaging. Green color corresponds to non-neoplastic histology; purple color corresponds to adenomatous tissue; whereas ambiguous colored lesions can be associated with both non-neoplastic and adenomatous polyps.

Figure 5.1



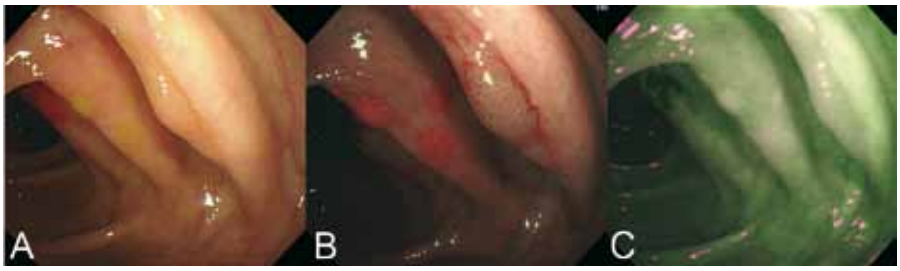
Examples of high resolution white light endoscopy (A, C, G, E) and narrow band imaging (NBI: B, D, F, H), demonstrating Kudo pit pattern type II (A-B), type III-L (C-D), type III-S (E-F), and type IV (G-H). During NBI the mucosal pattern is more clearly visualized

Figure 5.2



Different polyp colors demonstrated on autofluorescence imaging; (A) Green color, (B) Ambiguous color, and (C) Purple color

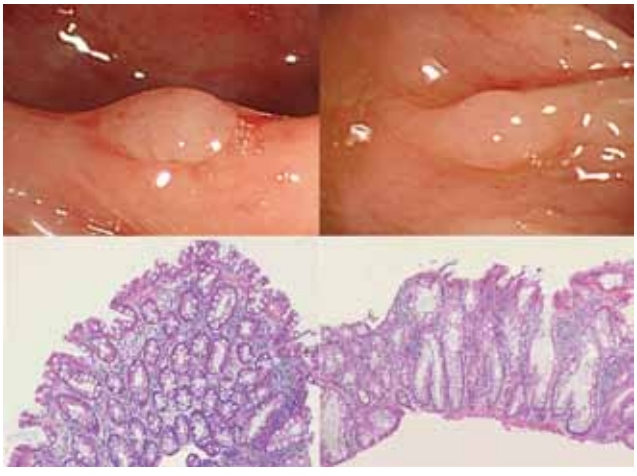
Figure 5.4



Polyp that proved to be a sessile serrated adenoma on histopathology; however, demonstrating a Kudo pit pattern type II on narrow band imaging (dark dots) and green color on autofluorescence imaging.

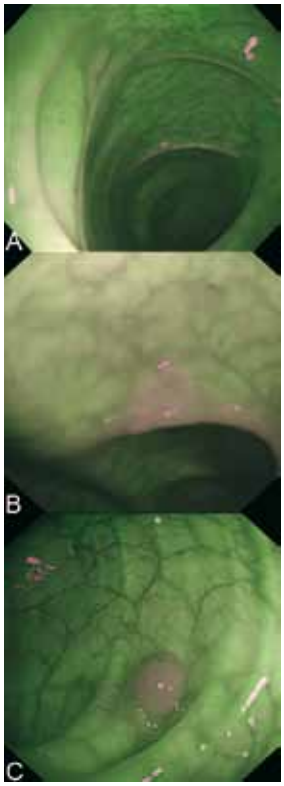
CHAPTER 6

Figure 6.1



Similar endoscopic appearance of a hyperplastic polyp (left) and a sessile serrated adenoma (right) using conventional white light endoscopy with corresponding haemotoxylin and eosin stains below

Figure 6.2



Green (A), ambiguous (B) and purple (C) coloured sessile serrated adenomas using autofluorescence imaging (AFI)

Figure 6.3

Variation of pit-pattern characteristics in sessile serrated adenomas using narrow-band imaging (NBI): Kudo I (A), Kudo II (B), Kudo IIIL (C)

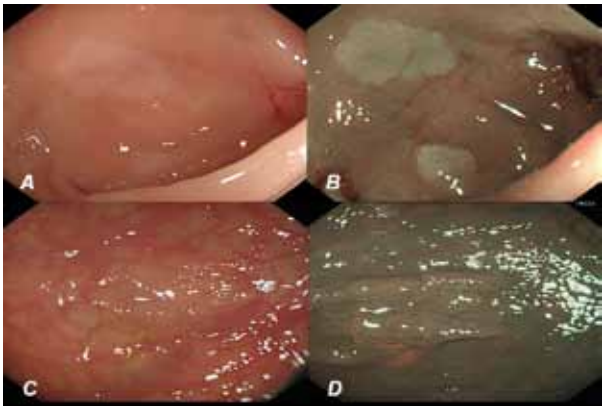
Figure 6.4

Weak (A), normal (B) and strong (C) vascular pattern intensity (VPI) displayed in three different sessile serrated adenomas using narrow-band imaging (NBI)

CHAPTER 7

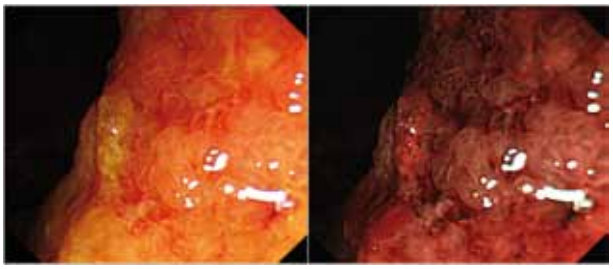
Figure 7.2

Examples of flat sessile serrated adenomas during high-resolution endoscopy (A + C) and corresponding images with narrow-band imaging (B+D)



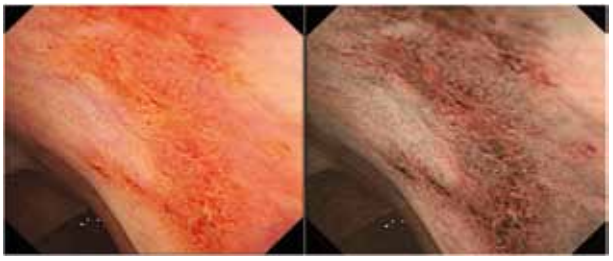
CHAPTER 9

Figure 9.2



Irregular mucosa with high grade neoplasia in a patient with long-standing ulcerative colitis. Left: WLE; right: NBI revealing Kudo type IV pit pattern

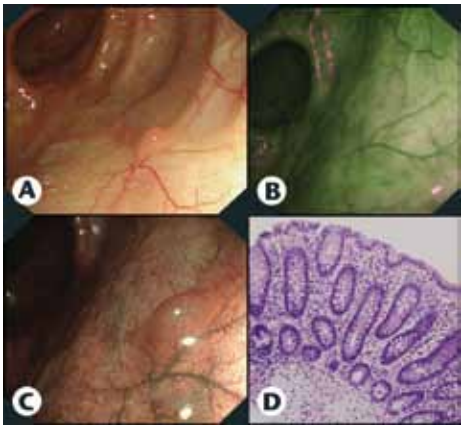
Figure 9.3



Flat lesion with low grade neoplasia in a patient with long-standing ulcerative colitis. Left: WLE; right: NBI with evidence of dark discoloration of the lesion

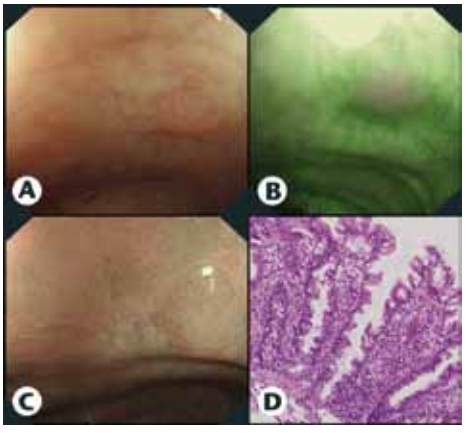
CHAPTER 10

Figure 10.1a



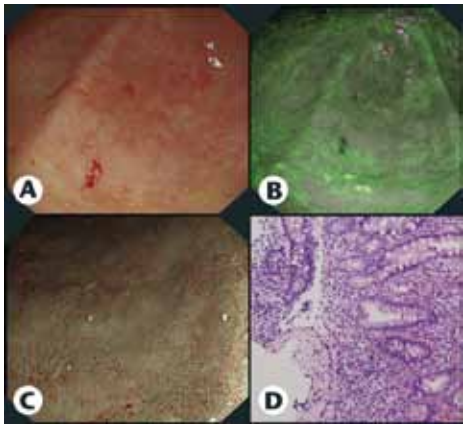
Images during high resolution white light endoscopy (WLE) (A), autofluorescence imaging (AFI) (B) and narrow band imaging (NBI) (C) of mucosa with no significant changes on histology (D). On AFI normal mucosa appears green; NBI shows a normal pit pattern (Kudo type I)

Figure 10.1b



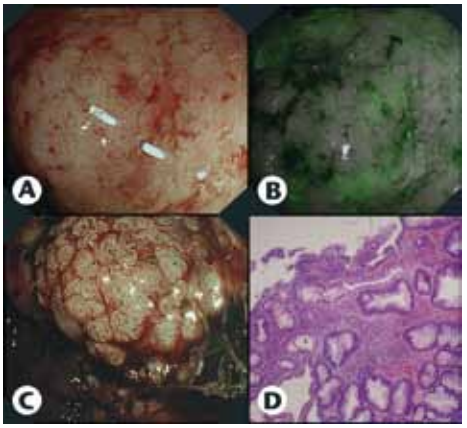
Images during WLE (A), AFI (B) and NBI (C) of a lesion revealing hyperplastic-like mucosal changes on histopathology (D). Tissue autofluorescence is disturbed leading to a purple (false positive) color on AFI; during NBI a normal pit pattern is seen.

Figure 10.1c



Images during WLE (A), AFI (B) and NBI (C) of an area showing inflammation on histopathology (D). On AFI, inflammation becomes purple (false positive), drawing attention of the endoscopist. On NBI, an irregular pit pattern is seen, partly with elongated pits (Kudo type IIIL).

Figure 10.1d



Images during WLE (A), AFI (B) and NBI (C) of a mass revealing low grade intraepithelial neoplasia on histopathology (D). The neoplastic lesion appears deep purple on AFI and reveals Kudo pit pattern type IV on NBI.

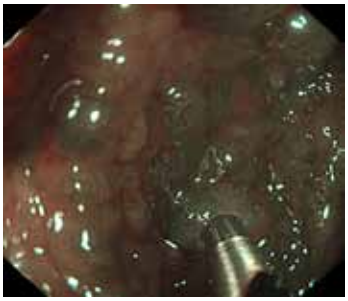
CHAPTER 11

Figure 11.2

Aspect of a rectal colonic segment from which a random biopsy later turned out to contain confirmed low-grade intraepithelial neoplasia. Besides increased vascular pattern intensity and some mucosal scarring, no other abnormalities were seen.

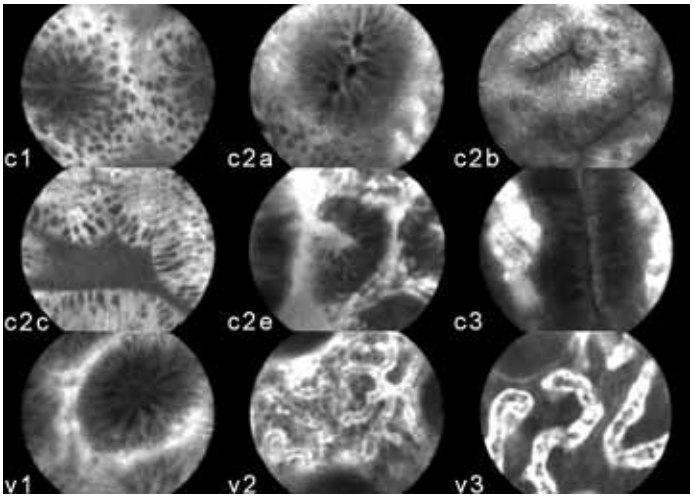
CHAPTER 12

Figure 12.2



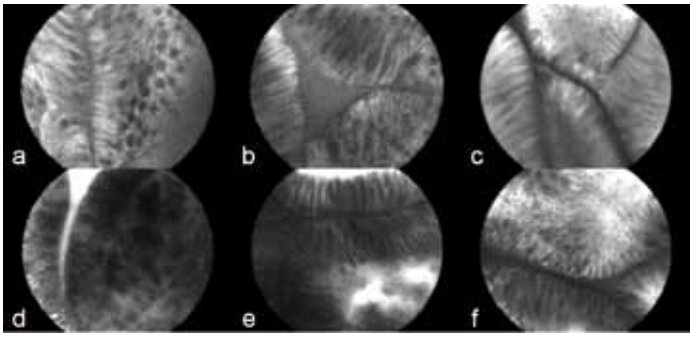
Endoscopic view of a dysplasia associated lesion or mass (histology: low grade intraepithelial neoplasia) demonstrating the pCLE probe, which is put through the working channel of the endoscope, on the lesion.

Figure 12.3



pCLE image examples demonstrating the different crypt-types and vessel-types of the used pCLE classification scheme. Crypt-types; c1: normal mucosal crypt with goblet cells (dark dots); c2a: branching crypt; c2b: star-shaped crypt with slightly reduced number of goblet cells; c2c: star-shaped widened crypt with normal goblet cell distribution; c2e: irregularly sized and disrupted crypts; c3: tubular-shaped crypt with dark striped epithelial layer. Vessel-types; v1: honeycomb-shaped blood vessels surrounding the crypts; v2: increased number of blood vessels with normal diameter and shape; v3: dilated and tortuous blood vessels.

Figure 12.4



pCLE image examples of colonic mucosa that were scored false negative (a-c) or false positive (d-f) by both endoscopists according to the used pCLE classification scheme. Final histopathology demonstrated low grade intraepithelial neoplasia in images a-c, active inflammation in d-e, and normal to mild chronic mucosal changes in f.

CHAPTER 7

Narrow-band imaging improves the detection of polyps in patients with hyperplastic polyposis syndrome: a randomized study comparing narrow-band imaging versus high-resolution endoscopy

Karam S. Boparai
Frank J.C. van den Broek
Susanne van Eeden
Paul Fockens
Evelien Dekker

Submitted

ABSTRACT

Background: Hyperplastic polyposis syndrome (HPS) is associated with colorectal cancer and is characterized by multiple hyperplastic polyps (HPs) and premalignant sessile serrated adenomas (SSAs) and adenomas. Narrow-band imaging (NBI) may improve the detection and differentiation of polyps.
Objective: Compare NBI with high-resolution endoscopy (HRE) for the detection of polyps and evaluate NBI for the differentiation of polyps in HPS.
Design: Randomized cross-over study
Setting: Academic Medical Centre Amsterdam
Methods: Consecutive HPS patients underwent tandem colonoscopy with HRE and NBI, in randomized order. All detected polyps were assessed by NBI and removed immediately after detection.
Outcome measures: Polyp miss-rates of NBI vs. HRE; and diagnostic accuracy of NBI for differentiating HPs from SSAs and adenomas.
Results: In 22 patients with HPS, 209 polyps were detected: 27 normal histology, 116 HPs, 42 SSAs and 24 adenomas. Within patients assigned to HRE first (n=11) a total of 78 polyps was detected; subsequent NBI added 44 polyps. Among patients examined with NBI first, 78 polyps were detected and subsequent HRE added 9. Polyp miss-rates of HRE and NBI were 36% and 10% (OR 0.21; 0.09-0.45). Flat polyp shape was independently associated with increased miss-rate. For differentiating HPs from SSAs and adenomas, NBI had a sensitivity, specificity and accuracy of 46%, 75% and 65% respectively.
Limitations: Small sample size
Conclusion: NBI significantly reduces polyp miss-rates in HPS patients but is insufficiently accurate for differentiating HPs from SSAs and adenomas. We recommend using NBI for colonoscopic surveillance of HPS patients with removal of all detected polyps.

Introduction

Hyperplastic polyposis syndrome (HPS) is characterized by the presence of multiple hyperplastic polyps (HPs) spread throughout the colon and is associated with an increased colorectal cancer (CRC) risk.[1-4] Besides HPs, sessile serrated adenomas (SSAs) and conventional adenomas are common findings in this condition as well. The presence of SSAs is even considered typical for HPS.[5-7]

Whereas sporadic HPs are traditionally considered to be low-risk lesions, a novel *serrated neoplasia pathway* has been suggested which describes the progression of serrated polyps (i.e. HPs, SSAs and traditional serrated adenomas) to CRC through accumulation of genetic mutations.[8-15] Molecular research in serrated polyps strongly suggests that SSAs in particular are lesions which may lead to CRC with *BRAF* and CPG-island methylator phenotype (CIMP). *BRAF* mutations (which are linked with inhibition of apoptosis) and CIMP (which causes gene silencing) are considered to be the key mechanisms in this pathway evolving in SSAs and leading to CRC.[16-20] Besides the fact that HPS patients have far more serrated polyps than the general population, these patients also have an increased risk of CRC based on molecular studies showing increased BRAF mutations and CIMP in their serrated polyps as compared to sporadic serrated polyps.[16, 21, 22] Indeed, numerous HPS patients with CRC arising in a serrated polyp have been reported.[23] Therefore SSAs seem to represent direct premalignant lesions resulting in the recommendation that these should be managed as conventional adenomas.[24] Detection and removal of SSAs in particular thus seems necessary to prevent CRC in patients with HPS.

In HPS patients however, SSAs and HPs are generally small and flat.[25-27] These features are associated with polyp miss-rates of up to 26% using standard colonoscopy.[28-30] Improved detection of these polyps by using advanced endoscopic techniques seems therefore desirable. In addition, as HPs and SSAs appear endoscopically very similar, accurate differentiation may aid the endoscopist in only removing SSAs and leaving HPs, which display relatively lower levels of BRAF mutations and CIMP, *in situ*.[31] Since HPS patients have many polyps, this may considerably prevent complications from unnecessary endoscopic resections.[5]

Chromoendoscopy has previously been shown to improve the detection of small and flat lesions, specifically HPs, in patients undergoing surveillance colonoscopy.[29, 30, 32-34] Whereas chromoendoscopy may also aid in the differentiation of HPs and adenomas, it is unknown whether this is possible for HPs and SSAs as well.[35-37] However, chromoendoscopy is a labour-intensive and time-consuming technique. Narrow-band imaging (NBI) is an easier push-on-a-button technique that enhances mucosal and vascular detail without the use of dyes, and has proven to be superior to high-resolution endoscopy (HRE) for the detection of sporadic HPs.[38, 39] With respect to the differentiation of HPs and adenomas, NBI has shown comparable results as chromoendoscopy but data are lacking regarding the differentiation of SSAs from HPs.[40]

The aims of this randomized trial were to compare NBI and HRE for the detection of polyps, and to evaluate the value of narrow band imaging for the differentiation of HPs, SSAs and adenomas in patients with HPS.

Patients and methods

Patients

Between October 2007 and October 2008, consecutive HPS patients were recruited for this study at the Academic Medical Center in Amsterdam. A diagnosis of HPS was based on the following criteria: 1) ≥20 HPs found during previous colonoscopies; 2) ≥5 HPs proximal to the sigmoid colon of which 2 were larger than 1cm; or 3) any HP occurring proximal to sigmoid colon in an individual who has a first-degree relative with HPS.[1, 4] Owing to the common presence of both HPs and SSAs in HPS and the difficult histological differentiation between these two groups, both HPs and SSAs were used to fulfil the criteria. [24, 41-43] Patients were excluded in case of inflammatory bowel disease, severe coagulopathy, <18 years of age, insufficient bowel preparation (<90% of colonic mucosa visible) and a known germline *APC* mutation or bi-allelic *MYH* mutation. From included patients informed consent was obtained and the study was approved by our institutional review board.

Endoscopic equipment

For this study the Evis Lucera system (CV-260, Olympus Inc., Tokyo, Japan) and a high-resolution video colonoscope (CF-H260Z) were used integrating HRE, NBI and optical magnification (100x). The endoscopist could easily switch between the imaging modes by pressing a button on the shaft of the endoscope. As only high-resolution monitors were used, the high-definition signal of the system was not utilized.

Study design and randomization

We used a crossover study design with randomized order. Patients underwent tandem colonoscopy with HRE and NBI by the same endoscopist and the order of these techniques was randomized (figure 1). Randomization was done by opening sealed opaque envelopes (containing notes with 'HRE' or 'NBI' in a 1:1 ratio) once the cecum was reached

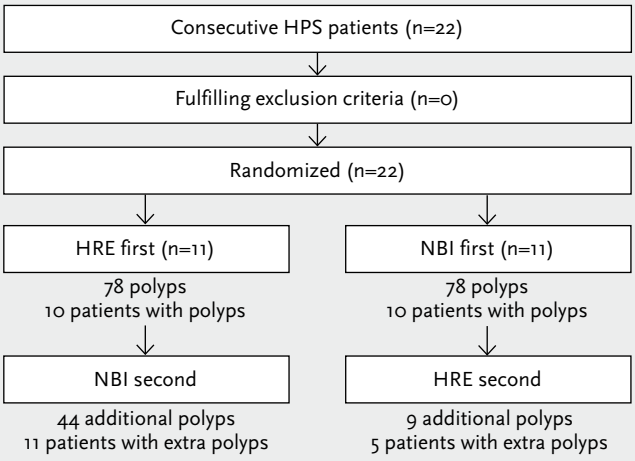


Figure 1: Flow diagram of the randomized cross-over trial including patients that were randomized to HRE or NBI as first colonoscopic procedure

Colonoscopic procedure

Patients were prepared with 4 liters polyethylene glycol solution (Kleanprep, Norgine Inc., Amsterdam, Netherlands) and underwent colonoscopy under conscious sedation with midazolam and fentanyl. All procedures were performed by the same endoscopist (ED) who was highly trained in NBI.

The colonoscope was advanced to the cecum in the HRE mode of the endoscope. No attention was paid to polyps during the insertion phase. Cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve. After extensive rinsing and suctioning of remaining stools, the level of bowel preparation was determined as excellent (100% of colonic mucosa visible), good (90-99%) or poor (<90%). Patients with poor bowel preparation were excluded from this study.

Hereafter, each colonic segment (ascending, transverse, descending and recto sigmoid colon) was examined twice, once with HRE and once with NBI. The order of the two techniques was determined by randomization. During withdrawal with the first technique, each segment of the colon was meticulously inspected for the presence of polyps. Of all detected polyps the size (estimated by an opened biopsy forceps), location (colonic segment and distance from the anus) and Paris classification were noted.[44] All lesions were additionally assessed with NBI (if detected with HRE it was allowed to switch to NBI for this purpose) for Kudo pit pattern analysis.[45] Hereafter, each polyp was immediately removed by endoscopic mucosal resection or biopsy removal (if <5mm) and sent for pathology in separate jars.

After first inspection and polyp clearance of each colonic segment, the colonoscope was advanced again to the beginning of the segment. The other imaging technique was then used for the second inspection of the same segment. In case of indistinctive hepatic or splenic flexures, a random biopsy was taken for reference of each colonic segment. If additional polyps were detected during the second examination, their size, location, Paris classification and Kudo pit pattern were noted before removal.

Withdrawal times during the HRE and NBI examinations were measured by using a stopwatch. Time for performing polypectomy was not included in these withdrawal times. A maximum colonoscopy time of 2 hours was set for the entire endoscopic procedure; otherwise the procedure was too long and inconvenient for the patient.

Histopathology

Resection specimens were evaluated by an expert GI pathologist (SvE) who was blinded for endoscopic technique and Kudo classification. Lesions were classified as normal mucosa, HP, SSA, traditional serrated adenoma, mixed polyp or conventional adenoma based on the morphological features on H&E staining.[19, 24, 46]

Outcome measures

Primary outcome measure was the polyp miss-rate of each technique, defined as the number of polyps detected during the second inspection divided by the total number of polyps detected during both examinations. Secondary outcome measures were the sensitivity, specificity and overall accuracy of the Kudo classification for differentiating HPs, SSAs and conventional adenomas by using NBI.

Statistical analysis and sample size

Polyp miss-rates of NBI and HRE were compared by Chi-square testing. Logistic regression analysis was used to evaluate associations between polyp characteristics and polyp miss-rate (i.e. dependent variable), using odds ratios (OR) plus 95%-conficence interval to represent the strength of the association. Cross-tabs were used to calculate the sensitivity, specificity and accuracy of the Kudo classification with NBI. Kudo pit patterns I-II were considered non-neoplastic, whereas Kudo pit patterns III-V were considered neoplastic. Histopathology of each polyp served as reference standard. The STARD statements were used for reporting diagnostic test accuracy.[47]

Previous research comparing NBI and HRE for adenoma detection showed a 3.3-fold increase in detection of HPs with NBI.[48] As the general polyp miss-rate is 22%, we hypothesized a 3.3-fold decrease in miss-rate with NBI resulting in a polyp miss-rate of 6.7%.[28] To detect this difference in polyp miss-rate with a power of 80% and significance level of 5%, a total of 188 polyps were required. In a previous analysis of HPS patients undergoing surveillance endoscopies at our department we found a mean number of 9 polyps per HPS patient, resulting in (188/9=) 22 patients for inclusion in this trial.[31]

Results

A total of 22 patients with HPS were randomized to tandem colonoscopy with either HRE first (n=11) or NBI first (n=11). Patient characteristics are demonstrated in table 1 and were comparable between the randomization groups.

Demographics	Randomization		
	HRE (n=11)	NBI (n=11)	P
Mean age, yrs (range)	58 (33-73)	62 (43-76)	.331
Male	8 (73%)	4 (36%)	.198
Personal history of high-grade neoplasia or CRC	6 (55%)	4 (36%)	.670
Partial colectomy	5 (45%)	3 (27%)	.659
Number of previous polyps (mean nr per patient)			
Hyperplastic polyps	18.1	11.3	.121
Sessile serrated adenomas	4.4	7.6	.183
Adenomas	2.9	4.2	.508
Bowel preparation			
Excellent	10 (91%)	6 (55%)	.149
Good	1 (9%)	5 (45%)	
Examination time (minutes), mean (±SD)			
First inspection	15.0 (3.7)	13.9 (3.8)	.485
Second inspection	11.2 (3.6)	8.9 (2.3)	.115

Table 1: demographics of patients randomized to HRE and NBI as first inspection technique.

Polyp miss-rates

High-resolution endoscopy: During HRE as first examination technique, a total number of 78 polyps (mean size 6.0mm; range 2-15) were detected. Histology demonstrated normal tissue in 8 polyps, HP in 56, SSA in 5 and traditional adenoma in 7. Subsequent inspection with NBI added 44 polyps (mean 6.1mm; 2-20) of which 4 with normal, 29 HP, 8 SSA and 3 with adenomatous histology. The corresponding overall polyp miss-rate of HRE hence was 36% (95%-CI: 28-45).

Narrow-band imaging: During NBI as first examination technique, a total number of 78 polyps (mean size 5.4mm; range 2-20) were found (13 normal, 26 HP, 25 SSA, 14 adenomas). Subsequent inspection with HRE added 9 polyps (mean 4.7mm; 2-10) of which 2 had normal histology, 3 were HP and 4 SSA. The corresponding overall polyp miss-rate of NBI was 10% (95%-CI: 5.5-19).

	HRE	NBI	P
Overall polyps			
First inspection, n	78	78	.741
Second inspection, n	44	9	-
Miss-rate, % (95%-CI)	36 (28-45)	10 (5.5-19)	<.001
Hyperplastic polyps			
First inspection, n	58	26	.181
Second inspection, n	29	3	-
Miss-rate, % (95%-CI)	33 (24-44)	10 (3.6-26)	.017
Sessile serrated adenomas			
First inspection, n	5	25	.081
Second inspection, n	8	4	-
Miss-rate, % (95%-CI)	62 (36-82)	14 (5.5-31)	.003
Adenomas			
First inspection, n	7	14	.271
Second inspection, n	3	0	-
Miss-rate, % (95%-CI)	30 (11-60)	0 (0-22)	.059

Table 2: polyp detection during the first and second inspection and polyp miss-rates among patients randomized to either HRE or NBI as first inspection technique, subdivided for histopathological outcome of polyps.

The overall polyp miss-rate for NBI was significantly lower than for HRE (OR 0.21; 95%-CI: 0.094-0.45; p<0.001). Table 2 demonstrates the polyp miss-rates for HPs, SSAs and adenomas separately. Table 3 shows the polyp miss-rates for flat (Paris 0-IIa, 0-IIb, 0-IIa+c) and protruded (Paris 0-Is, 0-Ip) lesions and for proximal and distal colonic locations of polyps.

On multivariable logistic regression analysis, the use of NBI was independently associated with a reduction in polyp miss-rate (OR 0.17; 95%-CI: 0.08-0.39), whereas flat macroscopic appearance was associated with an increased miss-rate (OR 3.73; 1.72-8.05). Polyp size, colonic location and histology were not associated with the miss-rate.

	HRE	NBI	P
Flat polyps			
First inspection, n	37	50	.665
Second inspection, n	35	7	-
Miss-rate, % (95%-CI)	49 (37-60)	12 (6.1-23)	<.001
Protruded polyps			
First inspection, n	41	28	.595
Second inspection, n	9	2	-
Miss-rate, % (95%-CI)	18 (9.8-31)	6.7 (1.9-21)	.195
Proximal location			
First inspection, n	31	45	.349
Second inspection, n	19	5	-
Miss-rate, % (95%-CI)	38 (26-52)	10 (4.4-21)	.001
Distal location			
First inspection, n	47	33	.302
Second inspection, n	25	4	-
Miss-rate, % (95%-CI)	35 (25-46)	11 (4.3-25)	.011

Table 3: polyp detection during the first and second inspection and polyp miss-rates among patients randomized to either HRE or NBI as first inspection technique, subdivided for macroscopic appearance and colonic location of polyps.

Differentiation of polyps

A total number of 209 polyps were detected during either HRE or NBI, irrespective of order of detection technique. In 12 polyps (5.7%) no Kudo pit-pattern could be recognized during colonoscopy (i.e. inconclusive test results). All other polyps were scored for pit-pattern during ongoing endoscopy. Histopathology showed 27 polyps with normal histology, 116 HPs, 42 SSAs and 24 adenomas (see Table 4).

For differentiating HPs from SSAs, the Kudo classification using NBI had a sensitivity of 27% (95%-CI: 15-43), specificity of 75% (67-83) and overall accuracy of 63% (55-71). For differentiating HPs from adenomas these figures were 75% (55-88), 75% (67-83) and 75% (67-82). Finally, for differentiating HPs from SSAs and conventional adenomas thes these figures were 46% (34-58), 75% (67-83) and 65% (58-72).

	Normal	HP	SSA	Adenoma
NBI - Kudo classification				
I	5 (19)	12 (10)	0 (0)	1 (4)
II	14 (52)	71 (61)	27 (64)	5 (21)
III-L	4 (15)	17 (15)	7 (17)	13 (54)
III-S	3 (11)	9 (8)	3 (7)	5 (21)
IV	0 (0)	1 (1)	0 (0)	0 (0)
unrecognizable	1 (4)	6 (5)	5 (12)	0 (0)

Table 4: correspondence between the endoscopically assessed Kudo classification (NBI) and the reference standard (histopathology). HP hyperplastic polyp; SSA sessile serrated adenoma; NBI narrow band imaging.

Discussion

Previous large prospective randomized trials comparing NBI with HRE for adenoma detection showed that NBI was associated with an increased sporadic HP detection rate, although adenoma detection rates were equal.[48-50] This study demonstrated that NBI had a significantly lower polyp miss-rate than HRE (10% versus 36%; OR 0.21; p<0.001) in HPS patients harboring multiple serrated polyps. As in previous studies, NBI did not prove of additional value for the detection of adenomas. These findings could be viewed as disappointing. However, whereas in the general population serrated polyps are considered to be harmless lesions, especially when they are small, molecular research in serrated polyps in HPS suggests these are high-risk lesions leading to CRC.[11, 16, 21, 22] Furthermore, a previous large cohort study showed that 5/77 (7%) HPS patients developed CRC despite endoscopic surveillance of which 4/5 were detected within diminutive serrated polyps (range: 4-16mm).[23] In this light, we believe that the increased detection of serrated polyps with NBI in HPS is of clinical relevance.

Our study additionally showed that NBI is of particular value for the detection of serrated polyps which are flat in shape (HRE miss-rate 49% *vs.* NBI miss-rate 12%; p<0.001). Previous studies demonstrated that NBI did not detect more flat adenomas than HRE.[48-50] A possible reason for this incongruence could be the fact that flat adenomas are generally red in colour and therefore easier visible than flat HPs and SSAs, which have the same colour as their surroundings and are often covered by a layer of mucus. During NBI, serrated polyps appear whiter in colour, thereby increasing the contrast between the polyps and surrounding colonic tissue (see figure). These features may particularly explain the higher miss-rate of serrated polyps by HRE. Therefore NBI appears to be the technique of choice for colonoscopic surveillance of HPS patients.

Several remarks on this study must be mentioned before definitely making any recommendation based on our results. Adler *et al* previously postulated that the level of experience with NBI may induce a learning effect for improved recognition of polyps with HRE as well, causing the difference in polyp detection between NBI and HRE to be larger at the beginning of the learning curve.[51] However, in our study the endoscopist had already performed more than 500 colonoscopies with NBI, making a learning effect with regard to HRE unlikely. Second, there

was an unequal total number of detected polyps within the randomization groups (a total of 122 polyps for HRE randomization *vs.* 87 for NBI). This difference was difficult to overcome considering the fact that both a patient with >5 proximal HPs as well as a patient with more than 30 HPs satisfied the criteria for HPS. The large variance of the number of polyps within each patient will always lead to unequal numbers of polyps after randomization of only 22 patients. Therefore we chose a crossover study design enabling comparison of proportions (i.e. polyp miss-rates) between the randomization groups. We assumed that the order of the two techniques (either NBI or HRE first) did not influence the total number of polyps detected within each group. Since we compared the polyp miss-rates of HRE versus NBI as a proportion of the total number of polyps, the analysis therefore was valid and unbiased, despite unequal distribution of the number of polyps.

Another objective of advanced imaging in HPS patients is the real-time differentiation between HPs, SSAs and adenomas. Patients with HPS generally have a multitude of polyps (predominantly HPs; 55%), as a result of which it is desirable to differentiate HPs from SSAs and adenomas in order to achieve targeted removal of the latter high-risk polyps. Accurate real-time differentiation may prevent multiple endoscopic resections of HPs, whereas direct premalignant lesions such as SSAs and adenomas may be resected immediately. HPs that progress to SSA or adenoma could then be dealt with during follow-up surveillance colonoscopies. However, this study demonstrated that NBI was unable to reliably differentiate between HPs, SSAs and adenomas. The diagnostic accuracy achieved for differentiating SSAs and adenomas from HPs was only 65% (58-72) which is far from clinically practical. Previous research by our group already demonstrated a disappointing diagnostic accuracy of NBI for differentiation of polyps in HPS patients.[31] That study however evaluated the combined use of HRE, NBI and autofluorescence imaging, i.e. trimodal imaging, in only a small number of patients. The results of the present study support our previous results that NBI is unreliable to differentiate between different types of histology in HPS patients. As it is already difficult to discriminate between HPs and SSAs during conventional histopathology, it was expected that NBI would have a disappointing accuracy for this purpose. To ultimately achieve this goal, other imaging modalities such as confocal laser endomicroscopy or targeted molecular techniques may be necessary.

With regard to the management of HPS patients, considering that in these patients CRCs as small as 4mm have been described, removal of all polyps ≥3mm seems indicated in any case, but needs to be prospectively assessed. Concerning polyps <3mm, a previous study analyzing the differentiation of polyps in HPS showed that 20/35 polyps <3mm were high-risk sessile serrated adenomas (9/35) and conventional adenomas (11/35).[31] Differentiating these diminutive premalignant polyps from HPs with NBI by means of polyp colour differentiation (lighter than the surrounding mucosa is unsuspicious; darker or same than the surrounding mucosa is suspicious) rendered a sensitivity of 95% for sessile serrated adenomas and conventional adenomas (diagnostic accuracy: 78%). For this reason removal of polyps darker than or same as the surrounding mucosa may be sufficient for this size group.

In summary, this study demonstrated that NBI is associated with a reduced polyp miss-rate when compared to HRE in patients with HPS. Furthermore, the use of NBI was insufficiently accurate to differentiate between harmless HPs and premalignant SSAs and adenomas. We therefore advise that all polyps in patients with HPS need to be resected during colonoscopic surveillance, which should be done using NBI.

>> **For figure 2; see page 139**

Reference List

1 Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. Dis Colon Rectum 2004;47:2101-2104.

2 Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol 2001;25:177-184.

3 Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. Endoscopy 2006;38:266-270.

4 Rashid A, Houlihan PS, Booker S, Petersen GM, Giardiello FM, Hamilton SR. Phenotypic and molecular characteristics of hyperplastic polyposis. Gastroenterology 2000;119:323-332.

5 Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, Brown G, Winship I, Barker M, Buchanan D, Cowie S, Nasioulas S, du SD, Young J, Leggett B, Jass J, Macrae F. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30-39.

6 Ferrandez A, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol 2004;99:2012-2018.

7 Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;110:748-755.

8 Hawkins NJ, Ward RL. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. J Natl Cancer Inst 2001;93:1307-1313.

9 Iino H, Jass JR, Simms LA, Young J, Leggett B, Ajioka Y, Watanabe H. DNA microsatellite instability in hyperplastic polyps, serrated adenomas, and mixed polyps: a mild mutator pathway for colorectal cancer? J Clin Pathol 1999;52:5-9.

10 Jass JR, Biden KG, Cummings MC, Simms LA, Walsh M, Schoch E, Meltzer SJ, Wright C, Searle J, Young J, Leggett BA. Characterisation of a subtype of colorectal cancer combining features of the suppressor and mild mutator pathways. J Clin Pathol 1999;52:455-460.

11 Jass JR, Iino H, Ruszkiewicz A, Painter D, Solomon MJ, Koorey DJ, Cohn D, Furlong KL, Walsh MD, Palazzo J, Edmonston TB, Fishel R, Young J, Leggett BA. Neoplastic progression occurs through mutator pathways in hyperplastic polyposis of the colorectum. Gut 2000;47:43-49.

12 Jass JR, Young J, Leggett BA. Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum. Histopathology 2000;37:295-301.

13 Jass JR. Serrated route to colorectal cancer: back street or super highway? J Pathol 2001;193:283-285.

14 Makinen MJ, George SM, Jernvall P, Makela J, Vihko P, Karttunen TJ. Colorectal carcinoma associated with serrated adenoma--prevalence, histological features, and prognosis. J Pathol 2001;193:286-294.

15 Yao T, Nishiyama K, Oya M, Kouzuki T, Kajiwara M, Tsuneyoshi M. Multiple 'serrated adenocarcinomas' of the colon with a cell lineage common to metaplastic polyp and serrated adenoma. Case report of a new subtype of colonic adenocarcinoma with gastric differentiation. J Pathol 2000;190:444-449.

16 Kambara T, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, Barker MA, Arnold S, McGivern A, Matsubara N, Tanaka N, Higuchi T, Young J, Jass JR, Leggett BA. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut 2004;53:1137-1144.
17 Minoo P, Baker K, Goswami R, Chong G, Foulkes WD, Ruszkiewicz AR, Barker M, Buchanan D, Young J, Jass JR. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. Gut 2006;55:1467-1474.
18 Spring KJ, Zhao ZZ, Karamatic R, Walsh MD, Whitehall VL, Pike T, Simms LA, Young J, James M, Montgomery GW, Appleyard M, Hewett D, Togashi K, Jass JR, Leggett BA. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology 2006;131:1400-1407.
19 Jass JR, Baker K, Zlobec I, Higuchi T, Barker M, Buchanan D, Young J. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a 'fusion' pathway to colorectal cancer. Histopathology 2006;49:121-131.
20 Beach R, Chan AO, Wu TT, White JA, Morris JS, Lunagomez S, Broaddus RR, Issa JP, Hamilton SR, Rashid A. BRAF mutations in aberrant crypt foci and hyperplastic polyposis. Am J Pathol 2005;166:1069-1075.
21 Beach R, Chan AO, Wu TT, White JA, Morris JS, Lunagomez S, Broaddus RR, Issa JP, Hamilton SR, Rashid A. BRAF mutations in aberrant crypt foci and hyperplastic polyposis. Am J Pathol 2005;166:1069-1075.
22 Chan AO, Issa JP, Morris JS, Hamilton SR, Rashid A. Concordant CpG island methylation in hyperplastic polyposis. Am J Pathol 2002;160:529-536.
23 Boparai KS, Mathus-Vliegen EM, Koornstra JJ, Nagengast FM, van LM, van Noesel CJ, Houben M, Cats A, van Hest LP, Fockens P, Dekker E. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut 2009.
24 Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. Am J Clin Pathol 2005;124:380-391.
25 Jaramillo E, Watanabe M, Rubio C, Slezak P. Small colorectal serrated adenomas: endoscopic findings. Endoscopy 1997;29:1-3.
26 Matsumoto T, Mizuno M, Shimizu M, Manabe T, Iida M, Fujishima M. Serrated adenoma of the colorectum: colonoscopic and histologic features. Gastrointest Endosc 1999;49:736-742.
27 Rubio CA, Jaramillo E. Flat serrated adenomas of the colorectal mucosa. Jpn J Cancer Res 1996;87:305-309.
28 van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-350.
29 Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, Cardwell CR, Williams CB. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56:333-338.
30 Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376-380.

31 Boparai KS, van den Broek FJ, van ES, Fockens P, Dekker E. Hyperplastic polyposis syndrome: a pilot study for the differentiation of polyps using high resolution endoscopy, autofluorescence imaging and narrow-band imaging. Gastrointest Endosc 2009.
32 Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy 2006;38:444-448.
33 Le RM, Coron E, Parlier D, Nguyen JM, Canard JM, Alamdari A, Sautereau D, Chaussade S, Galmiche JP. High resolution colonoscopy with chromoscopy versus standard colonoscopy for the detection of colonic neoplasia: a randomized study. Clin Gastroenterol Hepatol 2006;4:349-354.
34 Park SY, Lee SK, Kim BC, Han J, Kim JH, Cheon JH, Kim TI, Kim WH. Efficacy of chromoendoscopy with indigocarmine for the detection of ascending colon and cecum lesions. Scand J Gastroenterol 2008;43:878-885.
35 Chiu HM, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373-379.
36 Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101:2711-2716.
37 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.
38 Adler A, Pohl H, Papanikolaou IS, bou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rosch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? Gut 2008;57:59-64.
39 Aschenbeck J, Adler A, Yenerim T, Mayr M, Aminalai A, Drossel R, Schroder A, Scheel M, Wiedenmann B, Rosch T. Narrow-Band Versus White-Light HDTV Endoscopic Imaging for Screening Colonoscopy: A Prospective Randomized Trial. Gastroenterology 2008.
40 van den Broek FJ, Reitsma JB, Curvers WL, Fockens P, Dekker E. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon (with videos). Gastrointest Endosc 2009;69:124-135.
41 Farris AB, Misdraji J, Srivastava A, Muzikansky A, Deshpande V, Lauwers GY, Mino-Kenudson M. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol 2008;32:30-35.
42 Sandmeier D, Seelentag W, Bouzourene H. Serrated polyps of the colorectum: is sessile serrated adenoma distinguishable from hyperplastic polyp in a daily practice? Virchows Arch 2007;450:613-618.
43 Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol 2003;27:65-81.
44 Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570-578.
45 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.

46 Hamilton SR, Vogelstein B, Kudo S, et al. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of the Digestive System. Lyon, France: IARC Press, 2000:104-119.

47 Simel DL, Rennie D, Bossuyt PM. The STARD statement for reporting diagnostic accuracy studies: application to the history and physical examination. J Gen Intern Med 2008;23:768-774.

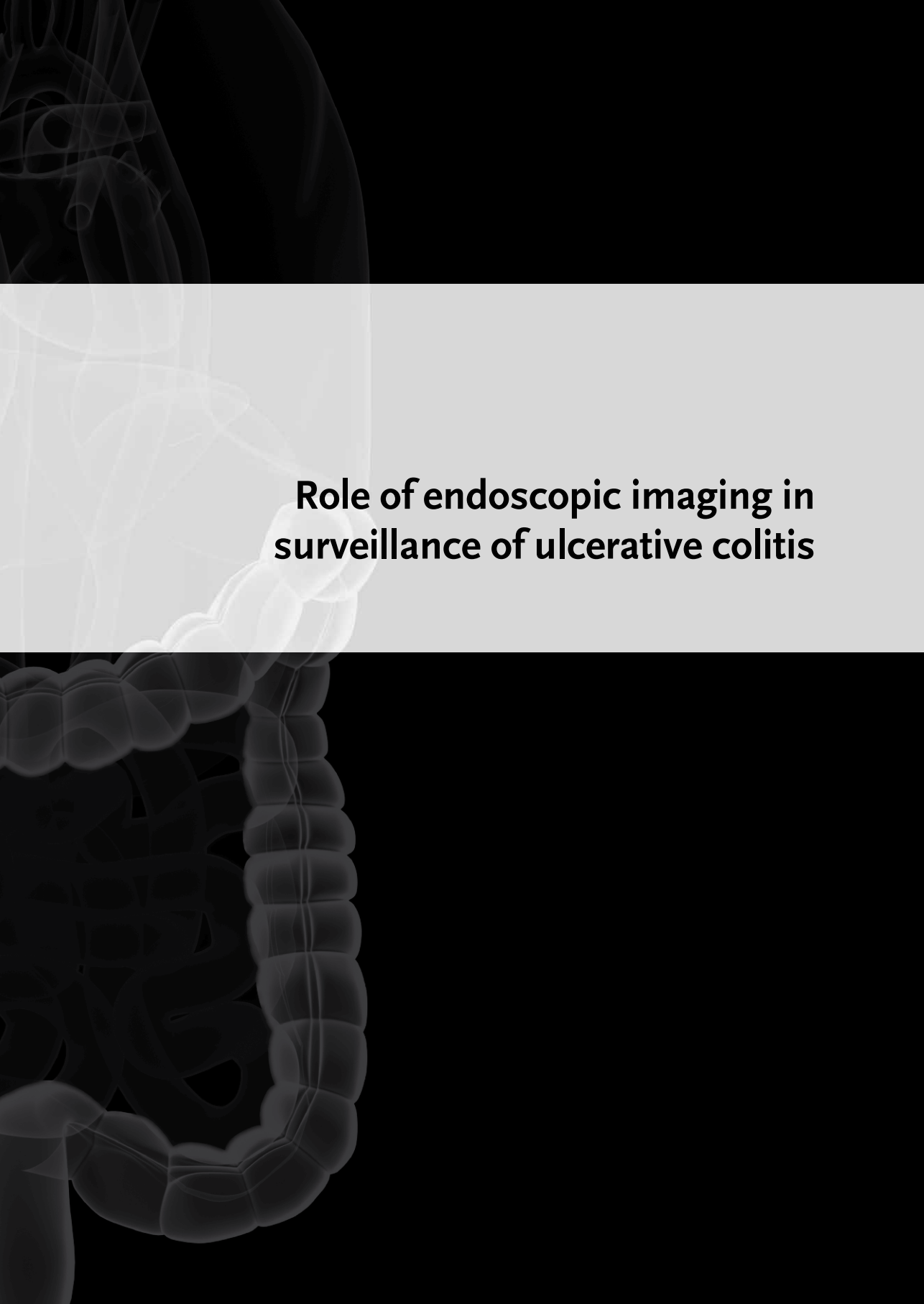
48 Adler A, Pohl H, Papanikolaou IS, Abou-Rebyeh H, Schachschal G, Veltzke-Schlieker W, Khalifa AC, Setka E, Koch M, Wiedenmann B, Rosch T. A prospective randomised study on narrow-band imaging versus conventional colonoscopy for adenoma detection: does narrow-band imaging induce a learning effect? Gut 2008;57:59-64.

49 Adler A, Aschenbeck J, Yenerim T, Mayr M, Aminalai A, Drossel R, Schroder A, Scheel M, Wiedenmann B, Rosch T. Narrow-Band Versus White-Light High Definition Television Endoscopic Imaging for Screening Colonoscopy: A Prospective Randomized Trial. Gastroenterology 2008.

50 Kaltenbach T, Friedland S, Soetikno R. A randomised tandem colonoscopy trial of narrow band imaging versus white light examination to compare neoplasia miss rates. Gut 2008;57:1406-1412.

51 Adler A. Narrow Band Imaging (NBI) Influences the Learning Curve for Conventional Endoscopy - Final Results of a Prospective Randomized Study in the Detection of Colorectal Adenomas. 65 ed. 2007:AB116.

PART III



Role of endoscopic imaging in surveillance of ulcerative colitis

CHAPTER 8

Random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis: low yield and absence of clinical consequences

Frank J.C. van den Broek
Pieter C.F. Stokkers
Johannes B. Reitsma
Robin P.B. Boltjes
Cyriel Y. Ponsioen
Paul Fockens
Evelien Dekker

Submitted

ABSTRACT

Objective: To evaluate the yield and clinical impact of random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis (UC).
Design: Retrospective analysis of 1,010 colonoscopies performed from 1998-2008. Colonoscopy and pathology reports were reviewed to assess the yield and clinical impact of random biopsies.
Setting: Academic Medical Centre Amsterdam
Patients: 475 patients with UC
Main outcome measures: neoplasia yield per-colonoscopy and clinical impact per-patient of random biopsies
Results: Of all colonoscopies, 466 were performed for surveillance (in 167 patients) during which 11,772 random biopsies were taken (median 29).
Overall, neoplasia was detected in 88 colonoscopies (53 patients): in 75 colonoscopies (85%) by targeted biopsies only and in 8 (9.1%) by both targeted and random biopsies. Neoplasia was detected in random biopsies only in 5 (5.7%) colonoscopies in 4 (7.5%) patients. Two of these 4 patients with neoplasia detected only by random biopsies had visible neoplasia in previous colonoscopies. One patient had unifocal low grade neoplasia (LGIN) that could not be confirmed in 3 subsequent colonoscopies. The last patient had multifocal LGIN and suspicious appearing ulcerations. Proctocolectomy confirmed the presence of neoplasia.
Conclusion: The yield of random biopsies is low whereas UC-associated neoplasia is macroscopically visible in 94% of colonoscopies. During 10-year surveillance, neoplasia was detected in only random biopsies in 4 patients of whom only 1 had clinical consequences. The low yield and lack of clinical consequences from random biopsies in this high-risk population do not warrant their routine use during UC surveillance.

Introduction

As the risk of colorectal cancer is increased in patients with longstanding ulcerative colitis (UC), guidelines recommend colonoscopic surveillance in these patients in order to detect neoplasia at an early and potentially curable stage.[1, 2] Surveillance implies performing biannual colonoscopies, even annually in case of concomitant primary sclerosing cholangitis (PSC). During these colonoscopies targeted biopsies of suspicious lesions and random sampling of inconspicuous appearing mucosa for pathological evaluation should be performed. The rationale for taking random biopsies is that UC-associated neoplasia may be difficult to visualize and, if present, generally occurs multifocal. To obtain a high sensitivity for the detection of neoplasia, 4 random biopsies every 10cm of colon are presumed to be necessary.[3]

Recent reports however suggest that most UC-associated neoplasia is in fact macroscopically visible.[4-6] Advanced endoscopic techniques have also demonstrated improved neoplasia detection compared to conventional colonoscopy. Pancolonic dye-spraying has shown to be superior to conventional colonoscopy in several reports,[7-11] and recently autofluorescence imaging has shown promising results as well.[12] Remarkably, when using advanced techniques for surveillance the yield of random biopsies diminishes as a result of which their need is more and more questioned.[8, 12]

In addition, Rutter *et al* suggested that a number of endoscopic features could help to predict an increased risk of neoplasia in individual patients.[13] Certain endoscopic appearances that were a result of severe inflammation in the past (e.g. post-inflammatory polyps) were associated with neoplasia. The authors even postulated to reduce the surveillance interval in case no endoscopic features were present. This raises the question whether random biopsies may be reserved only for patients with endoscopic features of previous severe inflammation.

The aims of this retrospective study were to evaluate (1) the yield of neoplasia from random biopsies during a 10-year surveillance program of patients with UC in a tertiary referral centre in the Netherlands, (2) to determine whether random biopsies had clinical consequences, and (3) to validate whether endoscopic features were associated with neoplasia in our UC population.

Methods

Study population and period

All UC patients who underwent colonoscopy between January 1998 and March 2008 at the Academic Medical Centre Amsterdam, the Netherlands, were retrospectively reviewed. At our institution patients with inflammatory bowel disease are entered into a clinical computerized database, which was used to retrieve all UC patients. The database is being updated after each visit of the patients to our outpatient or inpatient clinic. The UC diagnosis was made and entered in the database by the treating physician and was based on both colonoscopic and pathological findings. Patients were excluded if they did not undergo any colonoscopy in the study period or had undergone a proctocolectomy before January 1998.

Colonoscopic data collection

The computerized database, medical records, endoscopy reports and pathology reports were reviewed to obtain data on patient demographics, year of onset of UC symptoms (in case this variable was absent the year of UC diagnosis was used), presence of concomitant PSC, history of colonic neoplasia before January 1998, medication use, and colonoscopy findings.

At our institution, all UC surveillance colonoscopies are performed or supervised by certified staff endoscopists having specific expertise in inflammatory bowel disease. Available endoscopes in the study period were CF-(Q)140/160/180 colonoscopes (Olympus Medical Systems Europe, Hamburg, Germany). The standard bowel preparation consisted of 4 liters of polyethylene glycol solution.

Colonoscopy reports were assessed for reason of endoscopy: either *surveillance* (if explicitly stated, if 4 quadrant random biopsies were mentioned, or if a history of neoplasia was mentioned) or *on indication* (symptoms or control after medical therapy). Endoscopic features were noted as backwash ileitis, shortened colon, tubular colon, featureless colon, scarring, segment of severe inflammation, post-inflammatory polyps and colonic strictures.[13] If none of these endoscopic features were mentioned in the endoscopy report or if a normal appearing colon was explicitly stated, absence of these features was noted. Furthermore, the extension of disease was scored according to the Montreal classification: inflammation or endoscopic features proximal to the splenic flexure was defined as extensive disease; distal to the splenic flexure as left-sided disease; and distal to the rectosigmoid junction as proctitis.[14]

The number of random biopsies was calculated from the pathology report. The number of suspicious lesions was recorded from both the endoscopy and pathology report. Suspicious lesions were defined as macroscopically visible lesions of which targeted biopsies were taken (explicitly mentioned as 'targeted' in the endoscopy or pathology report). In case visualized abnormalities were described in the endoscopy report but biopsies were not explicitly mentioned to be 'targeted', these were noted as random biopsies.

Histopathology

All biopsy specimens were evaluated by experienced pathologists of our institution. In case neoplasia or 'indefinite for neoplasia' was diagnosed, the specimens were reviewed by at least one additional gastrointestinal expert pathologist and discussed in a conjoint meeting with gastroenterologists for a final management plan. The pathology was categorized as: absence of neoplasia; unifocal low grade intraepithelial neoplasia (LGIN); multifocal LGIN, unifocal high grade intraepithelial neoplasia (HGIN); multifocal HGIN; or invasive neoplasia.[15] In case the degree of neoplasia was not explicitly mentioned, it was recorded as 'unspecified neoplasia'. A diagnosis of 'indefinite for neoplasia' was not regarded as neoplasia.

Clinical management of neoplasia

The clinical management of neoplasia during or after colonoscopy was recorded as endoscopic resection, proctocolectomy, intensified surveillance or regular surveillance. If one of these policies was explicitly mentioned, this was recorded. To differentiate between intensified and regular surveillance, we defined 'regular' surveillance as having an interval between two surveillance

colonoscopies of >1.5yrs if the UC duration was <30yrs; or an interval of >0.75yrs if the UC duration was >30yrs or if the patient had concomitant PSC. If 'indefinite for neoplasia' was diagnosed during colonoscopy, a subsequent interval of >0.75yrs was defined as 'regular' surveillance; and if LGIN was diagnosed an interval of >0.5yrs was defined as 'regular'. We chose these intervals since at our institution a diagnosis of 'indefinite for neoplasia' implies intensified surveillance within 0.5yrs and LGIN implies intensified surveillance within 0.25yrs or proctocolectomy. Invasive neoplasia or HGIN always implies proctocolectomy. Shorter intervals than mentioned above were scored as 'intensified' surveillance. For the interval calculations we neglected colonoscopies that were performed *on indication*.

Outcome measures

Primary outcome measures were the number of colonoscopies and the number of patients in whom neoplasia was detected by random biopsies only.

Secondary outcome measures were the clinical management of patients with neoplasia that was detected by random biopsies only and the correspondence between colonoscopic features and detected neoplasia.

Statistical analysis

Descriptive statistics were used to describe the study population and the yield of neoplasia. Means were represented with their range and medians with their interquartile range (p25-p75). A multivariable logistic regression model was made to analyze associations between the presence of neoplasia during colonoscopy (i.e. dependent variable) and the presence of endoscopic features (i.e. independent variables). Known patient-related risk factors of neoplasia (i.e. personal history of neoplasia, PSC, extensive disease, no disease modifying drug use, age and UC duration) were included in the multivariable model as well. As these patient-related risk factors may be overrepresented in patients undergoing multiple colonoscopies, generalized estimation equations were used for multivariable logistic regression analysis. Variables that were associated with neoplasia on univariable analysis ($p<0.1$) were analyzed in the multivariable model. Odds ratios (OR) plus 95%-confidence interval (95-CI) were used to express the strength of the association.

Results

Study population

At March 2008 our clinical database enclosed 729 patients with UC. Of those patients, 254 were excluded as they did not undergo any colonoscopy in the study period (n=181) or had prior proctocolectomy (n=73). Demographics of the remaining 475 patients are demonstrated in table 1.

In the 10-year study period a total of 1,010 colonoscopies were performed, of which 466 (46%) were performed for the purpose of *surveillance* (in 167 patients) and 544 were performed *on indication* (in 308 patients).

Per-lesion analysis

During the 466 *surveillance* colonoscopies, a total of 11,772 random biopsies were taken, corresponding to a median of 29 (15-36) per surveillance colonoscopy. Only 24 random biopsies (0.2%) demonstrated neoplasia (23 LGIN; 1 HGIN). Furthermore, 431 suspicious lesions were detected of which 101 (23%) were neoplastic (29 LGIN, 56 unspecified, 13 HGIN, 3 invasive).

During the 544 colonoscopies that were performed *on indication* an additional number of 129 suspicious lesions were detected, of which 23 (18%) were neoplastic (20 unspecified, 3 invasive).

Overall, 148 neoplastic sites were found in this study of which 124 (84%) were detected by targeted biopsies and 24 by random biopsies (per-lesion yield 16%).

Demographic	Number	Percentage
Mean age at first colonoscopy in this study, yrs (range)	42 (3-87)	
Male	253	53%
Median UC duration until first colonoscopy, yrs (p25-p75)	5.9 (1-14)	
Until first *surveillance* colonoscopy *	14 (11-20)	
Until first colonoscopy *on indication*	3 (1-9)	
Concomitant diagnosis of PSC	31	6.5%
Extension of UC		
Extensive colitis	237	50%
Left-sided colitis	89	19%
Proctitis	105	22%
Current absence of any sign of previous inflammation	44	9.3%
Personal history of neoplasia	21	4.4%
Neoplasia at our institution before 1998	15	3.2%
Endoscopic resection of prior neoplasia	10	2.1%
Partial colectomy of prior neoplasia	5	1.1%
Referred to our institution due to colorectal neoplasia	6	1.3%
Using disease modifying drugs (mostly mesalamines)	422	89%
Mean number of colonoscopies per patient (range)	2.1 (1-12)	
Surveillance colonoscopies †	2.8 (1-12)	
Colonoscopies *on indication* †	1.4 (1-5)	

Table 1: Demographics of the study population (475 patients with UC who underwent at least one colonoscopy between January 1998 and March 2008)

* 12 patients received their first *surveillance* colonoscopy before 8yrs of UC duration, due to concomitant PSC or neoplasia detected during previous colonoscopies *on indication*.

† Mean number of colonoscopies per patient who underwent at least one *surveillance* colonoscopy or at least one colonoscopy *on indication*.

Per-colonoscopy analysis

Neoplasia was detected by targeted or random biopsies in a total of 88 colonoscopies (8.7%), either during *surveillance* colonoscopy (n=72) or during colonoscopy *on indication* (n=16).

Of these colonoscopies, neoplasia was detected by only random biopsies in 5 (per-colonoscopy yield 5.7%). Three showed unifocal LGIN and 2 multifocal LGIN. One multifocal LGIN led to proctocolectomy; the remainder led to regular or intensified (one unifocal LGIN) surveillance.

Random biopsies detected neoplasia in 8 additional colonoscopies (9.1%) in which neoplasia was detected by targeted biopsies as well. The random biopsies showed unifocal LGIN in 4, unifocal HGIN in 1, and multifocal LGIN in 3. Proctocolectomy was performed in 1 (unifocal HGIN in random and intramucosal cancer in targeted biopsies), intensified surveillance in 2 (one unifocal and one multifocal LGIN) and regular surveillance in 5.

In 75 colonoscopies (85%) neoplasia was detected by only targeted biopsies of suspicious lesions, of which 49 led to endoscopic resection, 11 to proctocolectomy (invasive neoplasia postoperatively found in 7), 11 to intensified surveillance and 4 to regular surveillance. Table 2 demonstrates the worst pathological outcome per colonoscopy and its detection method.

Detection of neoplasia by random biopsies was independently associated with the presence of visible neoplastic lesions (OR 14.8; 95-CI: 3.57-61.1) and primary sclerosing cholangitis (OR 8.96; 2.44-32.9). In a normal appearing colon, i.e. absence of endoscopic features of severe inflammation in the past, random biopsies never yielded neoplasia.

Per-patient analysis

Neoplasia was detected in at least one colonoscopy in 53 patients (11%); 16 during colonoscopy *on indication* and 37 during *surveillance* colonoscopy. Seven of these patients had visible invasive neoplasia (13%), of which 3 were diagnosed during colonoscopy *on indication*. Visible invasive neoplasia was furthermore diagnosed during surveillance in one patient who had LGIN in two suspicious lesions 6 months earlier (same colonic segment) and in one patient (two cancers) who was referred from another hospital. Two additional patients had visible intraepithelial neoplasia (unifocal HGIN and multifocal unspecified neoplasia) during surveillance, but turned out to have invasive neoplasia in their surgical resection specimen. None of these patients with invasive cancer had neoplasia detected by random biopsies.

Of the 53 patients with neoplasia, 4 had at least one colonoscopy in which neoplasia was detected by random biopsies only (per-patient yield 7.5%). In 5 additional patients (9.4%) neoplasia was detected by both targeted and random biopsies. The successive colonoscopies with their findings in these 9 patients are demonstrated in figure 1. The remaining 44 patients (83%) had neoplasia detected by only targeted biopsies of visible lesions.

Three of the 9 patients (33%) with positive random biopsies underwent proctocolectomy versus 11 of the 44 patients (25%) in whom neoplasia was detected by only targeted biopsies (p=0.684).

Worst pathological outcome per colonoscopy	Detection method		
	Random	**Targeted**	**Targeted and random**
Neoplasia			
Unifocal LGIN	3	11	2
Multifocal LGIN	2	4	1
Unifocal UIN	0	37	2†
Multifocal UIN	0	13	1#
Unifocal HGIN	0	3	1
Multifocal HGIN	0	3*	0
Invasive neoplasia	0	5	0
Totals	5	76	7

Table 2: Worst pathological outcome per colonoscopy and its detection method (either by random biopsies only, targeted biopsies only, or by both targeted and random biopsies)

LGIN, low-grade intraepithelial neoplasia; UIN, unspecified intraepithelial neoplasia; HGIN, high-grade intraepithelial neoplasia
* One colonoscopy with multifocal HGIN as worst outcome in targeted biopsies had multifocal LGIN in random biopsies; † Two colonoscopies with unifocal UIN as worst outcome in targeted biopsies had unifocal LGIN in random biopsies; # One colonoscopy with multifocal UIN as worst outcome in targeted biopsies had multifocal LGIN in random biopsies

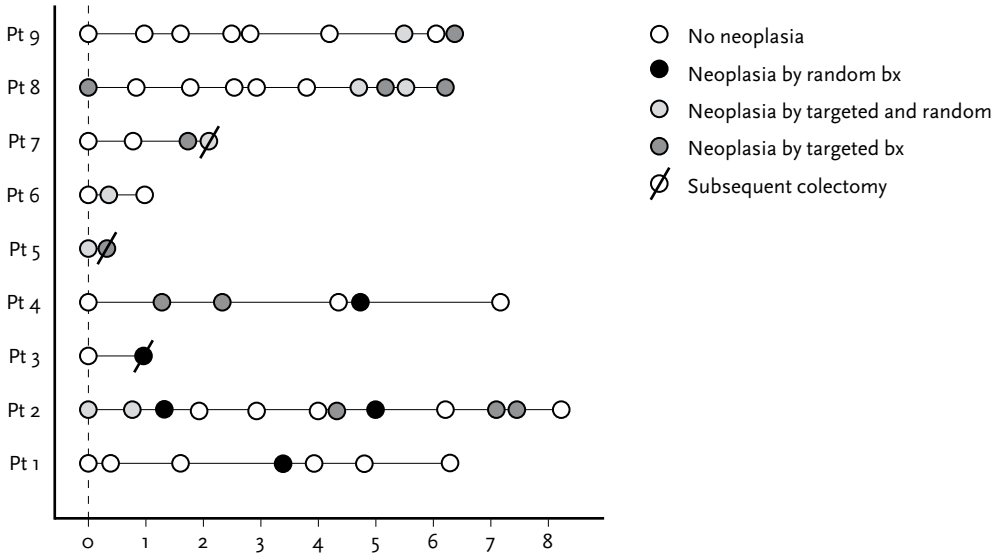


Figure 1: Colonoscopic findings of the 9 patients (1.9%) who had neoplasia detected by random biopsies in at least one of their colonoscopies. Bx = Biopsies.

Management of patients with neoplasia detected by only random biopsies

The first patient (Pt 1, male, 49yrs) in whom neoplasia was detected by only random biopsies had unifocal LGIN. He furthermore had a shortened, tubular, featureless and scarred colon with post-inflammatory polyps and a colonic stricture. As neoplasia could not be confirmed in three subsequent intensified surveillance colonoscopies, he is currently scheduled for normal surveillance again.

The second case (Pt 2, female, 56yrs, PSC) had a tubular, featureless, scarred and actively inflamed colon with colonic strictures in which multifocal LGIN and unifocal LGIN was detected by only random biopsies during two colonoscopies. However, this patient was already known to have visible dysplasia-associated lesions/masses (DALMs) during two earlier colonoscopies for which she refused proctocolectomy. After a follow up of 8.9 yrs (and 11 additional surveillance colonoscopies) in this study, no cancer was detected.

The third case (Pt 3, male, 51yrs, PSC) had multifocal LGIN detected by only random biopsies. Several suspicious ulcerations were also described in combination with a shortened, tubular, featureless, scarred and actively inflamed colon. However, as no targeted biopsies of the suspicious ulcerations were mentioned in the endoscopy report, all LGIN was ascribed to the random biopsies. Subsequent proctocolectomy even showed multifocal HGIN.

The fourth patient (Pt 4, female, 54yrs) also had a tubular, featureless, scarred and actively inflamed colon with post-inflammatory polyps in which unifocal LGIN was detected by only random biopsies. Two previous colonoscopies yielded visible adenoma-like masses (LGIN) that were endoscopically resected. Although a 3mm polypoid lesion was photographed this time too, it was not described in the endoscopy report and hence the LGIN was ascribed to the random biopsies only. This patient is currently scheduled for normal surveillance again.

Colonic feature	Univariable analysis		Multivariable analysis	
	Odds ratio (95%-CI)	**p**	**Odds ratio (95%-CI)**	**p**
backwash ileitis	0.00 (0.00-.)	.998	-	-
shortened colon	1.77 (0.31-10.1)	.519	-	-
tubular colon	2.43 (1.41-4.17)	.001	2.09 (1.14-3.84)	.018
featureless colon	1.22 (0.71-2.09)	.459	-	-
scarring	2.13 (1.28-3.55)	.004	1.54 (0.87-2.74)	.140
segment of inflammation	0.60 (0.19-1.87)	.373	-	-
post-inflammatory polyps	1.02 (0.51-2.01)	.962	-	-
colonic strictures	3.76 (1.01-14.0)	.049	4.51 (1.55-13.1)	.006

Table 4: Univariable and multivariable logistic regression analysis using generalized estimation equations evaluating associations between endoscopic features of (previous) severe colonic inflammation and the presence of neoplasia during colonoscopy

Endoscopic features and risk of neoplasia

Backwash ileitis was documented in 22 colonoscopies (2.2%), shortened colon in 15 (1.5%), tubular colon in 158 (16%), featureless colon in 415 (41%), scarring in 227 (23%), and post-inflammatory polyps in 215 (21%). Severe inflammation in at least one colonic segment was documented in 96 colonoscopies (9.5%) and colonic strictures in 24 (2.4%). On multivariable regression analysis 'tubular colon' and 'colonic strictures' were independently associated with detected neoplasia (OR 2.09; 95%-CI: 1.14-3.84 and OR 4.51; 1.55-13.1 respectively); see Table 4.

Table 5 demonstrates multivariable regression analysis combining 'tubular colon' and 'colonic strictures' together with known risk factors of neoplasia: history of neoplasia (n=15), PSC (n=31), extensive disease (n=237), no disease modifying drug use (n=51), age and UC duration. The appearance of a 'tubular colon' during colonoscopy remained independently associated with the detection of neoplasia (OR 1.69; 95%-CI: 0.95-3.02) with a trend towards statistical significance (p=0.074). Patient age (OR 1.06 per year; 1.04-1.09) was the only significant independent risk factors of neoplasia (p<0.001).

Risk factors of neoplasia	Univariable analysis		Multivariable analysis	
	Odds ratio (95%-CI)	p	Odds ratio (95%-CI)	p
History of neoplasia	5.77 (2.22-15.0)	.000	1.43 (0.36-5.71)	.616
Colonic strictures	3.76 (1.01-14.0)	.049	2.52 (0.53-11.9)	.243
PSC	3.53 (1.55-8.07)	.003	2.09 (0.82-5.33)	.122
Tubular colon	2.43 (1.41-4.17)	.001	1.69 (0.95-3.02)	.074
No UC modifying drug use	2.19 (1.06-4.52)	.035	1.48 (0.62-3.50)	.377
Extensive colonic disease	1.97 (1.01-3.84)	.046	1.58 (0.83-3.01)	.165
Age at colonoscopy (per yr)	1.06 (1.04-1.08)	.000	1.06 (1.04-1.09)	.000
UC duration (per yr)	1.06 (1.03-1.08)	.000	1.02 (0.98-1.05)	.393

Table 5: Univariable and multivariable logistic regression analysis using generalized estimation equations to evaluate associations between patient risk factors of neoplasia (including tubular colonic appearance and colonic strictures) and the detection of neoplasia during colonoscopy (i.e. dependent outcome variable)
PSC, primary sclerosing cholangitis

Discussion

Several authors have recently questioned the need for random biopsies during colonoscopic surveillance of UC patients.[8, 16] One of the reasons is that advanced endoscopic techniques (e.g. chromoendoscopy, autofluorescence imaging) showed to improve the visualization of neoplasia, thereby reducing the yield of random biopsies.[7-9, 11, 12] Moreover, random biopsies may distract endoscopists from carefully inspecting for visible neoplasia and therefore provoke overlooking it. In previous studies conventional colonoscopic equipment was already able to visualize 61-88%

of neoplastic sites in the colon.[4-6] In the present retrospective study 84% of neoplastic sites could be visualized by conventional video endoscopy.

Although other retrospective studies showed that most neoplasia is endoscopically visible, none of them evaluated the clinical management of invisible neoplasia (i.e. detected by random biopsies only).[6] Whereas in previous studies 11-17% of patients with neoplasia were detected by random biopsies only, this figure was 7.5% (4 of 53 patients) in the present study. Random biopsies could therefore still have had clinical consequences for 4 out of the 167 patients (2.4%) who underwent surveillance colonoscopies in this study.

However, when exploring the clinical management of invisible neoplasia we found that random biopsies led to a relevant change in just one patient (0.6%). This patient had multifocal LGIN in random biopsies only and subsequently underwent proctocolectomy. Although visible suspicious ulcerations were also described in the endoscopy report, no targeted biopsies were mentioned. The presence of these visible suspicious ulcerations may also have contributed to the decision of performing proctocolectomy, although this cannot be verified in retrospect. Furthermore, one may argue that the use of chromoendoscopy or other advanced imaging techniques would have better defined the suspicious ulcerations leading to targeted biopsies as well.

Except for this one patient, all others with neoplasia detected by random biopsies only (n=3) did not have an altered clinical management in our institution. One patient was known to have visible DALMs but kept refusing proctocolectomy. Another patient had a history of ALMs and a polypoid lesion was photographed this time too, although without mentioning it in the endoscopy report. This polypoid lesion was considered an ALM by the treating physician and hence this patient underwent continued surveillance with regular intervals. The third patient had truly invisible unifocal LGIN (in a colon with multiple post-inflammatory polyps) that led to intensified surveillance only. During 4 years of follow-up no further neoplasia could be confirmed and this patient is currently scheduled for regular surveillance again. Although the clinical management in these 3 patients may be debated, the advantage of our retrospective study design is that it reflects the factual clinical practice at our institution. However, we have to consider the fact that others may have executed a different clinical management in these 3 patients and hence may find the yield of random biopsies more relevant.

Next to detecting neoplasia, the pathological outcome of random biopsies might also aid in deciding whether to perform proctocolectomy or not. In our study however, patients with neoplasia plus positive random biopsies did not undergo proctocolectomy more frequently than patients with neoplasia and negative random biopsies. Besides, random biopsies did not yield neoplasia in seven patients who turned out to have invasive neoplasia. In the study by Marion *et al*, all patients who underwent proctocolectomy had negative random biopsies as well, suggesting that these biopsies have a low impact on clinical decision making.[11]

When assessing our results, one has to consider that only conventional video endoscopy was used for surveillance. Previous studies have demonstrated that the yield of random biopsies will further decrease when using advanced endoscopic techniques.[7-9, 11, 12] Rutter *et al* demonstrated that random biopsies did not detect additional patients with neoplasia during UC surveillance, whereas chromoendoscopy increased this number by 3.5-fold.[8] Others have shown that only 0.01-0.16% of all random biopsies demonstrated neoplasia when using chromoendoscopy but did not reveal whether positive random biopsies changed clinical management on a per-patient

basis.[7, 9, 11] Recently our study group showed that random biopsies did not detect additional patients with neoplasia when using autofluorescence imaging for UC surveillance.[12] Therefore, we postulate that the yield and clinical impact of random biopsies would have been even lower in case advanced endoscopic techniques would have been routinely used.

Two chromoendoscopy studies still reported patients in whom neoplasia was detected by random biopsies only (1.2% and 2.0% of patients), as a result of which one may still be unwilling to omit random biopsies.[7, 11] Instead of omitting random biopsies, their selective use may also be a realistic option. Rutter *et al* evaluated endoscopic features of severe inflammation and found that 'post-inflammatory polyps' and 'strictures' were associated with the detection of neoplasia.[13] In our study 'tubular colon' and 'strictures' were also statistically significantly associated with the detection of neoplasia (OR 2.09 and 4.51 respectively). Multivariable analysis including established risk factors, such as history of neoplasia, PSC, age and UC duration, demonstrated that 'tubular colon' remained independently associated with the detection of neoplasia (OR 1.69). Furthermore, the yield of random biopsies was extremely low in case of absence of visible neoplasia or PSC and in case of a normal appearing colon. One may therefore consider omitting random biopsies in case of a normal appearing colon. Only the presence of visible suspicious lesions, colonic features of severe inflammation in the past (e.g. tubular colon) or PSC may still warrant taking random biopsies. In the present study, this approach would have made random biopsies redundant in 845 colonoscopies (84%) but would have led to missing 2 unifocal LGINs (results not shown). Since these unifocal LGINs did not lead to an altered clinical management and could not be confirmed during follow-up, this approach seems clinically useful.

Several limitations of our study should be mentioned regarding the low yield of random biopsies. First of all, the retrospective nature of the study may have introduced selection bias. As our hospital database of inflammatory bowel disease is being updated after each patient visit, it is likely that those who did not seek medical attention may not have been included in our study. However, these patients are likely to have mild or suppressed inflammation or do not have a history of neoplasia. If such selection bias would have occurred, it hence would direct towards including patients with a particularly high risk of neoplasia. In addition, one should consider that our hospital is a tertiary referral centre, already dealing with high risk patients. The true yield of random biopsies in general practice may therefore be even lower. Second, it may be difficult to retrospectively assess whether biopsies were taken in a targeted or random fashion. In several of our patients we retrieved images or descriptions of abnormalities in the endoscopy report without mentioning targeted biopsies. If the pathology report was inconclusive as well, biopsies were considered random. This may have increased the value of random biopsies. Third, in case endoscopic features of severe inflammation were not described in the endoscopy report, these were noted as absent. The associations between 'tubular colon', 'strictures' or 'normal appearing colon' and the detection of neoplasia may therefore be inaccurate. However, as these associations have been shown by others as well, it appears that these features indeed may predict the risk of neoplasia.[13, 17] Lastly, we did not consider 'indefinite for neoplasia' as neoplasia, since this diagnosis may refer to incorrect technical processing of biopsy specimens, serrated histology without neoplasia, reactive epithelium due to inflammation but with surface maturation, and active inflammation or ulceration. We felt confident with this approach since a diagnosis of

'indefinite for neoplasia' was always evaluated by a second expert pathologist to confirm the 'indefinite' nature of histology.

In summary, the present study evaluated the yield and clinical impact of random biopsies during 10-year surveillance of UC patients at a tertiary referral centre using conventional colonoscopy. The yield of neoplasia by random biopsies only was 16% per-lesion, 5.7% per-colonoscopy, and 7.5% per-patient. Remarkably, neoplasia detected by random biopsies only rarely led to an altered clinical management. We therefore propose to omit random biopsies during UC surveillance and use the gained endoscopy time for pancolonic chromoendoscopy. However, as endoscopic features of severe inflammation in the past (e.g. tubular colon), visible neoplasia and PSC were predictive of invisible neoplasia, random biopsies may still be considered in these circumstances until prospective follow-up studies have confirmed that additional random biopsies do not have any clinical impact.

Reference List

1 Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002;51 Suppl 5:V10-V12.

2 Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:314-321.

3 Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS, Dean PJ, Kimmey M, Perera DR, Rabinovitch PS. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology 1992;103:1611-1620.

4 Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? Gastrointest Endosc 2007;65:998-1004.

5 Blonski W, Kundu R, Lewis J, Aberra F, Osterman M, Lichtenstein GR. Is dysplasia visible during surveillance colonoscopy in patients with ulcerative colitis? Scand J Gastroenterol 2008;43:698-703.

6 Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. Gastrointest Endosc 2004;60:334-339.

7 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.

8 Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53:256-260.

9 Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005;37:1186-1192.

10 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.

11 Marion JF, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. Am J Gastroenterol 2008;103:2342-2349.

12 van den Broek FJ, Fockens P, van eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.

13 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. Gut 2004;53:1813-1816.

14 Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749-753.

15 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255.

16 Marion JF. An expensive and empty ritual: the continued use of random biopsy technique for detecting dysplasia in patients with colitis--pro. Inflamm Bowel Dis 2007;13:1271-1272.

17 Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451-459.

CHAPTER 9

Narrow band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis

Evelien Dekker
Frank J.C. van den Broek
Johannes B. Reitsma
James C. Hardwick
G. Johan Offerhaus
Sander J. van Deventer
Daan W. Hommes
Paul Fockens

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ABSTRACT

Background and study aim: Patients with longstanding ulcerative colitis (UC) are at increased risk of developing colorectal cancer. Colonoscopic surveillance is advised, but the detection of neoplasia by conventional colonoscopy is difficult. The aim of this study was to compare the accuracy of Narrow Band Imaging (NBI), a new imaging technique, with standard colonoscopy on the detection of neoplasia in patients with UC.

Patients and Methods: Prospective randomized cross-over study of 42 patients with longstanding UC. All participants underwent NBI and conventional colonoscopy with at least 3 weeks between the procedures. Randomization determined the order of techniques. Targeted biopsies were taken during both procedures; additional random biopsies were taken at conventional colonoscopy only. The number of patients with neoplasia detected by targeted biopsies reflected the sensitivity for each technique.

Results: With NBI 52 suspicious lesions were detected in 17 patients versus 28 suspicious lesions in 13 patients during conventional colonoscopy. Histopathological evaluation of targeted biopsies revealed 11 patients with neoplasia. In 4 patients neoplasia was detected by both techniques, in 4 only by NBI and in 3 only by conventional colonoscopy ($p=0.705$). Aside from targeted biopsies, 1522 random biopsies were taken. This revealed one additional patient with dysplasia, which was not detected by either technique.

Conclusions: The sensitivity of the studied first generation NBI system for the detection of patients with neoplasia seems to be comparable to conventional colonoscopy, although more suspicious lesions were found during NBI. At present we cannot preclude taking additional random biopsies.

Introduction

Patients with longstanding ulcerative colitis (UC) are at increased risk of developing colorectal cancer (CRC).[1,2] In a recent analysis of 600 patients followed-up in a colonoscopic surveillance program over a period of 30 years, 74 patients (12.3%) developed neoplasia, including 30 (5%) CRC's.[3] In the same study the cumulative incidence of CRC by colitis duration was 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years, which is considerably higher than in the general population.

To reduce the incidence of CRC in these patients, colonoscopic surveillance in those with longstanding extensive disease is generally recommended.[4,5,6] However, endoscopic detection of early neoplasia is difficult in patients with UC because these lesions may be subtle or even grossly invisible.[7,8] Therefore, surveillance guidelines recommend that in addition to targeted biopsies from suspicious lesions, 2-4 random biopsies should be taken every 10cm of colon.[4] Despite this laborious protocol, neoplastic lesions are still frequently missed as illustrated in a recent study, in which 16 of 30 cancers detected during the surveillance program were interval cancers.[3]

Improved image resolution and new optical techniques are continuously being developed to facilitate the detection of neoplasia, thereby attempting to increase the efficacy of surveillance programs.[9,10] Chromoendoscopy has been shown to improve the detection of neoplasia compared to conventional colonoscopy in patients with ulcerative colitis.[11,12,13] However, implementation of this technique in clinical practice has fallen short, mainly because chromoendoscopy is a labour-intensive technique and staining the whole colon may be associated with disproportionately lengthy examinations.

Narrow band imaging (NBI) is a novel real-time endoscopic imaging technique in which the mucosal surface contrast is enhanced by applying an optical filter to the light used for illumination.[14] Due to an increased relative contribution of blue light, which has a minimal penetration depth in the mucosa, NBI allows for superficial ('mucosal') imaging. When compared to chromoendoscopy, NBI eliminates the need for dye spraying and provides the opportunity to switch back and forth between the normal endoscopic view and NBI by pressing a button on the endoscope. Furthermore, the mucosal vascular network is visualized better by NBI than by conventional or chromoendoscopy.[15,16]

The aim of this prospective randomized cross-over study was to compare the accuracy of NBI colonoscopy with standard white light endoscopy (WLE) for the detection of patients with neoplasia in longstanding ulcerative colitis.

Patients and methods

Participants

Consecutive patients with longstanding ulcerative colitis scheduled for surveillance colonoscopy at the Academic Medical Centre Amsterdam between September 2003 and October 2004, were invited to participate in this study. The inclusion criteria for participation were an objective diagnosis of ulcerative colitis (based on endoscopic and/or histopathological assessment), a history of *pan*colitis, disease duration ≥8 years and inactive disease assessed by the Modified Truelove Witts

Severity Index (MTWSI ≤ 2).[17] Exclusion criteria were non-correctable coagulopathy, age ≤18 years and inability to give informed consent. All patients gave informed consent and the study was approved by the medical ethical committee of our institution.

Interventions and assignment

Patients were scheduled to undergo colonoscopy twice, once with NBI and once with WLE. A time interval of at least 3 weeks between the two procedures was chosen to allow healing of biopsies taken, so that sampling sites could not be recognised during the second examination. The two procedures were done by different endoscopists. The order in which the colonoscopies were performed was randomized, making use of opaque sealed envelopes. Randomization was performed to balance any order effect because small lesions might be more difficult to detect during the second colonoscopy if biopsies have been taken at the first examination. All colonoscopies were performed by one of three experienced endoscopists (E.D., S.v.D. and D.H.), who were blinded with respect to the endoscopic and histopathological findings of the first procedure (figure 1).

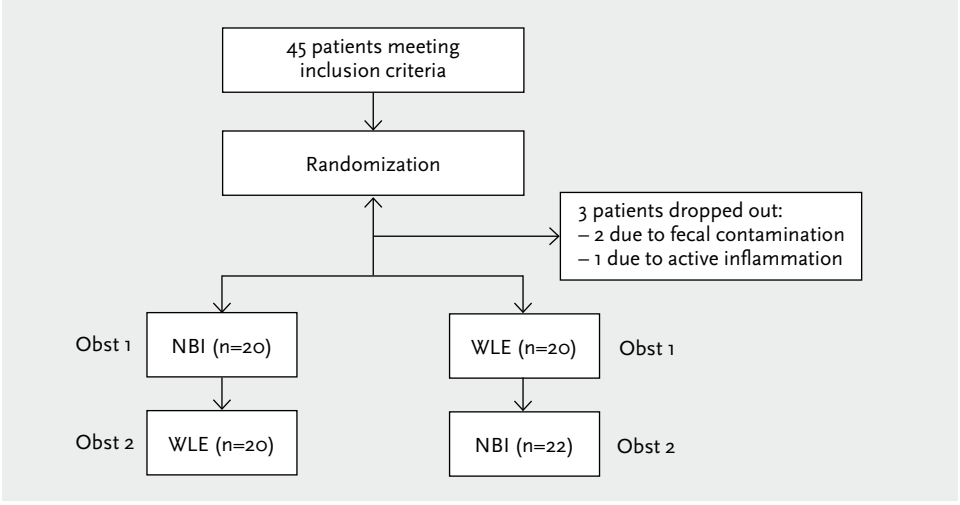

Figure 1: Flow chart of prospective randomized cross-over study design. WLE: standard white light endoscopy; NBI: narrow band imaging; Obs: observer

Endoscopic equipment

White light endoscopy was performed with conventional video colonoscopes (CF-140 or CF-160 series, Olympus Medical Systems Europe, Hamburg, Germany). No magnification or dye spray was used in this arm of the study.

Narrow band imaging was performed using a first generation prototype endoscopic imaging system (Olympus Evis CV-240; endoscope CF-Q240, Olympus Medical Systems, Tokyo, Japan), which has two imaging modes: WLE and NBI. An experimental light source (Olympus Evis CLV-U40) was used, in which the excitation light is sequentially separated into red, green and blue. The red, green and blue reflected lights are sequentially picked up by a high quality

monochromatic charge coupled device and transmitted to a video processor to be converted into one color image. In the NBI mode the band pass ranges for red, green and blue light have been narrowed to certain wavelengths (600–620 nm, 530–550 nm and 400–430 nm, respectively) with light filters. In addition, the intensity of blue light is increased allowing for optimal imaging of the mucosal morphology and vascular pattern since blue light has a minimal mucosal penetration depth.[18] The endoscopist can easily switch back and forth between the WLE and NBI mode by pushing a button on the shaft of the endoscope.

Colonoscopic protocol

All patients were prepared with four liters of hypertonic polyethylene glycol solution (Kleanprep; Helix Bio-pharma Corp., Aurora, Ontario, Canada). The procedures were performed under conscious sedation using midazolam and/or fentanyl. Cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve. At the start of withdrawal of the endoscope, 20 mg butylscopolamine was given intravenously to reduce colonic motility and repeated at the discretion of the endoscopist. When performing NBI colonoscopy, the endoscope was advanced into the cecum using the WLE mode. Upon reaching the cecum the imaging mode was switched to NBI, which was used for the entire withdrawal.

During colonoscopy by *both* NBI and WLE the number of lesions suspicious for neoplasia was noted and targeted biopsies were taken from these areas. Suspicious lesions on NBI were defined as polypoid or irregular mucosal structures with Kudo pit pattern III-V (figure 2), unusual ulcers, strictures or areas with increased vascular intensity revealing dark discoloration (figure 3). For WLE suspicion was based on polypoid or irregular mucosa, unusual ulcers or strictures. Only during WLE additional 4 quadrant random biopsies were taken every 10 cm of colon. For both procedures the number of suspicious lesions, number of targeted biopsies and procedural time were recorded.

Histopathological diagnosis

Histological samples were evaluated by two pathologists, at least one of them considered to be an expert in this field (G.J.O.). In case of discrepancy, discussion between the two led to consensus. The pathologists were not aware of the endoscopic detection technique and findings of the first procedure. Biopsies were classified according to the Vienna criteria of gastrointestinal epithelial neoplasia, ranging from no intraepithelial neoplasia/dysplasia to invasive neoplasia.[19] Lesions classified as indefinite for neoplasia were not considered as neoplasia.

Primary and secondary outcomes

The primary outcome of this study was the number of patients with detected neoplasia, reflecting the sensitivity of each technique. Secondary outcomes were number of patients with false positive findings, number of detected neoplastic lesions and number of false positive lesions for each technique.

Data analysis

Descriptive statistics were used to characterize the study population. Normally distributed variables were represented by the mean and standard deviation (SD) and skewed distributed data by the median and quartiles (P25-P75). Differences in mean were analyzed by the student's t-test and differences in median by the Wilcoxon rank test. Two main analyses were carried out to compare NBI and WLE. In the first analysis, we compared the accuracy of both techniques only in targeted biopsies. In the second analysis, we compared the accuracy of the strategy 'NBI taking only targeted biopsies' with 'WLE taking targeted plus random biopsies'. In both analyses we took advantage of the paired design of the study by comparing findings within an individual. However, matching at the level of individual lesions was not possible because the exact anatomical location cannot be reliable determined and uncertainty will exist whether suspicious lesions detected by both techniques within a single patient are indeed the same. Only the number of lesions and the colonic segment in which a particular lesion was detected (ascending, transverse, descending, sigmoid or rectum) could be compared between both procedures.

To test for a difference in sensitivity between NBI and WLE we compared the number of patients with discordant results: the number of patients with neoplasia (primary outcome) detected by one technique and not by the other. These numbers were compared using the McNemar test for paired data. A similar analysis was done for the number of patients with false positive findings. The numbers of true positive and false positive lesions (secondary outcome) were compared using the Wilcoxon matched pair signed rank test. A type I error (α) of 5% was chosen as cut off point for statistical significance.

Results

Forty-five patients were enrolled in the study. In 3 patients one of the procedures was interrupted or incomplete. In two cases this was due to fecal contamination which made meticulous inspection impossible and one patient had a MTWSI >2 at the second colonoscopy. Our analysis was therefore restricted to 42 patients in whom paired colonoscopic procedures were available. Among those patients, 37 subjects (88%) received disease modifying drugs, mostly (in 74% of cases) mesalamines or combined therapies with mesalamines and azathioprine. Therapy was not altered during the entire study period.

The study group comprised 31 men and 11 women with a mean age of 50 (SD 11.2) years. Their mean duration of ulcerative colitis was 21 (SD 8.6) years. Twelve patients (29%) had a concurrent diagnosis of primary sclerosing cholangitis. The median MTWSI at inclusion was 0 (P25-75: 0-1). Twenty-two patients were randomized to undergo WLE as the first procedure.

The mean procedural time for NBI colonoscopy was 50 minutes (SD 14.4) compared to 47 minutes (SD 12.1) for WLE (p=0.132). A total of 148 targeted biopsies were taken during the NBI procedure compared to 85 targeted biopsies for WLE.

Findings in targeted biopsies

During *NBI colonoscopy* 52 endoscopically suspicious lesions were detected in 17 patients (table 1). Histopathology confirmed 9 neoplastic lesions in 8 patients ('true positives'); the worst pathology per patient was low grade neoplasia (LGN) in 4 patients, high grade neoplasia (HGN) in 2 and carcinoma in 2. In the remaining cases histopathology was indefinite for neoplasia in 3 and negative for neoplasia in 6. Therefore, false positive results of NBI were found in 9 patients.

During *conventional colonoscopy* 28 suspicious lesions were detected in 13 patients (table 1). Histopathology revealed 12 neoplastic lesions in 7 of these patients; LGN in 2 patients, HGN in 4 and carcinoma in one. In 3 patients with suspicious lesions histopathology was indefinite for neoplasia and in 3 no neoplasia was diagnosed ('false positive results of the conventional procedure').

The number of patients with true positive (8 for NBI versus 7 for WLE) and false positive findings (9 for NBI versus 6 for WLE) for the two endoscopic procedures was not significantly different (p=0.705 and p=0.581, respectively). Also at the level of lesions there was no significant difference in the number of detected neoplastic lesions between the two techniques (9 for NBI versus 12 for WLE; p=0.672). Only the number of false positive lesions was significantly (p=0.015) higher for NBI than for WLE (43 versus 16).

Overall, in 11 patients one of the two procedures revealed neoplasia. In 4 patients this was diagnosed by both techniques, in 4 patients only by NBI and in 3 patients only by WLE (table 2 and 3).

Within the 4 cases with neoplasia detected by both techniques, in 2 patients lesions were detected in the same colonic segment, revealing the same grade of neoplasia. In 1 patient NBI revealed cancer in the cecum and WLE detected a cancer in the transverse colon. Pathologic evaluation of the operative specimen confirmed the presence of two synchronous cancers in this patient. In the last patient NBI detected LGN in a polyp in the transverse colon and WLE detected LGN in another polyp in the descending colon.

Within the 4 cases with neoplasia only detected by NBI, one patient (LGN detected with NBI) also had a suspicious lesion in the same colonic segment on WLE which was indefinite for neoplasia on histopathology. In the remaining three patients WLE had clearly missed two low grade neoplastic lesions and one intramucosal cancer.

Within the 3 cases with neoplasia detected by WLE only, 2 patients had also suspicious lesions in the same colonic segments during NBI which showed reactive changes on pathologic evaluation. In one of these 2 patients exactly the same lesion as detected by WLE was also found by NBI, but pathology could not confirm HGN in the NBI targeted lesion ('sampling error'). A third unblinded colonoscopy was subsequently performed which confirmed HGN in the NBI detected lesion. In the remaining patient NBI clearly missed a flat adenoma with HGN which was treated during WLE by endoscopic mucosal resection.

	NBI colonoscopy	Conventional colonoscopy	p-value
Per patient analysis			
Number of patients with suspicious lesions	17	13	0.344
Number of patients with true positive lesions	8	7	0.705
Number of patients with false positive lesions	9	6	0.581
Per lesion analysis			
Number of suspicious lesions	52	28	0.026
Number of true positive lesions	9	12	0.672
Number of false positive lesions	43	16	0.015

Table 1: Comparison of the paired endoscopic findings of NBI and conventional WLE among 42 patients with longstanding ulcerative colitis. The primary analysis at the level of patients showed equal outcomes of both techniques, whereas analysis at the level of lesions showed a significant increase in detection of suspicious lesions and false positive findings of NBI.

		Conventional WLE	
		Patients *with* neoplasia **(%)**	Patients *without* neoplasia **(%)**
NBI	Patients *with* neoplasia **(%)**	4 (9.5%)	4 (9.5%)
	Patients *without* neoplasia **(%)**	3 (7.1%)	31 (74%)

Table 2: Cross tabulation of paired results of NBI and conventional colonoscopies among 42 patients *with* and *without* neoplasia. Neoplasia was detected by both techniques in 4 patients, only by NBI in 4 and only by WLE in 3 patients. Differences in discordant results (4 vs. 3) were not significant (p=0.705).

Patient no.	NBI colonoscopy		Conventional WLE	
	Colonic segment	*histology*	*Colonic segment*	*histology*
# 1	Transverse	LGN	Transverse	Indefinite
# 2	Transverse	Invasive cancer		-
# 3	Sigmoid Transverse	Reactive changes Reactive changes	Sigmoid Transverse	LGN LGN
# 4	Ascending Descending	HGN HGN	Ascending Transverse Descending	HGN 2 LGN HGN, LGN
# 5	Descending	LGN	Transverse	LGN
# 6	Ascending	LGN		-
# 7	Ascending	HGN	Ascending	HGN
# 8	Descending	LGN		-
# 9		-	Sigmoid	HGN
# 10	Sigmoid	Reactive changes	Sigmoid	HGN
# 11	Ascending	1 invasive cancer	Transverse	1 invasive cancer
# 12		No neoplasia *		No neoplasia *

Table 3: Characteristics of the lesions in 12 patients with neoplasia, comparing detection technique with respect to the location and histology of the lesions
LGN = Low Grade Neoplasia, HGN = High Grade Neoplasia, Indefinite = Indefinite Neoplasia, * = LGN detected by random biopsy.

Additional findings in random biopsies

A total of 1522 random biopsies were taken during the conventional procedure in 42 patients (mean 36). Histopathology revealed neoplasia in 9 of the random biopsies taken (6 patients). The random biopsy protocol detected one additional patient with focal LGN, in whom NBI and WLE only demonstrated scarring and pseudopolyps. In the remaining 5 patients with positive random biopsies, neoplasia was already detected in the same colonic region by targeted biopsies.

When comparing the surveillance strategies 'NBI with targeted biopsies only' to 'WLE with targeted plus random biopsies', both strategies would detect 8 patients with neoplasia. Thus both strategies failed to detect 4 patients with neoplasia (miss rate of 33% for each strategy).

Discussion

To our knowledge, we have performed the first prospective randomized study evaluating the use of NBI compared to WLE for the detection of dysplasia in patients with longstanding UC. The results of this study show that during NBI twice as many suspicious lesions are detected and that NBI enables the endoscopist to take more targeted biopsies compared to WLE. However, the increase in targeted biopsies during NBI did not lead to a significantly higher detection rate of patients with neoplasia compared to WLE (8 versus 7 patients with neoplasia, respectively).

From the secondary analysis of our results it appeared that WLE detected even more neoplastic lesions than NBI (12 versus 9), although this difference was also not statistically significant. The most striking observation however was that both NBI and WLE failed to detect approximately one third of all patients with neoplasia, which reflects the low sensitivity of both methods; only the sequential use of both techniques would detect 11 out of 12 patients with neoplasia.

A possible explanation for the disappointing yield of NBI is that the endoscopic imaging system used in this study was a first generation prototype. Because of the relatively low light intensity in this first generation NBI system, the brightness of the imaging was sometimes insufficient to assure a good overview and the mucosal surface had to be evaluated by close approximation of the endoscope tip. Therefore, NBI colonoscopies were performed with a spiral rotation, increasing the possibility that certain areas were missed. This might have had an unfavourable influence on the results of NBI in our study. Recently, a new NBI system was commercially launched by Olympus Medical Systems. It is very possible that this new NBI system (Evis Exera II) will perform better than the first generation prototype, since our study group noted an improved brightness and resolution when using this new system. We therefore have already initiated a next study examining the performance of this new NBI system for surveillance of patients with longstanding UC.

Another possible explanation for the low sensitivity of our colonoscopies is sampling error. Although we could not exactly compare the location of lesions between NBI and WLE, we feel that lesions have been inaccurately sampled in a few instances. In one patient WLE described a reddish fold at 30 cm from the anus which turned out to be a high grade neoplastic lesion; during NBI also a reddish mucosal fold at the same distance from the anus was detected but histopathology revealed only reactive changes to the epithelium. A third colonoscopy with multiple biopsies from the same lesion confirmed the diagnosis of HGN in this patient. It appears that both techniques detected the same lesion but histopathology was clearly different. This specific problem was underlined in a recent consensus conference in which the authors stated that the number of biopsies taken affects whether sampling error is present.[4] Too few sampling or sampling errors may have happened more often, although we are not able to confirm this since information about the exact location of lesions is lacking. In order to minimize errors from histopathology we followed current pathology guidelines for evaluation of all biopsies, which were reviewed by a second expert pathologist.[19]

The increased number of suspicious lesions by NBI did not improve the yield of neoplasia, but led to an increase in false positive findings. In order to decrease false positive findings, Kudo introduced a classification system in order to predict endoscopically whether a lesion is dysplastic or not.[20] The Kudo classification was not recorded from each suspicious lesion in this study and has not yet been described for the use of NBI in patients with UC. In our experience with NBI, chronic inflammation may well resemble neoplasia and pit patterns according to Kudo might not be very helpful in discriminating these two, as also found by East *et al.*[16] Consequently, in this study we sampled all polypoid and irregular areas with Kudo III-V pit patterns, as well as unusual ulcers, strictures and lesions with dark discoloration on NBI, resulting in a relatively high false positive rate for NBI. After increasing our experience with NBI and defining how dysplasia appears at NBI colonoscopy, we expect to reduce the false positive rate in the future. Therefore, evaluation of pit patterns and vascular intensity of neoplasia in patients with longstanding UC is an interesting object for further studies.

Previous studies have shown that the use of chromoendoscopy also led to an increase of targeted biopsies, but in these studies this was also accompanied by an increase in dysplasia detection.[11,12,13] The authors postulated that colonoscopists' time might be better spent carefully scrutinizing the mucosa with chromoendoscopy, rather than taking 20-40 random biopsies.[12] To further investigate this issue with the use of NBI instead of dye spraying, we compared the strategy of 'NBI with only targeted biopsies' to the strategy of 'WLE with targeted plus random biopsies'. Since the endoscopy time for both procedures was equal (50 versus 47 minutes), we conclude that the time used during NBI was spent on careful inspection and during WLE a great part of the time was devoted to taking random biopsies. A more important finding was that both strategies detected only 8 out of 12 patients with neoplasia, thus having a dysplasia miss-rate of 33% and a corresponding sensitivity of 67%.

Aside from the issue which technique to use for UC surveillance, another subject for debate is the value of additional non-targeted biopsies. In our study random biopsies revealed neoplasia in 6 patients, but only in one additional patient in whom both NBI and WLE failed to detect suspicious areas. The high yield of non-targeted biopsies in our study reflects the high prevalence of neoplasia (29%) in the studied cases, which is probably a consequence of the high prevalence of concurrent PSC (29%) and the long mean duration of UC of 21 years. Given the fact that we found one out of 12 cases (8%) with neoplasia only by non-targeted biopsies, we believe it is too early to omit random biopsies during surveillance colonoscopy. This should only be considered once better detection techniques have been identified by properly designed studies.

For the evaluation of NBI we used a delayed cross-over study design, which has the advantage of obtaining paired data from all patients, maximizing the power of this study because each patient serves as his or her own control. In order to prevent carry-over effects within observers, both colonoscopies were performed by different endoscopists who were blinded for the first procedure. Furthermore, a minimum time interval of 3 weeks was chosen between the two procedures in order to wait for healing of sampled areas and to prevent recognition of biopsy sites. As far as we know this has been the first study in this area using a delayed cross-over design and in our opinion it is the optimal design for evaluating new colonoscopic techniques in patients with UC. An important drawback of this study design is that matching individual lesions is unreliable because detected abnormalities with one technique might not be the same as with the other. Therefore, for each technique the worst pathology per patient was considered as the primary outcome in this study. We regard this as an appropriate analysis since multifocal or repeatedly detected unifocal dysplasia in patients with longstanding UC is generally considered as an indication for colectomy.[4,21]

In summary, we have shown that the use of NBI colonoscopy in patients with longstanding ulcerative colitis is not superior to conventional white light colonoscopy for the detection of neoplasia. Attention must be paid to our finding that both techniques failed to detect about a third of patients with neoplasia, also when random biopsies during WLE were taken into account. We feel that this study should be repeated with the recently commercially introduced new NBI system which hopefully will increase the efficacy of UC surveillance in terms of neoplasia detection. In such a study attention must be paid to sufficient and accurate sampling for histology.

>> **For figure 2 and 3; see page 140**

Reference List

1 Itzkowitz SH,Harpaz N Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 2004; 126: 1634-1648.

2 Eaden JA, Abrams KR,Mayberry JF The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001; 48: 526-535.

3 Rutter MD, Saunders BP, Wilkinson KH et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006; 130: 1030-1038.

4 Itzkowitz SH,Present DH Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005; 11: 314-321.

5 Eaden JA,Mayberry JF Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002; 51 Suppl 5: V10-V12.

6 Winawer SJ, Fletcher RH, Miller L et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594-642.

7 Tytgat GN, Dhir V,Gopinath N Endoscopic appearance of dysplasia and cancer in inflammatory bowel disease. Eur J Cancer 1995; 31A: 1174-1177.

8 Rutter M, Bernstein C, Matsumoto T et al. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. Endoscopy 2004; 36: 1109-1114.

9 Dekker E,Fockens P New endoscopic tools for the IBD physician. Inflamm Bowel Dis 2004; 10 Suppl 1: S7-10.

10 Dekker E,Fockens P Advances in colonic imaging: new endoscopic imaging methods. Eur J Gastroenterol Hepatol 2005; 17: 803-808.

11 Kiesslich R, Fritsch J, Holtmann M et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003; 124: 880-888.

12 Rutter MD, Saunders BP, Schofield G et al. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004; 53: 256-260.

13 Hurlstone DP, Sanders DS, Lobo AJ et al. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005; 37: 1186-1192.

14 Kuznetsov K, Lambert R,Rey JF Narrow-band imaging: potential and limitations. Endoscopy 2006; 38: 76-81.

15 Machida H, Sano Y, Hamamoto Y et al. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004; 36: 1094-1098.

16 East JE, Suzuki N, von HA et al. Narrow band imaging with magnification for dysplasia detection and pit pattern assessment in ulcerative colitis surveillance: a case with multiple dysplasia associated lesions or masses. Gut 2006; 55: 1432-1435.

17 Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955; 1041-1048.

18 Gono K, Obi T, Yamaguchi M et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568-577.

19 Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251-255.
20 Kudo S, Rubio CA, Teixeira CR et al. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001; 33: 367-373.
21 Ullman T, Croog V, Harpaz N et al. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. Gastroenterology 2003; 125: 1311-1319.

CHAPTER 10

Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions

Frank J.C. van den Broek
Paul Fockens
Susanne van Eeden
Johannes B. Reitsma
James C.H. Hardwick
Pieter C.F. Stokkers
Evelien Dekker

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ABSTRACT

Background: Endoscopic tri-modal imaging (ETMI) incorporates white light endoscopy (WLE), autofluorescence imaging (AFI) and narrow band imaging (NBI).
Aims: To assess the value of ETMI for the detection and classification of neoplasia in patients with longstanding ulcerative colitis.
Design: Randomized comparative trial of tandem colonoscopies.
Setting: Academic Medical Centre Amsterdam, Netherlands.
Patients and methods: Fifty patients with ulcerative colitis underwent surveillance colonoscopy with ETMI. Each colonic segment was inspected twice, once with AFI and once with WLE, in random order. All detected lesions were inspected by NBI for Kudo pit pattern analysis and additional random biopsies were taken.
Main outcome measures: Neoplasia miss-rates of AFI and WLE, and accuracy of the Kudo classification by NBI.
Results: Among patients assigned to inspection with AFI first (n=25), 10 neoplastic lesions were primarily detected. Subsequent WLE detected no additional neoplasia. Among patients examined with WLE first (n=25), 3 neoplastic lesions were detected; subsequent inspection with AFI added 3 neoplastic lesions. Neoplasia miss-rates for AFI and WLE were 0% and 50% (p=0.036). The Kudo classification by NBI had a sensitivity and specificity of 75% and 81%; however, all neoplasia was colored purple on AFI (sensitivity 100%). No additional patients with neoplasia were detected by random biopsies.
Conclusion: Autofluorescence imaging improves the detection of neoplasia in patients with UC and decreases the yield of random biopsies. Pit pattern analysis by NBI has a moderate accuracy for the prediction of histology, whereas AFI-color appears valuable in excluding the presence of neoplasia.

Trialregister.nl Identifier: ISRCTN05272746

Introduction

Patients with longstanding ulcerative colitis (UC) are at increased risk of developing colorectal cancer.[1, 2] Since colonoscopic surveillance in UC patients appears to lead to early detection and improved prognosis of neoplasia, guidelines recommend surveillance for these patients.[3-6] However, neoplasia mainly develops in flat mucosa, so it can easily be overlooked during colonoscopy.[7-10] Therefore, random biopsies are recommended in addition to targeted biopsies of suspicious lesions.[4-6] Despite these great efforts, neoplasia is still frequently being missed by colonoscopy, possibly leading to interval cancers.[11, 12]

New endoscopic imaging techniques aim to facilitate the detection of neoplasia.[13] Chromoendoscopy (CE) has proven to increase the detection of neoplasia in UC and additionally enables pit pattern analysis for an accurate endoscopic classification by experts.[14-17] Nevertheless, implementation of CE in clinical practice has fallen short since it is labour-intensive and requires special training. By contrast, narrow band imaging (NBI) utilizes spectral characteristics of endoscopic light to enhance mucosal details without dyes.[18-20] Recently, NBI failed to improve the detection of neoplasia in UC[11], yet has been judged a valuable tool for classification.[21, 22] Whereas the diagnostic accuracy of NBI for differentiation of neoplastic and non-neoplastic tissue in UC remains to be clarified, its accuracy for differentiating sporadic polyps has shown to be comparable to CE.[23-27]

Autofluorescence imaging (AFI) is another novel technique, using short wavelength (blue) light for excitation of endogenous tissue fluorophores which emit fluorescent light of longer wavelength.[28] Therefore, AFI highlights neoplastic tissue without administration of exogenous fluorophores as described before in UC patients.[29, 30]

Recently, high resolution white light endoscopy (WLE), AFI and NBI have been incorporated into one system: 'endoscopic tri-modal imaging' (ETMI).[31] To date, ETMI has only been evaluated in patients with Barrett's oesophagus and AFI has only been described in 2 patients with UC.[32, 33] The aims of this randomized study were to compare AFI and WLE for the detection of neoplasia in patients with longstanding UC, and to assess the accuracy of NBI for pit pattern classification.

Patients and Methods

Participants

Patients with inactive pan-UC ≥8 years scheduled for surveillance colonoscopy at the Academic Medical Centre Amsterdam were invited for this study. A modified Truelove & Witts severity index ≤2 was used to define inactive disease.[34] Exclusion criteria were insufficient bowel preparation, endoscopically active inflammation, age ≤18 years, non-correctable coagulopathy, and inability to give informed consent. The study was approved by the medical ethical committee of our institution.

Endoscopic equipment

All colonoscopies were performed with a prototype ETMI system (Olympus Inc., Tokyo, Japan). The light source (XCLV-260HP) contains two rotating RGB-filters; one conventional for WLE and one additional for NBI, in which the band-pass ranges are narrowed to wavelengths of 530-550nm (green) and 390-445nm (blue). For NBI, the relative intensity of blue light is increased. Since blue light penetrates the mucosa only superficially and is the main color absorbed by hemoglobin, this setting enhances surface and capillary details (Figure 1a-d).[18, 19]

The zoom video-colonoscope (XCF-H240FZL, magnification 100x) contains two charge-coupled devices: one for WLE/NBI and one for AFI. In the AFI mode, blue light (390-470nm) is used for excitation and green light (540-560nm) for reflection. A barrier filter is used to detect autofluorescence and reflection light with wavelengths of 500-630nm only. The sequentially detected images of autofluorescence and green reflection are integrated by the processor into a real-time pseudo-color image. During AFI normal mucosa appears green, while neoplasia appears purple (Figure 1a+1d).

A high-resolution monitor was used for all procedures, in which the endoscopist could easily switch between the three imaging modes by pressing a button on the shaft of the endoscope.

Colonoscopic procedure and randomization

Patients were prepared with 4 liters of hypertonic polyethylene glycol solution (Kleanprep; Norgine GmbH, Marburg, Germany) and received conscious sedation. The endoscope was advanced in the WLE mode and cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve. No biopsies were taken during insertion of the endoscope. All procedures were performed by three experienced colonoscopists (>2,500 colonoscopies).

Upon reaching the cecum, the level of bowel preparation was determined: good (100% visible mucosa), moderate (90-100%) or poor (<90%). On introduction of the endoscope efforts were made to optimally clean the bowel by rinsing and suctioning. Poor bowel preparation was an exclusion criterion, as well as endoscopically active disease in at least one colonic segment.

During withdrawal of the colonoscope, each colonic segment was inspected twice: once with AFI and once with WLE. The hepatic and splenic flexures separated the colonic segments; in case of indistinct flexures a biopsy was taken for reference during the second inspection. Patients were randomly allocated for inspection with AFI or WLE first in all segments (Figure 2). One hundred opaque sealed envelopes contained notes with 'AFI' or 'WLE' written on (1:1) for randomization. At the moment of cecal intubation, a research fellow opened a randomly chosen envelope for allocation. The endoscopists were instructed to have equal inspection times for AFI and WLE. In a random sample of 10 patients inspection times were measured for both AFI and WLE, strictly excluding time for rinsing, taking pictures and taking biopsies. Suspicious lesions detected during the first inspection were sampled immediately after detection. During second inspection only additionally detected suspicious lesions were sampled. Finally, 4 quadrant random biopsies were taken every 10cm of colon. Of each lesion, the detection technique (WLE or AFI), size (estimated by a biopsy forceps), Paris classification, and location (part of colon and distance from the anus) were noted.[35] Furthermore, AFI-color (green, ambiguous or purple) was scored as well as the Kudo classification by NBI and magnification.[36]

During inspection with WLE, suspicious lesions were defined as polypoid or irregular mucosal structures, unusual ulcers and strictures. During AFI, all areas with ambiguous/purple color were considered suspicious.

Histopathological diagnosis

Biopsies were evaluated by two blinded pathologists, one of them considered a gastrointestinal expert. Biopsies were classified according to the Vienna criteria of gastrointestinal epithelial neoplasia.[37] In case of discrepancy between the pathologists, discussion led to a consensus diagnosis. Low grade (LGIN) and high-grade intraepithelial neoplasia (HGIN), as well as invasive neoplasia were defined as neoplasia; lesions diagnosed as indefinite for neoplasia were not considered neoplastic.

A significant number of biopsies showed hypermucinous serrated epithelial changes reminiscent of hyperplastic polyps, which could not be recognized as overt intraepithelial neoplasia and of which the significance is unknown. These lesions appear similar to the lesions described by Kilgore *et al* in Crohn's disease as hyperplastic-like mucosal changes (HPC).[38] The presence of these lesions was recorded separately and the term 'HPC' was adopted from the study by Kilgore *et al*.

Primary and secondary outcomes

The primary outcomes were the proportions of neoplastic lesions missed by AFI or WLE, and the accuracy of the Kudo classification assessed by NBI. Secondary outcomes were proportions of patients with missed neoplasia, patients with neoplasia detected by random biopsies only, number of false positive lesions and the accuracy of AFI-color.

Statistical methods

Continuous data were represented by their mean ± standard deviation (SD) or by their median ± interquartile range (IQR) when appropriate. Differences were tested by the student's t-test or Wilcoxon rank test respectively. Proportions were compared by the Chi-square or Fisher's exact test.

Since lesions were sampled immediately after detection, only missed lesions could be detected by the second technique, which precludes a paired analysis. In order to compare AFI and WLE for neoplasia detection, we therefore compared the number of neoplastic lesions detected by the second inspection divided by the total number of detected neoplastic lesions (first ánd second inspection), representing the miss-rate for each technique. These proportions were compared using Fisher's exact test. The proportions of patients with missed neoplasia were compared in the same manner.

Contingency tables were used to determine sensitivity, specificity and overall accuracy (95%-confidence intervals) of the Kudo classification by NBI and of the AFI-color. Histopathology was used as gold standard.

The number of false positive lesions during AFI and WLE (suspicious lesion on endoscopy but negative for neoplasia on histology) was compared using the paired Wilcoxon rank test.

Sample-size

When previously applying identical inclusion criteria, the neoplasia prevalence was 29% and the neoplasia miss-rate for WLE was 54% (per lesion analysis).[11] We assumed the neoplasia miss-rate for AFI to be 10% and expected patients with neoplasia to have an average of 2.5 lesions. This resulted in a sample size of 50 patients (α-error 0.05 and β-error 0.2).

Results

Patient characteristics

From April 2005-November 2006 a total of 58 patients gave informed consent. Eight patients were excluded because of poor bowel preparation (n=3) or endoscopically active disease (n=5). Therefore, 50 patients were randomized for tandem colonoscopy; in 25 patients the first inspection was done with AFI, in the other 25 patients WLE was used first (Figure 2). Baseline characteristics are summarized according to randomization in Table 1. The 3 endoscopists performed 18, 18 and 14 procedures each and no complications occurred in any of the patients.

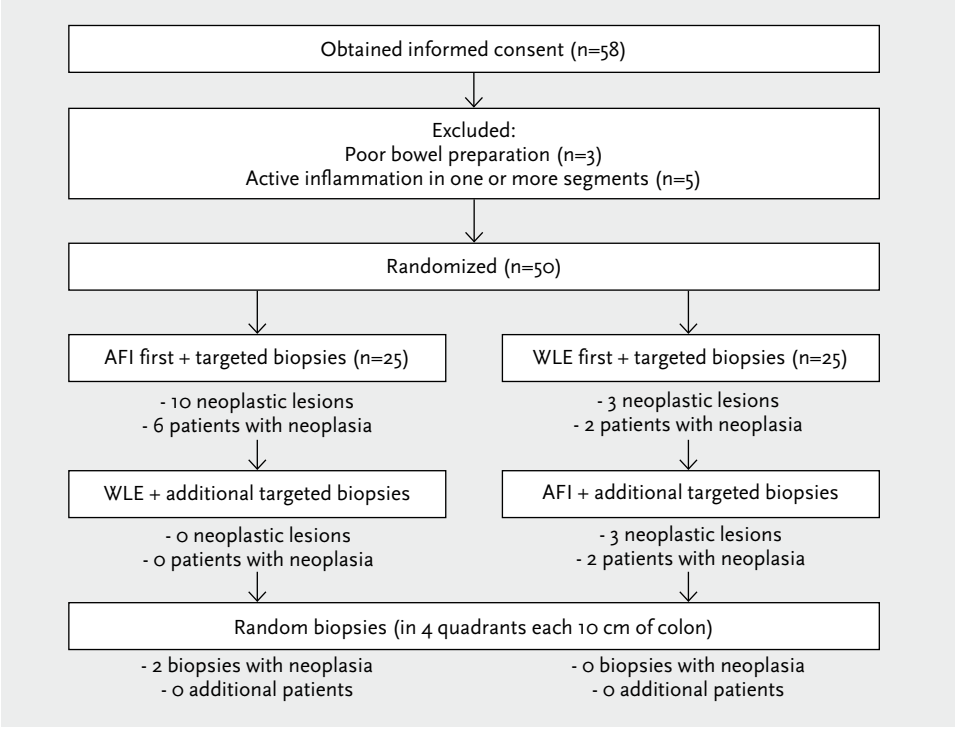

Figure 2: Study design and flow chart of patients who obtained informed consent during the study. The number of detected neoplastic lesions and number of patients with neoplasia are summarized per randomization group. During WLE, 3 neoplastic lesions (50%) were missed which were detected by AFI. Two random biopsies showed neoplasia after inspection with AFI and subsequent WLE; these were found in a patient in whom AFI already detected three areas of flat neoplasia.

	randomization		p-value
	AFI first (n=25)	WLE first (n=25)	
Male n (%)	17 (68%)	14 (56%)	0.382
Mean age – years (SD)	50 (11)	51 (13)	0.889
Median UC duration - years (IQR)	16 (12-21)	14 (12-20)	0.651
History of neoplasia n (%)	3 (12%)	4 (16%)	1.0
Primary sclerosing cholangitis n (%)	3 (12%)	4 (16%)	1.0
Disease modifying drug use n (%)	23 (92%)	18 (72%)	0.138
Good colon preparation n (%)	14 (56%)	20 (80%)	0.069

Table 1: Baseline patient characteristics among patients randomly assigned to AFI and WLE as first examination technique.

Duration of colonoscopy and number of suspicious lesions

The mean inspection time for AFI was 8.1 (±2.7) minutes and for WLE 7.9 (± 3.9) minutes (p=0.757). During examination with AFI first, 37 suspicious lesions were detected (16 patients); second inspection with WLE added 7 lesions (7 patients). Inspection with WLE first yielded 34 suspicious lesions (18 patients) and subsequent AFI added 20 lesions (11 patients).

Neoplasia in targeted biopsies

AFI first: Among the 25 patients assigned to inspection with AFI first, 10 neoplastic lesions were detected with AFI (6 patients). Subsequent examination with WLE detected no additional neoplasia (Figure 2). No lesions indefinite for neoplasia were found in this group.

The first patient had 3 flat elevated lesions of 4-10cm throughout the colon, all harboring LGIN; subsequent colectomy demonstrated LGIN and focal HGIN at the same colonic sites as during colonoscopy. The second patient also had 3 flat elevated lesions, all 4mm in size revealing LGIN. Given the small size, these lesions were considered as adenoma-like masses (ALMs) and removed by endoscopic mucosal resection; repeat colonoscopy within one year again revealed LGIN. Three other patients harbored one flat lesion each (of 3, 5 and 17mm) with LGIN, which were considered as ALMs although one of these patients had 3 areas of flat LGIN detected within one year. The last patient harbored a 10cm irregular area with focal HGIN, which had already been noticed on introduction of the endoscope. This patient underwent colectomy in which no neoplasia could be demonstrated; after reviewing the original biopsies there was no doubt about the initial diagnosis of HGIN.

WLE first: Among 25 patients assigned to WLE first, 3 neoplastic lesions were detected with WLE (2 patients). Subsequent inspection with AFI added 3 neoplastic lesions (2 patients). No lesions indefinite for neoplasia were found.

The first patient with WLE detected neoplasia had a 6mm flat elevated lesion with LGIN, considered as ALM. The second patient harbored a 6cm nodular flat lesion in the cecum and a 1cm polypoid lesion in the descending colon both revealing LGIN. Total colectomy in that patient only confirmed LGIN in the cecum. All WLE detected neoplastic lesions were colored purple on AFI. White light endoscopy failed to detect 3 lesions with LGIN in 2 patients, which

were detected by AFI during the second inspection. In one patient 2 sessile lesions of 3mm were missed in the sigmoid colon revealing LGIN; in the other patient a sessile lesion of 5mm was missed revealing LGIN. Repeat colonoscopy within one year again revealed LGIN at other areas in both patients with missed neoplasia.

Of the 10 patients with neoplasia, 3 were referred to our hospital to confirm the presence of neoplasia, 3 had a history of ALM resection at our own institution and one had previous neoplasia in random biopsies. Only one patient with neoplasia had a history of PSC. There were no differences in neoplasia detection between endoscopists or between early or late ETMI procedures.

Neoplasia in random biopsies

In total, 1992 random biopsies were taken among 50 patients. In 2 biopsies (0.1%) histopathology revealed LGIN, both taken in a patient in whom AFI already demonstrated 3 neoplastic lesions, confirmed by colectomy. The first positive random biopsy was taken in an AFI-purple region of which targeted biopsies revealed inflammation on histology; the second was taken just proximal to an AFI detected neoplasia. Furthermore, 8 random biopsies showed mucosal changes indefinite for neoplasia (4 patients), 252 inflammation, 100 HPC and 1632 showed no significant changes.

Two of the 4 patients with indefinite neoplasia in random biopsies underwent colectomy for neoplasia in targeted biopsies as well; in the remaining 2 patients with indefinite neoplasia, three subsequent follow-up colonoscopies did not reveal any neoplasia.

Neoplasia miss-rates

The percentage of missed neoplastic lesions was 0% (0/10) for AFI and 50% (3/6) for WLE (p=0.036). The percentage of patients with neoplasia missed by AFI was 0% (0/6) versus 50% (2/4) for WLE (p=0.133).

When including neoplasia detected by random biopsies (n=2), corresponding neoplasia miss-rates for AFI and WLE were 17% (2/12) and 50% (3/6) respectively (p=0.268).

False positive findings

During inspection with AFI, a total number of 44 false positive lesions were found compared to 38 during WLE (p=0.882). Of all false positive lesions by AFI, histology showed inflammation in 22 lesions (50%) and HPC in 2 (4.5%). Histology of false positive lesions by WLE showed inflammation in 6 lesions (16%) and HPC in 13 (34%). All other false positive lesions showed no significant changes on histology.

Findings on NBI and AFI compared to histology

Fifty-seven suspicious lesions were found with AFI and 41 with WLE, which were al inspected by NBI before taking biopsies. Of the 16 histologically proven neoplastic lesions, 4 showed non-neoplastic pit patterns (type I-II) on NBI; of the 82 remaining non-neoplastic lesions, 16 demonstrated neoplastic pit patterns (type III-V) due to chronic inflammation. The sensitivity, specificity and overall accuracy of the Kudo classification by NBI were 75% (95%-CI: 51-90), 81% (71-88) and 80% (71-86) respectively (Table 2).

		Histopathology		
		Neoplastic	Non neoplastic	
NBI Classification	Suspicious	12	16	28 PPV 43%
	Non-suspicious	4	66	70 NPV 94%
		16 Sensitivity 75%	82 Specificity 81%	98

Table 2: Correspondence between the Kudo pit pattern classification (by NBI) and histopathology (gold standard) of all detected lesions. Kudo pit pattern type I-II was considered as non-suspicious and Kudo type III-V as suspicious for neoplasia.
PPV *positive predictive value*, NPV *negative predictive value*

All suspicious lesions were also scored for color on AFI. Considering AFI-green as non-neoplastic and AFI-purple/ambiguous as neoplastic the sensitivity, specificity and overall accuracy of AFI-color were 100% (81-100), 42% (31-52) and 51% (41-61) respectively.

When combining AFI and NBI findings, thereby considering AFI-green as well as all AFI-ambiguous lesions with Kudo type I-II on NBI as negative for neoplasia, the sensitivity, specificity and overall accuracy were 100% (81-100), 72% (61-81) and 77% (67-84). This combined use of AFI plus NBI could hypothetically have prevented taking targeted biopsies of 59 lesions (60%) without leaving neoplasia *in situ*.

Discussion

This is the first randomized study comparing AFI to WLE for detection and NBI for classification of neoplasia in patients with longstanding UC. We have demonstrated that ETMI is feasible for colonic use, provided that the colon is properly prepared and not actively inflamed. Insufficient bowel preparation and active inflammation interrupt tissue autofluorescence, resulting in discoloration on AFI and resembling neoplasia.[39-42] Active inflammation is an exclusion criterion for surveillance in any UC patient, since histopathological distinction between inflammation and neoplasia can be extremely difficult or even impossible in this situation.[43, 44] Disrupted autofluorescence due to residual feces may explain why patients allocated to AFI inspection first were less often judged to have good colon preparation as shown in Table 1 (p=0.069). However, insufficient bowel preparation not uniquely precludes scrutinizing the colon during AFI, but this is true for WLE as well. When getting accustomed to AFI during the study period, the percentage colon preparation judged as good increased from 22% to 75% (early *vs.* late procedures; p=0.017) among patients allocated to AFI first.

The present study demonstrated a neoplasia miss-rate of 50% for WLE compared to a miss-rate of 0% for AFI (p=0.036). Although all missed neoplastic lesions were considered ALMs and have been treated by endoscopic mucosal resection, repeat colonoscopy within one year confirmed the presence of neoplasia in these patients. Debate still exists about whether ALMs should prompt colectomy or can safely be removed by endoscopic resection.[45] An important

consideration is whether ALMs are located within or proximal to the extent of inflamed colon. All included patients had pancolitis and therefore hold a higher risk for cancer development, even if neoplasia was considered as an ALM. Since only intraepithelial neoplasias have been found in our study, the value of AFI for the detection of early invasive cancers could not be evaluated.

We found a high prevalence of neoplasia in our study population, probably caused by the tertiary referral function of our institution, selection of patients with pancolitis, and inclusion of patients with a history of neoplasia without colectomy. This high prevalence at our institution has been demonstrated before in a study comparing standard WLE and NBI, revealing a neoplasia miss-rate of 42% for WLE.[11] The even higher miss-rate for high resolution WLE in the present study suggests that AFI may correctly visualize a significant part of neoplasia, which remains invisible for WLE. Despite appropriate powering of the present study, however, the relatively small sample-size prompts confirmation of these results in larger trials.

In a retrospective study, standard colonoscopy missed 39% of all neoplasia which was only detected by additional random biopsies.[10] The authors included neoplasia detected by random biopsies in the denominator for measuring sensitivity and no additional imaging techniques were used, as opposed to our study. The neoplasia miss-rate for high resolution WLE in our study was 50%, only missing lesions that were subsequently visualized by AFI. Random biopsies did not add neoplasia in any of these cases. Among patients examined with AFI first and WLE second, two random biopsies revealed neoplasia, which may be analyzed as neoplasia missed by both AFI ánd WLE. When including positive random biopsies, the neoplasia miss-rate of AFI was 17% (2/12), which is still lower than current practice. Two remarks must be made concerning those random biopsies revealing 'invisible' neoplasia. First, the positive biopsies were both derived from one patient in whom AFI already demonstrated three 'visible' neoplastic lesions. Second, one out of two biopsies was taken in an AFI-purple region and one was taken adjacent to an AFI visualized neoplasia. The presence of neoplasia in biopsies taken adjacent to visible neoplasia merely reflects the nature of dysplasia associated lesions or masses instead of missed neoplasia.[46] Therefore, we conclude that random biopsies did not add relevant neoplasia.

The need for random biopsies in addition to the use of advanced imaging techniques has been questioned several times.[11, 15, 47] Random biopsies have a low yield of neoplasia when used next to CE.[16] Also in the present study the diagnostic yield of random biopsies was low, only finding neoplasia in 0.1% of biopsies. Random biopsies increase examination time and pathology costs, may distract the endoscopist from scrutinizing the colon and have a risk of bleeding. The fact that all neoplasia in this study was colored purple on AFI and that random biopsies did not detect neoplasia in additional patients, underlines the question whether these biopsies should be taken if AFI reveals a normal appearing 'green' colon.

The high yield of neoplasia with AFI must be weighed against the results of CE in previous studies.[14-17] In our experience, the use of AFI is easier and more convenient for both patients and endoscopists. Only pressing a button in stead of applying dyes to the mucosa will provide enhanced imaging, thereby saving time. We experienced AFI to have a lower resolution compared to high resolution WLE, although it served well as red flag technique. The need for high resolution might be questioned in the circumstance where AFI correctly visualized all neoplasia by coloring purple. The results of the present study support the use of AFI, but the small sample-

size and expert setting prompt larger trials comparing AFI and CE in general practice to provide practical recommendations.

Although AFI has demonstrated a high rate of false positive findings in Barrett's oesophagus, the present study showed that there was no difference in false positive rate among AFI or WLE in UC surveillance.[32, 41, 48] As known from previous research, active inflammation colors purple during AFI.[42] The present study demonstrated purple coloration of chronic inflammation as well, which was the main cause of false positive finding for AFI, whereas hyperplastic-like mucosal change (HPC) was the most notable false positive finding for WLE. These HPCs might be similar to the lesions described before in Crohn's disease, in which an association was shown between the prevalence of HPC and concomitant neoplasia.[38] We could not demonstrate a correlation between HPC and neoplasia in our study (results not shown), although prospective evaluation and molecular analysis of these lesions might be an interesting subject for future studies.

Confocal endomicroscopy has recently proven to be a good candidate to reduce false positive biopsies and to increase the effectiveness of surveillance, although this technique requires expensive equipment and special training.[15, 49] In the present study the Kudo classification with NBI had an unsatisfactory specificity and sensitivity of 81% and 75%, figures which are comparable to a recent report on pit pattern analysis with CE.[49] On the contrary, all neoplasias were colored purple on AFI. Therefore, the sensitivity of NBI could be improved by adding the information about AFI-color in the rule for defining a positive test result. All AFI-green lesions and all AFI-ambiguous lesions with Kudo type I-II on NBI revealed non-neoplastic histology, suggesting that those lesions can safely be left *in situ*. Prospective studies should validate this finding, which might lead to a sensitivity of 100% and specificity of 77%.

Instead of Kudo pit pattern analysis with NBI, the vascular intensity pattern has also been used for differentiation of lesions in the non-inflamed colon.[24-26] In a recent study by East *et al*, the accuracy of the Kudo classification was comparable to the vascular intensity pattern in the non-inflamed colon.[27] However, the value of vascular pattern analysis in patients with UC is still unknown.

In summary, ETMI appears a feasible option for colonoscopic surveillance of patients with UC, although additional studies are imperative. In the present trial AFI reduced the neoplasia miss-rate to 0% and made random biopsies become superfluous. For the endoscopic classification of lesions, NBI had a sensitivity of only 75% but the additional information about color obtained by AFI increased the sensitivity to 100%. Larger studies in non-expert setting are needed to confirm these results, as well as comparative trials with chromoendoscopy and confocal endomicroscopy in order to demonstrate which technique performs better and is more convenient for the detection and classification of neoplasia.

>> For figures 1a-d; see page 140-141

Reference List

1. Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 2004;126(6):1634-48.
2. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48(4):526-35.
3. Collins P, Mpofu C, Watson A et al. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2006;(2):CD000279.
4. Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11(3):314-21.
5. Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002;51 Suppl 5:V10-V12.
6. Labianca R, Beretta GD, Mosconi S et al. Colorectal cancer: screening. Ann Oncol 2005;16 Suppl 2:ii127-ii132.
7. Ransohoff DF, Riddell RH, Levin B. Ulcerative colitis and colonic cancer. Problems in assessing the diagnostic usefulness of mucosal dysplasia. Dis Colon Rectum 1985;28(6):383-8.
8. Tytgat GN, Dhir V, Gopinath N. Endoscopic appearance of dysplasia and cancer in inflammatory bowel disease. Eur J Cancer 1995;31A(7-8):1174-7.
9. Rutter M, Bernstein C, Matsumoto T et al. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. Endoscopy 2004;36(12):1109-14.
10. Rubin DT, Rothe JA, Hetzel JT et al. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? Gastrointest Endosc 2007;65(7):998-1004.
11. Dekker E, van den Broek FJ, Reitsma JB et al. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39(3):216-21.
12. Rutter MD, Saunders BP, Wilkinson KH et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006;130(4):1030-8.
13. Dekker E, Fockens P. New imaging techniques at colonoscopy: tissue spectroscopy and narrow band imaging. Gastrointest Endosc Clin N Am 2005;15(4):703-14.
14. Kiesslich R, Fritsch J, Holtmann M et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124(4):880-8.
15. Kiesslich R, Goetz M, Lammersdorf K et al. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132(3):874-82.
16. Rutter MD, Saunders BP, Schofield G et al. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53(2):256-60.
17. Hurlstone DP, Sanders DS, Lobo AJ et al. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005;37(12):1186-92.
18. Gono K, Obi T, Yamaguchi M et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004;9(3):568-77.

19. Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38(1):76-81.
20. Gheorghe C. Narrow-band imaging endoscopy for diagnosis of malignant and premalignant gastrointestinal lesions. J Gastrointestin Liver Dis 2006;15(1):77-82.
21. East JE, Suzuki N, von HA et al. Narrow band imaging with magnification for dysplasia detection and pit pattern assessment in ulcerative colitis surveillance: a case with multiple dysplasia associated lesions or masses. Gut 2006;55(10):1432-5.
22. Matsumoto T, Kudo T, Jo Y et al. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc 2007;66(5):957-65.
23. Machida H, Sano Y, Hamamoto Y et al. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36(12):1094-8.
24. Su MY, Hsu CM, Ho YP et al. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. Am J Gastroenterol 2006;101(12):2711-6.
25. Chiu HM, Chang CY, Chen CC et al. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2006;56(3):373-9.
26. Hirata M, Tanaka S, Oka S et al. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007;65(7):988-95.
27. East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66(2):310-6.
28. DaCosta RS, Wilson BC, Marcon NE. Optical techniques for the endoscopic detection of dysplastic colonic lesions. Curr Opin Gastroenterol 2005;21(1):70-9.
29. Messmann H, Endlicher E, Freunek G et al. Fluorescence endoscopy for the detection of low and high grade dysplasia in ulcerative colitis using systemic or local 5-aminolaevulinic acid sensitisation. Gut 2003;52(7):1003-7.
30. Ochsenkuhn T, Tillack C, Stepp H et al. Low frequency of colorectal dysplasia in patients with long-standing inflammatory bowel disease colitis: detection by fluorescence endoscopy. Endoscopy 2006;38(5):477-82.
31. Kara MA, Bergman JJ. Autofluorescence imaging and narrow-band imaging for the detection of early neoplasia in patients with Barrett's esophagus. Endoscopy 2006;38(6):627-31.
32. Curvers WL, Singh R, Song LM et al. Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system. Gut 2008;57(2):167-72.
33. Matsumoto T, Moriyama T, Yao T et al. Autofluorescence imaging colonoscopy for the diagnosis of dysplasia in ulcerative colitis. Inflamm Bowel Dis 2007;13(5):640-1.
34. Lichtiger S, Present DH, Kornbluth A et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330(26):1841-5.
35. Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37(6):570-8.

36. Kudo S, Rubio CA, Teixeira CR et al. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33(4):367-73.
37. Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47(2):251-5.
38. Kilgore SP, Sigel JE, Goldblum JR. Hyperplastic-like mucosal change in Crohn's disease: an unusual form of dysplasia? Mod Pathol 2000;13(7):797-801.
39. Brand S, Stepp H, Ochsenkuhn T et al. Detection of colonic dysplasia by light-induced fluorescence endoscopy: a pilot study. Int J Colorectal Dis 1999;14(1):63-8.
40. Haringsma J, Tytgat GN, Yano H et al. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53(6):642-50.
41. Kara MA, Peters FP, ten Kate FJ et al. Endoscopic video autofluorescence imaging may improve the detection of early neoplasia in patients with Barrett's esophagus. Gastrointest Endosc 2005;61(6):679-85.
42. Matsumoto T, Kudo T, Yao T et al. Autofluorescence imaging colonoscopy in ulcerative colitis: Comparison with conventional and narrow-band imaging colonoscopy. Digestive Endoscopy 2007;19(SUPPL. 1):S139-S144.
43. Riddell RH, Goldman H, Ransohoff DF et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol 1983;14(11):931-68.
44. Rubin DT, Turner JR. Surveillance of dysplasia in inflammatory bowel disease: The gastroenterologist-pathologist partnership. Clin Gastroenterol Hepatol 2006;4(11):1309-13.
45. Bernstein CN. ALMs versus DALMs in ulcerative colitis: polypectomy or colectomy? Gastroenterology 1999;117(6):1488-92.
46. Hurlstone DP, Sanders DS, Atkinson R et al. Endoscopic mucosal resection for flat neoplasia in chronic ulcerative colitis: can we change the endoscopic management paradigm? Gut 2007;56(6):838-46.
47. Rutter MD, Saunders BP, Wilkinson KH et al. Most dysplasia in ulcerative colitis is visible at colonoscopy. Gastrointest Endosc 2004;60(3):334-9.
48. Kara MA, Peters FP, Fockens P et al. Endoscopic video-autofluorescence imaging followed by narrow band imaging for detecting early neoplasia in Barrett's esophagus. Gastrointest Endosc 2006;64(2):176-85.
49. Hurlstone DP, Kiesslich R, Thomson M et al. Confocal chromoscopic endomicroscopy is superior to chromoscopy alone for the detection and characterisation of intraepithelial neoplasia in chronic ulcerative colitis. Gut 2008;57(2):196-204.

CHAPTER 11

Narrow-band imaging versus high definition endoscopy for the diagnosis of neoplasia in ulcerative colitis

Frank J.C. van den Broek
Paul Fockens
Susanne van Eeden
Pieter C.F. Stokkers
Cyriel Y. Ponsioen
Johannes B. Reitsma
Evelien Dekker

Submitted

ABSTRACT

Background & aims: Controversy exists about which colonoscopic technique is most sensitive for the diagnosis of neoplasia in patients with ulcerative colitis (UC). We compared new-generation narrow-band imaging (NBI) to high-definition endoscopy (HDE) for the detection of neoplasia and evaluated NBI for the differentiation of neoplastic from non-neoplastic mucosa.
Design: Randomized cross-over trial.
Setting: Academic Medical Centre Amsterdam.
Patients: Patients with UC underwent both NBI and HDE colonoscopy in random order with at least 3 weeks between the two procedures which were performed by different endoscopists. Lesions detected during the first examination were left in-situ in order to enable detection during the second examination also.
Interventions: NBI and HDE colonoscopy.
Main outcome measures: Neoplasia detection and diagnostic accuracy of NBI for differentiating neoplastic from non-neoplastic mucosa by using the Kudo classification and vascular pattern intensity (VPI).
Results: Twenty-five patients were randomized to HDE first and 23 to NBI. Of 16 neoplastic lesions, 11 (69%) were detected by HDE and 13 (81%) by NBI (p=0.727). Of 11 patients with neoplasia, 9 (82%) were diagnosed by HDE and 8 (73%) by NBI (p=1.0). The sensitivity, specificity and accuracy of the Kudo classification were 76%, 66% and 67%. Corresponding figures for VPI were 80%, 72% and 73%.
Conclusion: NBI does not improve the detection of neoplasia in patients with UC compared to HDE. In addition, NBI proves unsatisfactory for differentiating neoplastic from non-neoplastic mucosa. Studies comparing chromoendoscopy with NBI may reveal which technique is best for the diagnosis of neoplasia in UC patients.

Trialregister.nl Identifier: ISRCTN56671833

Introduction

Chronic inflammation of the colonic mucosa in patients with ulcerative colitis (UC) can lead to intraepithelial neoplastic changes that may ultimately develop into colorectal cancer.[1, 2] Colonoscopic surveillance is recommended in these patients in order to detect intraepithelial neoplasia in an early and curable stage.[3] However, UC-associated neoplasia is difficult to visualize as it mainly develops in inconspicuous mucosa resembling inflamed tissue.[4, 5] Guidelines therefore recommend taking random biopsies of apparently normal tissue in addition to targeted biopsies of suspicious lesions.[6, 7]

Several endoscopic techniques have been evaluated with respect to their possibility to improve the detection of neoplasia in UC patients, as well as with respect to their ability to differentiate between neoplastic and non-neoplastic tissue in-vivo.[8] Chromoendoscopy (CE) has shown to improve the diagnosis of neoplasia in two randomized trials and in several observational studies when compared to conventional white light endoscopy.[9-13] Kiesslich *et al* demonstrated a 3-4.5 fold increase in neoplasia detection by using CE. In addition, mucosal pit pattern analysis enabled differentiation between neoplasia and non-neoplastic histology with an overall accuracy of 93%. Nevertheless, implementation of CE in clinical practice has hampered since it is labour-intensive, time-consuming and requires additoinal expertise and experience.

Narrow band imaging (NBI) is a push-on-a-button technique that utilizes optical light filters in order to enhance mucosal details without dyes.[14-16] In a previous study NBI failed to improve the detection of neoplasia; however, a first generation prototype NBI-system was used which rendered low quality NBI-images.[17] Optical improvements and high-definition technology have been inserted in the currently commercially available NBI-system which has never been evaluated for UC surveillance.

Next to these advanced endoscopic techniques, continuous technical improvements have led to an enhanced endoscopic image during conventional white light endoscopy as well. Currently available endoscopes contain charge coupled devices with >800,000 pixels (i.e. high-definition). These endoscopes provide much clearer images than the conventional colonoscopes, which contained <400,000 pixels.

The aims of this study were to compare the new generation NBI versus high-definition endoscopy (HDE) for the detection of neoplasia in UC patients and to evaluate NBI for the real-time differentiation of neoplasia from non-neoplastic mucosa.

Methods

Patients

Patients with UC who were scheduled for colonoscopic surveillance at the Academic Medical Centre, University of Amsterdam, were invited for participation. The inclusion criteria were: disease history ≥8 years, endoscopically proven colitis proximal to the splenic flexure in the past with currently inactive disease defined by a Truelove and Witts activity index of ≤2.[18] An objective diagnosis of UC was also mandatory, based on former endoscopic and histopathological findings. Exclusion criteria were: non-correctable coagulopathy, age ≤18 years, insufficient

bowel preparation for accurate mucosal inspection and inability to provide informed consent. The study was approved by our institutional review board.

Endoscopic equipment

Colonoscopies were performed using the Lucera system with sequential red-green-blue illumination (CV-H260, Olympus, Tokyo, Japan) incorporating HDE, NBI and optical magnification (100x). Switching between these imaging modes was done by pressing a button on the shaft of the endoscope (CF-H260, Olympus, Tokyo, Japan). High-definition monitors (1080i) were used during the procedures.

Study design and randomization

This was a randomized cross-over trial in which all patients underwent colonoscopy twice on different occasions, once with NBI and once with HDE in randomized order (see figure 1). A time interval of at least 3 weeks between the two procedures was chosen to allow healing of biopsy sites, so that sampling sites could not be recognized during the second examination. Apart from taking biopsies, no lesions were removed during the first examination. The two procedures were performed by different, experienced endoscopists, who were blinded for the endoscopic and histological findings of the first examination. Randomization was done by opening opaque sealed envelopes (containing notes with either 'HDE first' or 'NBI first' in a 1:1 ratio) once the cecum had been reached during the first procedure.

Colonoscopy

Patients were prepared with four litres of hypertonic polyethylene glycol solution (Kleanprep, Norgine Inc., Amsterdam, the Netherlands) and underwent both colonoscopies under conscious sedation with midazolam and/or fentanyl. The level of bowel preparation was scored as poor (<90% of colonic mucosa visible), good (90-99%) or excellent (100%). In case the bowel preparation was scored as poor, the patient was excluded.

The endoscope was first advanced to the cecum using the HDE mode in all patients. Lesions found during the insertion phase were neglected and left unharmed. When performing the NBI examination, the endoscope was switched to the NBI-mode once the cecum had been reached. Cecal intubation was confirmed by identification of the appendiceal orifice and ileocecal valve or by intubation of the ileum. At the start of withdrawal, 20 mg butyl scopolamine was given to reduce colonic motility and repeated at the discretion of the endoscopist.

During withdrawal from the cecum, the colon was scrutinized for the presence of dysplasia-associated lesions or masses (DALM's), mucosal irregularities, ulcers and strictures. Detected lesions were classified according to the macroscopic classification of early gastrointestinal neoplasia.[19] In addition, the size (mm), segment of the colon (cecum, ascending, transverse, descending, sigmoid colon and rectum) and distance from the anus (cm) of each lesion were recorded. Digital still images of all detected lesions were taken in both HDE and NBI mode for reference. If lesions were detected during HDE, the imaging mode was switched briefly to NBI in order to take these images. During NBI-inspection of each lesion, its pit pattern (type I-V) was scored according to Kudo *et al* as well as its vascular pattern intensity (VPI; paler, same or darker than surrounding mucosa) according to East *et al*.[20] For both procedures the total procedural time (excluding time for introduction but including time for biopsies or resections) were recorded.

Biopsy protocol

During the first of the two examinations all detected lesions were only biopsied but otherwise left *in situ*. Hence all primarily detected lesions could be detected again during the second colonoscopy. Only during the second procedure it was allowed to perform endoscopic resection of lesions. Biopsy material and endoscopic resection specimens were sent for histopathological examination.

During the second colonoscopy four quadrant random biopsies were taken every 10cm of colon. Images were captured from all areas of which random biopsies were taken in order to visualize areas in which random biopsies later turned out to be positive.

Matching of lesions

Lesions that were detected during the two colonoscopies were matched between the procedures by comparing four lesion-related characteristics: size, shape, location (distance ab ano and colonic segment) and appearance on digital images. Matching of lesions was done by an independent observer who reviewed findings and images made during both colonoscopies and who was blinded for histology at the time of matching lesions. Differences up to 2mm in size and up to 10cm in distance ab ano were regarded as equal. Lesions were considered as definitely matched in case all 4 lesion-related characteristics corresponded between the procedures; otherwise lesions were considered as non-matched.

Histopathology

Biopsy material and endoscopic resection specimens were processed using standard procedures and evaluated by two pathologists, one of whom was a gastrointestinal expert. The pathologists were blinded for detection technique and endoscopic diagnosis. Histology was classified according to the Vienna criteria of gastrointestinal epithelial neoplasia, ranging from no intraepithelial neoplasia to invasive neoplasia.[21]

Outcome measures

The primary outcome measure was the neoplasia detection rate of NBI versus HDE. Secondary outcome measure was the sensitivity, specificity and overall accuracy of NBI for the differentiation of neoplasia and non-neoplastic mucosa (both Kudo classification and VPI). The histological diagnosis was used as reference standard to calculate accuracy measures for the differentiation between neoplastic and non-neoplastic lesions.

Statistical analysis and sample size

Two main analyses were carried out to compare NBI and HDE: per-lesion and per-patient analysis (i.e. each neoplastic lesion or each patient with neoplasia served as outcome measure). For these analyses we compared the detection of neoplasia by targeted biopsies only. Testing for a difference in detection was done by comparing the number of discordant lesions, i.e. the number of lesions detected by NBI but missed by HDE *versus* the number of lesions detected by HDE but missed by NBI using the McNemar test.

The accuracies of the Kudo classification and VPI were calculated by comparing their endoscopic classification with histopathology (i.e. reference standard). A pit pattern type I/II was

considered non-neoplastic, as well as a VPI-score of paler/same. The sensitivity, specificity and overall accuracy of both classifications were compared by examining the number of discordant findings using the McNemar test. The Standards for Reporting of Diagnostic Accuracy (STARD) initiative was used for reporting of the diagnostic test accuracy.[22]

For sample size calculation we assumed that the yield of NBI for detecting neoplasia would be as high as CE, because both techniques enhance mucosal morphology.[23] Based on previous CE studies, we estimated a 3-fold increased neoplasia detection with NBI.[9, 11, 12] The percentage of patients with neoplasia on HDE was assumed to be 7.5%. A power of 90% and a significance level of 5% were selected, which resulted in a sample size of 49 patients.

Results

Patient characteristics and colonoscopy findings

Between December 2006 and July 2009 a total of 53 patients signed informed consent; 2 were excluded due to poor bowel preparation, 2 patients were unwilling to undergo the second colonoscopy, and 1 had endoscopically active pancolitis despite a low disease activity index. Hence, 48 patients underwent both colonoscopies of whom 25 were randomized to HDE first and 23 to NBI first (figure 1). None of the participants experienced complications.

Patient characteristics are presented in table 1. Because of the cross-over study design each patient could serves as his or her own control, thereby preventing any bias due to differences in patient characteristics by chance (such as can occur in a study with a parallel randomized design). The median examination time for NBI procedures was 26 minutes (12-86) versus 21 minutes (10-65) for HDE (paired Wilcoxon test; p=0.075).

During NBI colonoscopies, a total number of 105 lesions were identified and sampled versus 77 during HDE (p=0.048). Of those lesions, 19 were detected during both NBI and HDE. Hence, a total of 163 lesions were found during one or both of the two procedures within 42 patients (matched lesions that were found during both procedures were counted only once). The mean lesion size was 9.9mm (median 7.0; range 1-85) and 67 (41%) were ≤5mm. Eighty-nine lesions (55%) were located proximal to the splenic flexure; and 120 (74%) were macroscopically flat.

From 7 lesions no material for histology was retrieved, 19 lesions showed normal colonic mucosa, 47 hyperplastic changes, 29 reactive epithelial changes, 1 chronic inflammation, 7 active inflammation, 17 indefinite for neoplasia, 14 sessile serrated adenoma, 21 low-grade intraepithelial neoplasia (LGIN) and 1 high-grade IN. No invasive neoplastic lesions were found.

During the first of the two colonoscopies, 44 small lesions (27%) were completely removed by the biopsy forceps (due to diminutive size) and hence could not be detected during the second colonoscopy. Most of these removed small lesions (n=33; 75%) were removed during HDE examination. Five of these lesions were LGINs (4 removed during HDE first) and 1 was a HGIN (removed during HDE first). All primarily removed lesions were excluded from the main (paired) analysis, leaving 119 lesions for the comparison of HDE *vs.* NBI.

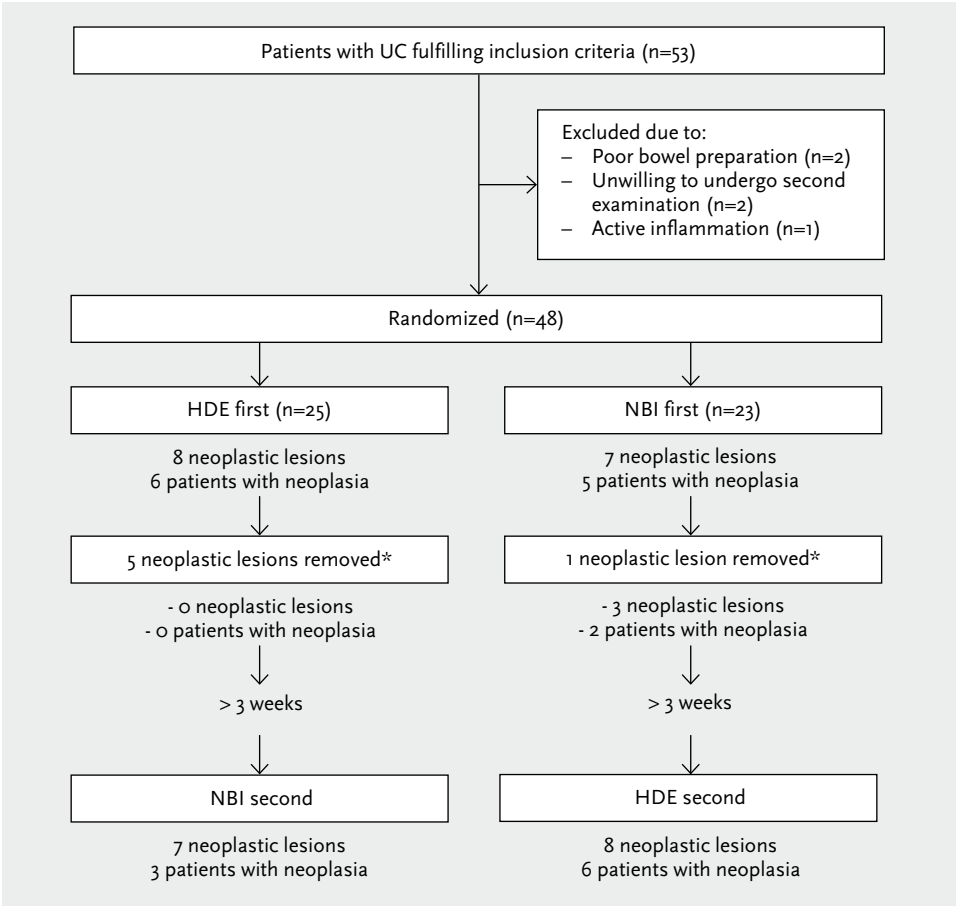

Figure 1: Flow chart of randomized cross-over trial with paired data-analysis. Lesions that were detected during the first examination (with either high-definition endoscopy or narrow-band imaging) were sampled by a biopsy forceps but largely left in situ, in order to enable detection during the second examination as well.

** Diminutive lesions, e.g. <5mm, that were completely removed by the biopsy forceps could not be detected again during the second examination.*

Demographic	
Mean age, yrs (SD)	56 (11)
Male	35 (73%)
Mean UC duration, yrs (SD)	23 (9.7)
Personal history of neoplasia	
No previous endoscopies	4 (8%)
Low-grade intraepithelial neoplasia	7 (15%)
High-grade intraepithelial neoplasia	2 (4%)
Invasive neoplasia	0
Primary sclerosing cholangitis	8 (17%)
Family history of colorectal cancer	7 (15%)
Anti-inflammatory drug use	39 (81%)
Mean duration of anti-inflammatory drug use, yrs (SD)	17 (12)
Number of previous neoplasias (mean nr per patient)	18 (0.38)
Bowel preparation	
Excellent – First colonoscopy	27 (56%)
Excellent – Second colonoscopy	30 (63%)
Examination time, median (range)	
First colonoscopy	19 (10-62)
Second colonoscopy	30 (13-86)

Table 1: demographics of all included patients

Neoplasia detection of HDE *vs.* NBI

Per-lesion analysis: Of the 119 lesions, 94 (79%) were detected by NBI and 44 (37%) by HDE (p<0.001). Of the 16 neoplastic lesions (histologically all were LGIN), 11 (69%) were detected by HDE and 13 (81%) by NBI (p=0.727); eight of the neoplastic lesions were detected by both NBI and HDE (see table 2). Seven of the neoplastic lesions were considered DALMs needing surgical intervention, either due to large size or due to the presence of neoplasia in their adjacent 'normal' mucosa. Six out of these 7 DALMs (86%) were detected by both NBI and HDE (p=1.0).

When including neoplastic lesions that were entirely removed during the first of the two colonoscopies, the total number of neoplastic lesions detected by HDE was 16 *vs.* 14 by NBI (paired Wilcoxon test; p=0.564).

Neoplasia detection capability (paired per-lesion analysis)		Narrow-band imaging	
		Detected	*Not detected*
High-definition endoscopy	*Detected*	8 (50%)	3 (19%) *
	Not detected	5 (31%) *	?

Table 2: Number of neoplastic lesions (all low-grade intraepithelial neoplasia) that were detected by either narrow-band imaging, high-definition endoscopy or both. Discordant ('shaded') cells demonstrate the number of neoplastic lesions that were detected by only narrow-band imaging or high-definition endoscopy. * McNemar test: p=0.727

Per-patient analysis: A total of 11 patients with neoplasia were left for the paired per-patient analysis, 9 (82%) of whom were diagnosed by HDE *vs.* 8 (73%) by NBI (p=1.0). When including neoplastic lesions that were entirely removed during the first colonoscopy, a total of 14 patients were diagnosed with neoplasia, 8 (57%) of whom were detected by NBI *vs.* 12 (86%) by HDE (McNemar; p=0.219).

Random biopsy protocol: A total number of 1580 random biopsies were taken, corresponding to a mean number of 33 per patient (range 15-60). Three biopsies (0.19%) demonstrated LGIN. Two of those positive random biopsies were taken just adjacent (within 10cm) of DALMs that were already visualized during both NBI and HDE inspection. The third positive random biopsy was an unequivocally confirmed LGIN that was missed by both NBI and HDE, taken in an area with increased vascularisation in a tubular colonic segment (figure 2). This patient is currently scheduled for an additional surveillance colonoscopy.

Differentiation of neoplasia and non-neoplastic mucosa

In 3 out of the 156 lesions with known histology, no Kudo classification could be assessed during colonoscopy due to unclear pit pattern (inconclusive test results); in 6 lesions no VPI could be assessed. The sensitivity, specificity and accuracy of the Kudo classification for differentiating neoplastic from non-neoplastic lesions were 76% (95%-CI: 55-89), 66% (57-73) and 67% (60-74) (see table 3). Corresponding figures for VPI were 80% (58-92), 72% (63-79) and 73% (65-79). Differences in overall accuracy between the Kudo classification and VPI were statistically non-significant (p=0.211).

NBI	Histopathology		
	Neoplasia	**Non-neoplastic**	
Kudo type III-V	16	45	PPV 26%
Kudo type I-II	5	87	NPV 95%
	Sensitivity 76%	Specificity 66%	Total: 153
VPI dark	16	37	PPV 30%
VPI light/same	4	93	NPV 96%
	Sensitivity 80%	Specificity 73%	Total: 150

Table 3: Correspondence between endoscopic real-time classification by narrow-band imaging (Kudo classification and vascular pattern intensity (VPI)) and histopathology (i.e. reference standard). Number of inconclusive test results: n=3 for Kudo and n=6 for VPI.
PPV, *positive predictive value*; NPV, *negative predictive value*

Discussion

Recently, several endoscopic studies have suggested CE to be superior to standard colonoscopy for the detection of neoplasia during UC surveillance.[9-13] The routine use of CE has however been hampered since it is time-consuming, operator-dependent, by some considered to be a messy technique and may even obscure lesions due to pools of dye. In addition, after dye-spraying it is impossible to switch back to the standard endoscopic view. Narrow-band imaging mimics CE by enhancing the mucosal surface using spectral characteristics of the endoscopic light.[14] Previous research in UC surveillance demonstrated that the use of a first generation prototype NBI-system did not improve the detection of neoplasia, possibly due to the lack of brightness and hence a too dark overall NBI image.[17] In the present study a new generation NBI-system was used with improved brightness and high-definition technology. Again NBI did not prove to be better than HDE as it detected 13 out of 16 neoplastic lesions (81%) versus 11 out of 16 (69%) with HDE (p=0.727). In the per-patient analysis HDE detected even more patients with neoplasia than NBI (9 *vs.* 8 out of 11 patients with neoplasia).

Several features of NBI and HDE may explain these disappointing results. First, the new generation NBI-system still provides a darker overall image when compared to HDE. This phenomenon forces endoscopists to inspect the colonic mucosa in close proximity instead of in overview. The longer inspection time with NBI when compared to HDE (29.6 *vs.* 24.4 minutes; p=0.039) may be explained by this issue. Secondly, the high-definition technology during white light endoscopy may level out any difference in contrast between NBI and HDE. Previous studies comparing NBI to HDE for sporadic adenoma detection also showed comparable detection rates, whereas those detection rates were higher than in historical studies using conventional colonoscopes.[24, 25] Thirdly, it must be mentioned that the NBI-system used in the present study was of the sequential illumination technology (CV-260, Olympus Inc, Tokyo, Japan), using a monochromatic charge coupled device (CCD). However, the colour CCD-chip which is used in most countries (CV-180, Olympus Inc) may lead to different results as the overall image brightness may still be different. Studies using this commercially available NBI-system should be performed as well to evaluate possible differences compared to the present study.

One may consider the limited number of included patients as a shortcoming of the present study. However, the paired nature of our study design highly increased the statistical power since each patient functioned as his or her own control. The statistical power increased even more by comparing the detection of each neoplastic lesion instead of each patient with neoplasia as outcome parameter. Our sample size therefore was sufficient to detect a difference between NBI and HDE that would be comparable to the difference that has previously been encountered for CE when compared to standard colonoscopy (3-fold increased neoplasia detection).[9] A true limitation of our study was that lesions may have become smaller during the second colonoscopy, since a biopsy was already taken during the first procedure, and hence may have been more difficult to detect. To prevent any systematic impact of this factor, we randomized the order of examinations. Furthermore, diminutive (≤5mm) lesions may even have been removed by the biopsy forceps during the first procedure and hence may have been undetectable during the second examination. Therefore we chose to exclude removed lesions from the paired analysis, which reduced the statistical power of the study. Differences between NBI and HDE in detection capa-

bility of small neoplastic lesions hence may have remained unobserved. However, the clinical significance of finding diminutive neoplastic lesions is debatable.

As our study demonstrated that NBI did not improve the detection of neoplasia in UC patients, the question arises whether we should routinely use CE for UC surveillance because two previous randomized trials demonstrated that CE was associated with a 3-4.5 fold increased neoplasia detection.[9, 10] However, both trials have been performed by the same research group from Mainz, Germany, including an endoscopist who was highly experienced in CE. No additional randomized trials have been performed at this moment; hence the results from Kiesslich *et al* should be confirmed by others. Some supporting evidence has already been provided by observational studies using either a (historical) cohort study or a back-to-back colonoscopy research design.[11-13] These study designs however prevent drawing firm conclusions for clinical recommendations. In addition, conventional white-light colonoscopes were used in these previous studies as opposed to the high-definition white-light colonoscopes in our study. Since we did not compare the new-generation NBI system to conventional colonoscopy, we are currently unable to compare the results of NBI against CE in any way. Although we expected (and powered our study) to find 7.5% of patients with neoplasia by HDE, we found 9 out of 48 patients (19%) to have neoplasia with HDE. This high yield of neoplasia may be induced by our inclusion criteria but any effect of the high-definition technology cannot be ruled out. Additional randomized trials are therefore needed, preferably comparing CE to NBI with respect to neoplasia detection in UC patients.

Our secondary objective was to evaluate NBI for the real-time differentiation of neoplastic and non-neoplastic mucosa. Accurate differentiation during ongoing endoscopy would enable selective use of targeted biopsies of endoscopically suspicious areas only. Both the Kudo classification and the VPI proved unsatisfactory for this purpose, as their respective sensitivities were only 76% and 80%, and their respective specificities 66% and 72%. If only biopsies would have been taken from lesions with either a suspicious Kudo pit pattern or suspicious VPI, still 3 out of 22 neoplastic lesions (14%) would have been left *in situ* (results not shown), which appears unacceptable.

The main explanation for the disappointing results of NBI for differentiating neoplasia from non-neoplastic tissue is that inflammatory changes in UC patients disrupt the normal colonic pit pattern and normal vascular intensity. This makes accurate differentiation between non-neoplastic and neoplastic mucosa more difficult. Previous studies support our findings that mucosal changes due to inflammation hamper the possibility to reliably differentiate between non-neoplastic (e.g. chronically inflamed) and neoplastic tissue. Assessment of the Kudo classification by NBI has previously shown to be associated with a sensitivity and specificity of 75% and 81% as well.[26] An alternative classification (honeycomb appearance, villous or tortuous pattern), introduced by Matsumoto *et al*, showed similar figures of 80% and 84% respectively.[27]

Two novel techniques have shown to be good candidates to overcome the disappointing diagnostic accuracy of NBI for differentiation purposes: autofluorescence imaging (AFI) and confocal laser endomicroscopy (CLE). Previous studies have demonstrated that the combined use of NBI together with AFI (i.e. tri-modal imaging) highly increased the diagnostic accuracy for real-time differentiation.[26, 28] By using tri-modal imaging, the sensitivity and negative predictive value among UC patients could be increased to 100% in a pilot study, a promising figure that

should be confirmed in larger studies.[26] Alternatively, CLE has shown promising results as well. Contrary to NBI and AFI, which are techniques that enable to predict histology, CLE in fact is in-vivo histology. Kiesslich *et al* showed that CLE was associated with a sensitivity and specificity of 95% and 98% in expert hands.[10] Future studies should confirm these figures and focus on learning curves among endoscopists to interpret histological images. Comparison of tri-modal imaging and CLE may then be very interesting.

Due to the current lack of an accurate technique for differentiation of neoplastic from non-neoplastic mucosa, it is still possible to detect neoplastic mucosal changes in random biopsies. In our study, 3 out of 1580 random biopsies demonstrated LGIN. Two of those positive random biopsies proved clinically non-relevant as these were found in mucosa adjacent to a visible DALM. The chance of finding neoplasia within 'normally' appearing mucosa in close proximity of a DALM is known to be high.[29] However, one LGIN in this study could not be visualized by either NBI or HDE and was only detected by random biopsies (figure 2). Therefore, the use of NBI cannot obviate the need for taking random biopsies at this moment. Since this single positive random biopsy was taken in a tubular colonic segment with augmented vascularisation, it may be postulated that random biopsies may have clinical significance in colonic segments with severe inflammatory changes (e.g. scarring, pseudo polyps, tubular colon) as suggested previously by Rutter *et al*.[30]

In summary, the present study demonstrated that NBI did not improve the detection of neoplasia in patients with longstanding UC when compared to HDE. Furthermore, the sensitivity and specificity of NBI, by using both the Kudo classification as well as the vascular pattern intensity, proved unsatisfactory for accurate real-time differentiation of neoplastic and non-neoplastic colonic mucosa. Whether the use of CE must be advocated during colonoscopic surveillance of patients with UC should be elucidated by additional head-to-head comparison studies of CE versus NBI or HDE.

>> **For figure 2; see page 141**

Reference List

1 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-535.

2 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006;130:1030-1038.

3 Collins P, Mpofu C, Watson A, Rhodes J. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2006;CD000279.

4 Rutter M, Bernstein C, Matsumoto T, Kiesslich R, Neurath M. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. Endoscopy 2004;36:1109-1114.

5 Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? Gastrointest Endosc 2007;65:998-1004.

6 Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002;51 Suppl 5:V10-V12.

7 Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:314-321.

8 Dekker E, Fockens P. New imaging techniques at colonoscopy: tissue spectroscopy and narrow band imaging. Gastrointest Endosc Clin N Am 2005;15:703-714.

9 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.

10 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.

11 Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004;53:256-260.

12 Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy 2005;37:1186-1192.

13 Marion JF, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. Am J Gastroenterol 2008;103:2342-2349.

14 Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004;9:568-577.

15 Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006;38:76-81.

16 Gheorghe C. Narrow-band imaging endoscopy for diagnosis of malignant and premalignant gastrointestinal lesions. J Gastrointestin Liver Dis 2006;15:77-82.

17 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, Van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.

18 Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, Michelassi F, Hanauer S. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841-1845.
19 Schlemper RJ, Hirata I, Dixon MF. The macroscopic classification of early neoplasia of the digestive tract. Endoscopy 2002;34:163-168.
20 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.
21 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255.
22 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ 2003;326:41-44.
23 Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004;36:1094-1098.
24 Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42-47.
25 Aschenbeck J, Adler A, Yenerim T, Mayr M, Aminalai A, Drossel R, Schroder A, Scheel M, Wiedenmann B, Rosch T. Narrow-Band Versus White-Light HDTV Endoscopic Imaging for Screening Colonoscopy: A Prospective Randomized Trial. Gastroenterology 2008.
26 van den Broek FJ, Fockens P, van eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.
27 Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. Gastrointest Endosc 2007;66:957-965.
28 van den Broek FJ, van Soest EJ, Naber AH, van Oijen AH, Mallant-Hent RC, Bohmer CJ, Scholten P, Stokkers PC, Marsman WA, Mathus-Vliegen EM, Curvers WL, Bergman JJ, van ES, Hardwick JC, Fockens P, Reitsma JB, Dekker E. Combining autofluorescence imaging and narrow-band imaging for the differentiation of adenomas from non-neoplastic colonic polyps among experienced and non-experienced endoscopists. Am J Gastroenterol 2009;104:1498-1507.
29 Hurlstone DP, Sanders DS, Atkinson R, Hunter MD, McAlindon ME, Lobo AJ, Cross SS, Thomson M. Endoscopic mucosal resection for flat neoplasia in chronic ulcerative colitis: can we change the endoscopic management paradigm? Gut 2007;56:838-846.
30 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. Gut 2004;53:1813-1816.

CHAPTER 12

Pilot study of probe-based confocal laser endomicroscopy during colonoscopic surveillance of patients with longstanding ulcerative colitis

Frank J.C. van den Broek
Jessica A. van Es
Susanne van Eeden
Pieter C.F. Stokkers
Cyriel Y. Ponsioen
Johannes B. Reitsma
Paul Fockens
Evelien Dekker

Submitted

ABSTRACT

Background: Surveillance of patients with ulcerative colitis (UC) consists of taking targeted and random biopsies, which is time-consuming and its efficiency is doubtful. The use of probe-based confocal laser endomicroscopy (pCLE) may increase efficiency.
Objective: To evaluate the feasibility and diagnostic accuracy of pCLE in UC surveillance.
Design: Prospective pilot-study
Setting: Academic Medical Centre Amsterdam
Methods: In 22 UC-patients, 48 visible lesions and 87 random areas were initially evaluated by real-time narrow-band imaging (NBI) and high-definition endoscopy (HDE). Before taking biopsies, fluorescein-enhanced pCLE was performed. All pCLE videos were scored afterwards by 2 endoscopists who were blinded for histology and endoscopy.
Outcome measures: (1) Feasibility of pCLE, expressed as: required pCLE imaging time; percentage of imaging time with clear pCLE histology; and pCLE video quality rated by 2 endoscopists. (2) Diagnostic accuracy of pCLE.
Results: The median required pCLE imaging time was 98 sec for lesions vs. 66 sec for random areas ($p=0.002$). The median percentages of imaging time with clear pCLE histology were 61% vs. 81% respectively ($p<0.001$). The pCLE video quality was rated as good/excellent in 69%. Feasibility was significantly poorer for sessile and pedunculated mobile lesions. The sensitivity, specificity and accuracy of blinded pCLE were 65%, 82% and 81%, whereas these figures were 100%, 89% and 92% for real-time endoscopic diagnosis with NBI and HDE.
Limitations: Small sample size, blinded pCLE assessment
Conclusion: This study demonstrates that pCLE for UC surveillance is feasible with reasonable diagnostic accuracy. Future research should show whether increased experience with pCLE improves its ease-of-use and whether real-time pCLE diagnosis is associated with higher diagnostic accuracy.

Introduction

As patients with ulcerative colitis (UC) have an increased risk of developing neoplasia, guidelines recommend colonoscopic surveillance including targeted biopsies of suspicious lesions and multiple random biopsies.[1-3] Taking many biopsies is time-consuming, has a low but non-negligible risk of secondary hemorrhage, and only has a moderate sensitivity for neoplasia detection. Furthermore, adenoma-like neoplasia may be treated inefficiently when first taking biopsies, whereas non-neoplastic lesions may be left *in situ* without biopsies at all.[4-6] It is therefore desirable to replace the inefficient procedure of targeted and random biopsies by a more efficient method.

Several endoscopic techniques may facilitate differentiation of neoplasia from non-neoplastic mucosa, thereby increasing the efficiency of UC surveillance.[7-10] Chromoendoscopy (CE) elucidates mucosal patterns that can be used for the prediction of histopathology in-vivo with an accuracy of 93%.[8] Narrow-band imaging (NBI) reveals mucosal and vascular patterns and has a comparable diagnostic accuracy as CE with respect to differentiating neoplastic from non-neoplastic sporadic polyps.[11]

Whereas CE or NBI can be used for predicting histology, confocal laser endomicroscopy (CLE) is in fact in-vivo histology and has shown high agreement with true histopathology.[12] Possible advantages of CLE during UC surveillance are that it may substitute random biopsies and may obviate targeted biopsies when CLE reveals non-neoplastic histology.[13] If CLE suggests neoplasia, the endoscopist can decide whether to take biopsies or to perform endoscopic resection.[14] To reach this goal however, CLE should be easy-to-use and have a high diagnostic accuracy when compared to true histopathology.

Until now, research on CLE in UC patients was limited to a system with the confocal technology integrated into the endoscope (Pentax inc., Tokyo, Japan).[15] Recently, probe-based CLE has been launched (Mauna Kea Technologies, Paris, France) making use of probes that fit through the working channel of any standard colonoscope.[16] The objective of our study was to evaluate the feasibility and diagnostic accuracy of probe-based CLE (pCLE) in UC surveillance.

Patients and Methods

Patients

Patients with UC, scheduled for colonoscopic surveillance at the Academic Medical Centre Amsterdam, were invited to participate when they met the following inclusion criteria: history of UC ≥8 yrs and inactive disease. Exclusion criteria were: contraindications to fluorescein, non-correctable coagulopathy, age ≤18 years, and inability to obtain informed consent. This study was approved by our institutional review board.

Endoscopic equipment

Colonoscopies were performed using the Lucera system (CV-260, Olympus, Tokyo, Japan), incorporating high-definition endoscopy (HDE), NBI, and optical magnification (100x). The accessory channel of the endoscopes (CF-H260Z, Olympus, Tokyo, Japan) was located at the right lower quadrant of the endoscopic view (Figure 1-2).

Confocal laser endomicroscopy was performed with the probe-based system (Cellvizio-GI, Mauna Kea Technologies, Paris, France). A laser scanning unit excites light with a wavelength of 488nm via a fiberoptic miniprobe (ColoFlex type UHD; Mauna Kea Technologies, Paris, France). The probe (diameter 2.5mm) can be inserted through the accessory channel of every standard colonoscope for contact with the mucosa (Figure 2). Only light of 500-650nm is collected by the probe to create optical slices with a field of view of 240μm, at a depth of 60μm below the mucosal surface (lateral resolution 1μm). The images are scanned with a rate of 12 frames per second, hence producing a real-time video on a second screen. For tissue contrast we used intravenous fluorescein (5mL, 10%) that has shown to be safe in ophthalmology and previous CLE studies.[17, 18]

Colonoscopic procedure

Patients underwent colonoscopy under conscious sedation using midazolam combined with fentanyl. Procedures were performed by 4 endoscopists with minimal experience in CLE. After cecal intubation, 20mg butyl-scopolamine was given to reduce colonic motility.

During withdrawal the colon was scrutinized for visible lesions (by either HDE or NBI at the discretion of the endoscopist). Detected lesions were assessed for size and location, and scored according to the revised Paris classification.[19] Furthermore, real-time diagnoses (scored as either neoplasia or non-neoplastic) were made of all lesions based on mucosal and vascular patterns by NBI and HDE.[20, 21]

After HDE/NBI evaluation, each lesion was inspected with pCLE with a maximum of 7 lesions per patient (for reasons of time). While positioning the probe on the lesion, its location was noted with respect to the quadrant of the endoscopic view (left upper, left lower, right upper, right lower, central; Figure 1). This was noted since the position of the working channel relative to the lesion may affect the ease-of-use of pCLE. The recording of pCLE frames was started at positioning the probe against the lesion and stopped when removing the probe. The probe was removed when the endoscopist decided to have a video that clearly depicted the microscopic mucosal and vascular structures. No real-time pCLE diagnoses were made, but all pCLE videos were stored on a computer for assessment afterwards. Finally, biopsies were taken for histopathology.

After scrutinizing each colonic segment for suspicious lesions, four quadrant random biopsies were taken every 10 cm of colon, according to current guidelines.[1] Of maximally 7 random areas a pCLE video was made which was also evaluated afterwards. Biopsy material that corresponded to the pCLE videos was sent in separate jars for histopathology.

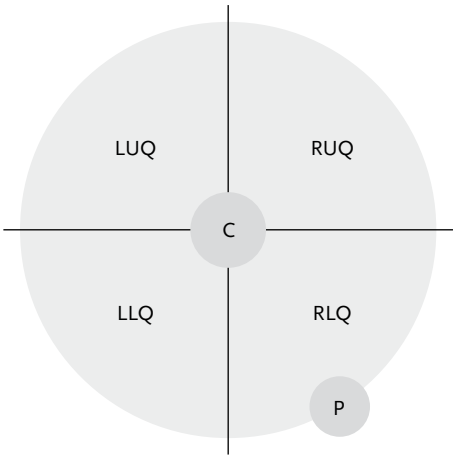

Figure 1: quadrants of the endoscopic view for defining the location of lesions while performing probe-based confocal laser endomicroscopy. LUQ left upper quadrant, LLQ left lower quadrant, RUQ right upper quadrant, RLQ right lower quadrant, C Center, P position of the working channel

Histopathology

Biopsies were evaluated by two pathologists who were blinded for endoscopic diagnosis. One of them was a gastrointestinal expert (SvE). Histopathology was classified according to the Vienna criteria.[22]

Evaluation of pCLE videos

The pCLE videos were stored as MKT-files (Cellvizio Viewer, Mauna Kea Technologies, Paris, France). Afterwards, only pCLE frames that demonstrated crypts/vessels were selected and converted into a new video in AVI-format. The total times of the original MKT-file and new AVI-file were noted.

The pCLE videos in AVI-format were subsequently scored by two endoscopists separately, blinded for histology and endoscopic information. Patient and time information was removed from the video, but no other post-processing was done. First, the videos were scored for quality (poor: no crypt/vessel visualization; moderate: visualization unsure and unclear; good: visualization sure but unclear; excellent: visualization sure and clear). Second, the pCLE histology was scored according to a recently developed classification scheme which categorizes crypt and vessel architecture (Table 1; Figure 3).[23] In accordance with the Mainz criteria, crypt- or vessel-type 3 were expected to be neoplastic on histopathology.[13]

pCLE classification	Crypt architecture	Vessel architecture
1	Regular luminal openings, size and distribution of the crypts covered by a homogeneous layer of epithelial cells, including goblet cells	Hexagonal, honeycomb appearance that presents a network of capillaries outlining the luminal openings of the crypts
2a	Focal branching of regular-shaped crypts	Hexagonal, honeycomb appearance with (no or) mild increase in the number of capillaries OR increased amount of normal vessels without leakage
2b	Star-shaped luminal crypt openings (narrow lumen) with a regular or reduced amount of goblet cells	
2c	Star-shaped luminal crypt openings (wide lumen) with a regular or reduced amount of goblet cells	
2d	Combination of branched and star-shaped crypts (2a-c)	
2e	Decreased number of crypts, irregular size of crypts, and irregular distribution of crypts, with a regular or reduced amount of goblet cells	
3	Variable width of epithelial lining with tubular shaped crypts and loss of goblet cells (striped dark epithelium); irregular and decreased volume of lamina propria	Dilated and distorted vessels with elevated leakage; irregular architecture with little or no orientation to adjunct tissue

Table 1: description of the recently developed pCLE classification in which crypts and vessels are scored separately on the pCLE videos

Outcome measures

Primary outcome was the feasibility of pCLE, expressed as: (a) total time of pCLE imaging that was necessary to make a video of colonic mucosa; (b) proportion of total imaging time in which crypts/vessels were visible on the pCLE images; and (c) pCLE video quality rated by the two endoscopists.

Secondary outcomes were sensitivity, specificity, and overall accuracy of the blinded pCLE classification and of the real-time endoscopic prediction of histology based on NBI and HDE. Histopathology was used as reference standard. Lastly, the interobserver agreement on the pCLE classification was calculated.

Statistical analysis

Descriptive statistics were used to analyze the feasibility measures of pCLE. Feasibility measures were compared for different locations of lesions by using either Kruskal-Wallis (time comparisons) or Chi-square testing (video quality).

For calculating sensitivity, specificity and accuracy, a pCLE classification of 1-2 was considered non-neoplastic whereas a pCLE classification of 3 (either crypt-type or vessel-type) was considered neoplastic.

Finally, interobserver agreement of the pCLE classification was expressed as (1) percentage of full agreement between the two observers; and (2) kappa statistics (± 95%-conficence interval). Kappa-values were interpreted according to Landis and Koch.[24] The manuscript was reported according to the STARD statements for diagnostic accuracy studies.[25]

Results

Patients

From October 2007-September 2008, 22 patients (mean age 54 yrs; 12 male) were included. Their median UC duration was 17 yrs (8-28); 18 had extensive colitis; and 4 had concomitant primary sclerosing cholangitis. Four endoscopists (ED, PF, PCFS, and CYP) performed 10, 9, 2 and 1 procedures each and no complications occurred.

Real-time endoscopy

Fourty-eight lesions were examined by NBI, HDE and pCLE. Their median size was 10mm (3-100) and 37 (77%) were flat. Histopathology demonstrated low-grade intraepithelial neoplasia (LGIN) in 10; normal mucosa in 3; hyperplasia in 15; chronic inflammatory changes in 9; and active inflammation in 11 lesions.

The sensitivity, specificity and accuracy of the real-time endoscopic diagnosis of lesions, based on HDE and NBI, had a sensitivity, specificity and accuracy of 100% (95%-CI: 72-100), 89% (76-96), and 92% (80-97).

In addition, 87 random areas were examined by pCLE. Histology showed LGIN in 2; normal mucosa in 51; hyperplasia 11; chronic inflammatory changes in 16; and active inflammation in 7.

Probe-based confocal laser endomicroscopy

Feasibility

The median required time to obtain a reliable pCLE video was 98 seconds (interquartile range: 61-142) for lesions *vs.* 66 seconds (50-97) for random areas (p=0.002). The median percentage of the total pCLE imaging time that clearly demonstrated crypts/vessels was 61% (40-72) for lesions *vs.* 81% (60-93) for random areas (p<0.001). In 2 videos (1.5%) no histology was visualized at all, and hence these were excluded from assessment by the blinded observers.

The required time to make reliable videos did not differ between the quadrants of the endoscopic view (Kruskal-Wallis; p=0.975). However, the percentage of pCLE time in which crypts/vessels were visible, was significantly lower for areas located in the left lower quadrant (22 areas; median 42%) compared to all other quadrants (113 areas; medians 74-80%) (p=0.001). In addition, required pCLE time was shorter and the percentage of pCLE time with clear crypts/vessels was higher among flat than among protruded mobile lesions: medians 70 *vs.* 105 seconds (p=0.027), and 74% *vs.* 41% (p<0.001) respectively.

Of the 133 pCLE videos that were blindly assessed, 69% was rated as having good/excellent quality. Videos of areas in the left lower quadrant of the endoscopic view were less often rated as good/excellent (52% *vs.* 70-76%; p=0.014). The percentage of videos rated as good/excellent did not differ between lesions and random areas (64% *vs.* 72%; p=0.196).

Diagnostic accuracy

Of the 133 videos that were evaluated using the pCLE classification scheme, the two observers felt unable to score 1 and 6 videos respectively for vessel-type; and 0 and 6 videos for crypt-type (=inconclusive index-test results). Their scores are presented in Table 2. Ten out of 20 assess-

ments of neoplastic areas (50%) were correctly scored as crypt-type 3; and 11 out of 20 (55%) as vessel-type 3. Active inflammation and hyperplasia were associated with crypt-/vessel-type 3 in 18-22% of cases as well.

	Histopathology (reference standard)				
	Normal	*Hyperplastic*	*Chronic inflammation*	*Active inflammation*	*Neoplasia*
Crypt-type					
1	65 (60)	14 (28)	12 (25)	1 (3.0)	1 (5.0)
2a	16 (15)	7 (14)	11 (23)	6 (18)	1 (5.0)
2b	6 (5.6)	6 (12)	8 (17)	5 (15)	3 (15)
2c	2 (1.9)	3 (5.9)	5 (10)	4 (12)	3 (15)
2d	2 (1.9)	2 (3.9)	5 (10)	2 (6.1)	1 (5.0)
2e	12 (11)	8 (16)	7 (15)	9 (27)	1 (5.0)
3	5 (4.6)	11 (22)	0 (0)	6 (18)	10 (50)
Vessel-type					
1	58 (54)	23 (46)	30 (64)	13 (38)	7 (35)
2	43 (40)	16 (32)	11 (23)	14 (41)	2 (10)
3	7 (6.5)	11 (22)	6 (13)	7 (21)	11 (55)

Table 2: Correspondence between the recently developed pCLE classification (scored by two endoscopists) and the final histopathology (i.e. reference standard). Data are represented as number of colonic random areas or lesions (%).

For differentiating neoplastic from non-neoplastic mucosa, the pCLE classification had a sensitivity of 65% (43-82), specificity of 82% (77-86), and accuracy of 81% (76-85). The accuracy was 84% for videos rated as good/excellent *vs.* 73% for videos rated as poor/moderate (p=0.037).

Interobserver agreement

The pCLE classification had a *fair* interobserver agreement (kappa 0.33; 0.23-0.42) for crypt-type and *moderate* agreement (kappa 0.52; 0.39-0.64) for vessel-type. Their respective percentages of full agreement were 44% and 67% (p<0.001).

When simplifying the classification to neoplasia (crypt-/vessel-type 3) versus non-neoplastic (all remaining types), the agreement became *moderate* (kappa 0.47; 0.29-0.66) with a percentage full agreement of 83%.

Discussion

The main objective of this study was to assess the feasibility of pCLE during UC surveillance, expressed as (a) required imaging time; (b) proportion of imaging time that crypts/vessels were visible; and (c) percentage of pCLE videos that had good/excellent quality. These parameters reflect the effort that is necessary to obtain pCLE videos of sufficient quality.

The median time required to obtain a pCLE video of lesions was 98 seconds, whereas this was 66 seconds for random areas. This difference was caused by the difficulty of performing pCLE for mobile (sessile/pedunculated) lesions. We did however not yet use a small transparent cap on the tip of the endoscope which should help to stabilize the probe and thus the image. With the miniprobe inserted through the working channel of an endoscope it is difficult to apply same-time suction for stabilization. Kiesslich *et al*, who used the integrated CLE, showed that the imaging time per lesion was approximately 34 seconds (calculated from their results).[13] The difference can be explained by their longer experience but also by their different system. The variable scanning depth of the integrated system (0-250mm) may contribute to an increased ability to visualize histology in a shorter time whereas pCLE has a fixed imaging plane at ~60mm. Moreover, the integrated system has a working channel opposite to the CLE-window, enabling same-time suctioning for stabilization.

Furthermore, 61%-81% (medians of lesions and random areas) of pCLE time led to actual visualization of crypts/vessels. After selecting frames that truly demonstrated crypts/vessels for assessing video quality, 69% was rated as good/excellent. These two feasibility measures were significantly inferior for lesions located in the left lower quadrant of the endoscopic view. As the miniprobe can be inserted through the accessory channel of any endoscope with variable locations of the working channel, this finding is likely to vary between different endoscopes. We used colonoscopes which have the opening of the working channel at the 5 o'clock position. By torquing the endoscope however, one can easily position the lesion in the most appropriate quadrant. Since integrated CLE has a fixed imaging window at the left lower quadrant, the area of interest should always be brought into this corner of the endoscopic view.[26] To the contrary, pCLE has the possibility of targeting areas further away from the endoscopic tip, enabling endomicroscopy of the upper quadrants as well. Kiesslich *et al* scored 84% of CLE images of lesions as having good quality.[13] The difference with our results again may be attributed to their higher experience but may also be caused by interobserver variability in the assessment of video or image quality and by the slightly higher lateral resolution (0.7 *vs.* 1mm) of the integrated system. Because studies using pCLE in the colon are lacking, our feasibility results cannot be compared to other studies using this system.

From our feasibility results and while still in our learning curve, it can be deduced that using pCLE would lead to an increase in colonoscopy time of about 30-40 minutes, as visualizing one random area would take 66 seconds. Additional pCLE of detected lesions would account for more colonoscopy time. A question that remains to be answered is whether increased experience with pCLE would substantially reduce this time and would increase the proportion of images with clear histology and good quality. Direct comparison between the integrated and probe-based system would then be interesting.

Secondary aim of our study was to assess the accuracy of our pCLE classification, which was 81% (sensitivity 65%; specificity 82%). The disappointing specificity may be caused by the fact that hyperplasia and inflammation also frequently led to reduced goblet cells and increased striped/irregular epithelium, which are associated with neoplasia too. On the other hand, neoplasia was associated with regenerative epithelium (crypt-type 2a-2e) in several cases, contributing to the poor sensitivity (Figure 4). In this regard, the classification scheme we developed should probably be refined to account for neoplasia more accurately.

We have to stress however that our observers were blinded and scored pCLE videos afterwards. Kiesslich *et al* used real-time CLE next to chromoendoscopy, showing an accuracy of 97.8%.[13] In order to put their results in perspective, we calculated that our endoscopic diagnosis, based on NBI/HDE in real-time, led to a sensitivity of 100% and specificity of 89%. One can imagine that real-time endoscopy and pCLE would also lead to a higher accuracy, since the endoscopist is aware of the endoscopic nature of the lesion. Alternatively, one may argue that there is little possible gain for CLE as add-on test next to HDE/NBI, as these already had an accuracy of 92%. The clinical value of pCLE as add-on test in UC surveillance should therefore also be studied as a real-time increment to HDE, with and without NBI.

Meining *et al* also used 2 blinded observers for pCLE evaluation with comparable accuracies of 74-82%.[16] Subanalysis of high quality videos led to an accuracy of ~93% in that study. The accuracy of pCLE in our study was maximally 84% when excluding videos of poor/moderate quality. Meining *et al* however included non-colonic lesions and used cresyl-violet as contrast agent instead of fluorescein, making comparison with our study difficult.

Lastly, we assessed the reproducibility of our pCLE classification that was created by an international collaboration of pCLE users.[23] The classification included 7 crypt-types which had a *poor* agreement (kappa 0.33; full agreement 44%). When simplifying the classification to neoplasia versus non-neoplastic, the agreement increased to *moderate* (kappa 0.47; full agreement 83%) which is acceptable in view of our learning phase. Hurlstone *et al* demonstrated a kappa value of 0.81 for integrated CLE, although they evaluated non-UC patients only.[27] Inflammation may interfere with reproducibility as the distinction between neoplasia and inflammation is more difficult. Nevertheless, our interobserver results force us to refine and simplify our pCLE classification in order to increase its clinical value in UC surveillance.

In summary, this study showed that pCLE is feasible during UC surveillance with reasonable results. Probe-based CLE in our first experience increased colonoscopy time significantly. Technical enhancements are needed to provide images of sufficient quality and increased experience should reveal whether enhanced technical skills improve its ease-of-use. Secondly, the achieved diagnostic accuracy and reproducibility are justifiable in view of our learning phase and blinded assessments, but are currently falling short when compared to the accuracy achieved with real-time HDE and NBI. Future research should focus on whether real-time use of pCLE will improve the overall diagnostic accuracy.

>> **For figures 2-4; see page 142**

Reference List

1 Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002;51 Suppl 5:V10-V12.

2 Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:314-321.

3 Collins P, Mpofu C, Watson A, Rhodes J. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2006;CD000279.

4 Rubin PH, Friedman S, Harpaz N, Goldstein E, Weiser J, Schiller J, Waye JD, Present DH. Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. Gastroenterology 1999;117:1295-1300.

5 Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. Clin Gastroenterol Hepatol 2004;2:534-541.

6 Hurlstone DP, Sanders DS, Atkinson R, Hunter MD, McAlindon ME, Lobo AJ, Cross SS, Thomson M. Endoscopic mucosal resection for flat neoplasia in chronic ulcerative colitis: can we change the endoscopic management paradigm? Gut 2007;56:838-846.

7 van den Broek FJ, Fockens P, Dekker E. Review article: New developments in colonic imaging. Aliment Pharmacol Ther 2007;26 Suppl 2:91-99.

8 Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124:880-888.

9 Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, Van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39:216-221.

10 van den Broek FJ, Fockens P, van eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: Randomized comparison of high resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow band imaging for classification of lesions. Gut 2008;57:1083-1089.

11 van den Broek FJ, Reitsma JB, Curvers WL, Fockens P, Dekker E. Systematic review of narrow-band imaging for the detection and differentiation of neoplastic and nonneoplastic lesions in the colon (with videos). Gastrointest Endosc 2009;69:124-135.

12 Kiesslich R, Burg J, Vieth M, Gnaendiger J, Enders M, Delaney P, Polglase A, McLaren W, Janell D, Thomas S, Nafe B, Galle PR, Neurath MF. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. Gastroenterology 2004;127:706-713.

13 Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 2007;132:874-882.

14 Hurlstone DP, Thomson M, Brown S, Tiffin N, Cross SS, Hunter MD. Confocal Endomicroscopy in Ulcerative Colitis: Differentiating Dysplasia-Associated Lesional Mass and Adenoma-Like Mass. Clin Gastroenterol Hepatol 2007.

15 Polglase AL, McLaren WJ, Delaney PM. Pentax confocal endomicroscope: a novel imaging device for in vivo histology of the upper and lower gastrointestinal tract. Expert Rev Med Devices 2006;3:549-556.
16 Meining A, Saur D, Bajbouj M, Becker V, Peltier E, Hofler H, von Weyhern CH, Schmid RM, Prinz C. In vivo histopathology for detection of gastrointestinal neoplasia with a portable, confocal miniprobe: an examiner blinded analysis. Clin Gastroenterol Hepatol 2007;5:1261-1267.
17 Lipson BK, Yannuzzi LA. Complications of intravenous fluorescein injections. Int Ophthalmol Clin 1989;29:200-205.
18 Kiesslich R, Burg J, Vieth M, Gnaendiger J, Enders M, Delaney P, Polglase A, McLaren W, Janell D, Thomas S, Nafe B, Galle PR, Neurath MF. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. Gastroenterology 2004;127:706-713.
19 Endoscopic Classification Review Group. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570-578.
20 Kudo S, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. Endoscopy 2001;33:367-373.
21 East JE, Suzuki N, Saunders BP. Comparison of magnified pit pattern interpretation with narrow band imaging versus chromoendoscopy for diminutive colonic polyps: a pilot study. Gastrointest Endosc 2007;66:310-316.
22 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000;47:251-255.
23 van den Broek FJC, Meining A, Wallace MB, Buchner AM, van Es JA, Fockens P, Dekker E. Accuracy and interobserver agreement of international experts on a new classification scheme for probe-based confocal fluorescence microscopy. Endoscopy 2008;40:A202.
24 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
25 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ 2003;326:41-44.
26 Polglase AL, McLaren WJ, Delaney PM. Pentax confocal endomicroscope: a novel imaging device for in vivo histology of the upper and lower gastrointestinal tract. Expert Rev Med Devices 2006;3:549-556.
27 Hurlstone DP, Baraza W, Brown S, Thomson M, Tiffin N, Cross SS. In vivo real-time confocal laser scanning endomicroscopic colonoscopy for the detection and characterization of colorectal neoplasia. Br J Surg 2008;95:636-645.

Summary and future perspective

Summary

The department of Gastroenterology and Hepatology of the Academic Medical Centre in Amsterdam has had a strong interest in novel endoscopic imaging techniques for many years. This thesis comprises the recent research of our department on endoscopic imaging in the colon. The purposes of our work were to obtain evidence for supporting to or dissuading from using advanced endoscopic imaging techniques in clinical practice and to supply a methodological background for future research in this field.

In chapter 1 of this thesis, written in the beginning of the year 2007, the existing evidence on the use of advanced colonoscopic imaging techniques was reviewed. Scientific evidence had been merely confined to chromoendoscopy (CE) at that time. Since the recognition of the existence of flat and depressed colonic lesions in western countries, many efforts were made to improve the visualization of these subtle lesions that appear to harbour a particularly high risk of malignant progression. Chromoendoscopy seemed to do quite well with respect to improving the detection of these lesions, especially in patients with ulcerative colitis (UC). Narrow-band imaging (NBI) and autofluorescence imaging (AFI) had scarcely been evaluated in a structural way, which prohibited us from doing any recommendation regarding their routine use in clinical practice. When critically appraising the trials that favoured CE however, we found that in these studies the CE procedures were performed by highly experienced endoscopists only and also that the examination time during CE was increased, possibly acting as confounder. Nevertheless, CE seemed to be a good candidate for implementation in surveillance programs for high risk patients (e.g. UC patients), but its labour-intensive and time-consuming nature has prevented its widespread use thus far.

As NBI became commercially available worldwide during the time span of this thesis, more and more research on NBI was published. Despite the analogy between NBI and chromoendoscopy, our systematic review in chapter 2 demonstrated that NBI did not improve the detection of sporadic adenomas and UC-associated neoplasia. With respect to endoscopic differentiation of neoplastic from non-neoplastic lesions, pooled data-analysis of diagnostic accuracy studies demonstrated that NBI had a comparable accuracy as CE. With a sensitivity of 92% and specificity of 86%, NBI appeared to have potential to be used in clinical practice for differentiation of innocent hyperplastic polyps and premalignant adenomas.

When critically reviewing the existing literature on endoscopic imaging techniques and their role for improving the detection of premalignant lesions, we found that highly different study designs and statistical analyses had been used despite similar objectives. Although endoscopic imaging techniques are diagnostic tests which appear to have to be evaluated by using a classical diagnostic accuracy study design, i.e. comparing index test results against reference standards, no feasible reference standard appears to exist for the evaluation of colonoscopic techniques with respect to their ability to detect polyps. We therefore evaluated the most commonly reported study designs in chapter 3, focusing on their validity and efficiency. The parallel randomized design has been used most but, although it is free from bias, its power turned out to be disappointingly low. Endoscopic researchers should carefully consider whether a cross-over study design can be used instead since this design has much greater power, but at the same time will

be more cumbersome for patients and endoscopic researchers. Whatever research design is finally chosen, reporting of possible confounders (i.e. gender, age, race, indication of colonoscopy, experience of endoscopists, degree of bowel preparation, examination time, and type of endoscope used) is important and should be considered an obligation.

Our randomized cross-over study described in chapter 4 was the first to report on the use of endoscopic tri-modal imaging for the diagnosis of colonic polyps. With respect to the detection of sporadic adenomas, the miss-rate of AFI was 20% *vs.* 29% by high-resolution endoscopy (HRE). Although the difference was not statistically significant, one may question whether the small sample size of the study may have accounted for this. In case the difference of 9% in adenoma miss-rate is considered clinically relevant, additional research seems necessary to further evaluate the value of AFI. As secondary outcome, we found that the sensitivity, specificity and accuracy of the Kudo classification by NBI for differentiating neoplastic from non-neoplastic lesions were 90%, 70% and 79% respectively, with a negative predictive value of 90%. These figures appear too low for routine use in clinical practice. Interestingly, an algorithm which combined information from AFI and NBI was able to reach a putative sensitivity, specificity and accuracy of 98%, 74% and 84%, and a negative predictive value of 98%. This algorithm was noticed during the analysis of the results and considered all AFI-purple as well as all AFI-ambiguous lesions with Kudo type III-V on NBI as suspicious for adenoma; whereas AFI-green and AFI-ambiguous lesions with Kudo type I-II on NBI were considered non-suspicious.

The algorithm from chapter 4 was subsequently assessed in the image evaluation study in chapter 5. Images of polyps taken with AFI and NBI were assessed by both experienced and non-experienced endoscopists. This study showed that experienced endoscopists had better interobserver agreement for NBI (κ=0.77) than AFI (κ=0.33), whereas non-experienced endoscopists had better interobserver agreement for AFI (κ=0.58) than NBI (κ=0.33). These findings suggest that AFI-colour is easier to assess by endoscopists without experience in endoscopic imaging than the more sophisticated Kudo classification. A more remarkable finding was that the simultaneous presentation of AFI- and NBI-images increased the interobserver agreement among non-experienced endoscopists, and significantly improved the overall specificity. It appeared that the combination of AFI and NBI synergistically improved their value regarding differentiation. The abovementioned algorithm led to a significantly increased accuracy (85%) when compared to AFI alone (74-77%) or NBI alone (63-70%). This finding was confirmed in the second part of the study among 6 non-experienced endoscopists from 5 non-university hospitals, who only received a training of 17 image examples and then already had a 'moderate' interobserver agreement (κ=0.53). Their sensitivity, specificity and overall accuracy were 96%, 69% and 80% which seem very reasonable for practical use.

In chapter 6 we addressed the use of HRE, AFI and NBI for differentiating polyps in patients with hyperplastic polyposis syndrome (HPS). This study demonstrated that the diagnostic accuracies of AFI and NBI were both unsatisfactory for differentiating sessile serrated adenomas from hyperplastic polyps (accuracies 55%; upper limit of the 95%-confidence interval was 68% at best). To the contrary, differentiating conventional adenomas from serrated polyps was well possible using both pit pattern and vascular pattern intensity with NBI. In the end, proximal colonic location combined with a size ≥3mm proved to be the most accurate variable for dif-

ferentiating sessile serrated adenomas from hyperplastic polyps with a diagnostic accuracy of only 76%. We therefore concluded that endoscopic tri-modal imaging appeared inadequate for differentiation purposes in patients with HPS.

Regarding the detection of polyps in HPS, we performed a randomized cross-over trial comparing polyp miss-rates between NBI and HRE in chapter 7. The miss-rate of NBI was 10% *vs.* 36% of HRE (odds ratio 0.21; 95%-CI: 0.094-0.45). Our study showed that NBI was of particular value for the detection of flat serrated adenomas. During NBI, all serrated polyps appeared light in colour, thereby increasing the contrast between these polyps and their surrounding colonic tissue, which might explain the lower miss-rate of serrated polyps by NBI. Therefore NBI appears to be the technique of first choice for colonoscopic surveillance of HPS patients. With respect to differentiating hyperplastic polyps from sessile serrated adenomas and conventional adenomas, NBI again proved unsatisfactory in this study. The achieved diagnostic accuracy was only 65% which is far from clinically practical.

In chapter 8 we presented our retrospective study assessing the yield and clinical value of random biopsies that were taken during a 10-year period of colonoscopic surveillance in UC patients at our institution. The yield of neoplasia by random biopsies was 16% per-site, 5.7% per-colonoscopy, and 7.5% per-patient. Hence, 84% of all detected neoplastic sites could be visualized by conventional colonoscopy. In addition, only 1 of 167 patients (0.6%) who underwent surveillance colonoscopy in our study had a relevant change in clinical management due to positive random biopsies. As the yield of random biopsies was low and their clinical consequences were very limited, we proposed to omit random biopsies during UC surveillance and use the extra endoscopy time for pancolonic CE.

Chapter 9 described the first randomized cross-over study comparing first generation (prototype) NBI to conventional colonoscopy for the detection of neoplasia in patients with UC. This study showed that NBI led to the detection of twice as many suspicious lesions and hence to more targeted biopsies, which however did not lead to an improved detection rate of neoplasia. Both NBI and conventional colonoscopy failed to detect approximately one third of all patients with neoplasia, reflecting the low sensitivity of these methods. Only the sequential use of both techniques would have detected 11 out of 12 patients with neoplasia.

In chapter 10, the use of endoscopic tri-modal imaging in patients with longstanding UC was described. Patients were randomized in a cross-over design to AFI or HRE showing a neoplasia miss-rate of 50% for HRE *vs.* 0% for AFI (p=0.036). In this study, the yield of random biopsies was low as well (0.1% of biopsies showed neoplasia). The fact that all neoplasia was coloured purple on AFI and that random biopsies did not detect neoplasia in additional patients, underlines the question whether random biopsies should be taken if AFI reveals a normal 'green' appearing colon. As secondary outcome measure, the accuracy of NBI for differentiating between neoplasia and non-neoplastic mucosa was assessed and again proved unsatisfactory with a sensitivity of 75% and specificity of 81%. The abovementioned algorithm combining AFI and NBI had a putative sensitivity of 100% and specificity of 77%. We concluded that endoscopic tri-modal imaging appeared promising for UC surveillance.

In chapter 11 new-generation NBI with a different spectral filter and improved brightness was compared against high-definition endoscopy (HDE) in patients with longstanding UC. Once again NBI proved suboptimal by detecting only 81% of neoplastic lesions *vs.* 69% by HDE (p=0.727). The disappointing results may be explained by the fact that NBI provided a darker overall image as well as by the fact that the high-definition technology may have levelled out any difference in contrast between NBI and HDE. Our secondary objective in this study was to evaluate NBI for real-time differentiation of neoplastic and non-neoplastic mucosa. Both the Kudo classification and the vascular pattern intensity proved unsatisfactory for this purpose as their respective sensitivities were only 76% and 80%, and their respective specificities 66% and 72%. In summary, NBI did not improve the detection of neoplasia and also was not accurate in the differentiation of neoplastic and non-neoplastic colonic mucosa.

As in published studies on patients with UC endoscopic confocal laser endomicroscopy (eCLE) had been shown to be a good candidate for accurate differentiation of neoplastic from non-neoplastic mucosa, we evaluated the feasibility and diagnostic accuracy of probe-based CLE (pCLE) in chapter 12. We found that pCLE was feasible during UC surveillance, even though in our first experience the colonoscopy time was significantly increased. Technical enhancements appear necessary to provide images of better quality and increased experience should reveal whether enhanced technical skills would improve the ease-of-use of pCLE. Furthermore, the achieved diagnostic accuracy (sensitivity 65%; specificity 82%) and reproducibility (κ=0.47; full agreement 83%) were justifiable in view of our learning phase and blinded assessments, but are currently falling short when compared to the accuracy that was achieved with real-time HDE and NBI.

Future perspective

Chromoendoscopy

Although pancolonic CE has shown promising results in several randomized studies regarding an improved detection of adenomas and UC-associated neoplasia, the technique remains cumbersome, operator-dependent, and is regarded by some as messy. Methodological inadequacies in the reported trials and the limited number of trials in general setting have prevented its widespread recommendation in guidelines. Future research should therefore focus on the practicability of CE in daily general practice (evaluating time and costs) and on training of less experienced endoscopists. Head-to-head comparisons of CE versus 'push-on-a-button' endoscopic imaging techniques have yet not been performed and would be an interesting field of future research. Finally, as it remains unknown which dye (methylene blue, indigo carmine, others) is preferred for usage, research aiming at answering this question seems also to be important.

Narrow-band imaging

Thus far, NBI did not lead to an improved detection of adenomas or UC-associated neoplasia compared to white-light endoscopy. High quality colonoscopy with HRE or HDE may be sufficient for these purposes. Future research on this topic should focus on comparing of CE with HDE and/or NBI. However, NBI did improve the detection of serrated polyps in HPS patients

when compared to HDE. Therefore, NBI may better prevent the occurrence of interval cancers during endoscopic surveillance of these patients. Future research should confirm our findings which may lead to new practical recommendations for this patient population.

Regarding the differentiation of neoplastic from non-neoplastic polyps, NBI appears to have a reasonable diagnostic accuracy as demonstrated by our systematic review. We believe that NBI is sufficiently accurate to be used routinely for this purpose among low- or intermediate-risk patients since in this population the negative predictive value of NBI will be high. However, as the negative predictive value among large polyps or within high-risk patients may be lower, future research should focus on assessing the accuracy of NBI among these subgroups. Since NBI is currently widely spreading throughout the world, research should aim to define a learning curve for NBI with respect to differentiation. In addition, we should aim to use only one validated and accurate classification system since many different classification systems (e.g. Kudo classification, vascular pattern intensity) have been used until now.

Autofluorescence imaging

Whereas NBI has failed to demonstrate an improved detection of sporadic adenomas and UC-associated neoplasia, AFI has shown promising results in this thesis. Although the relative gain in sporadic adenoma detection may be low, the results of our studies and those of others prompt further research to this technique for adenoma detection. Especially in patients with UC we found that AFI should be further evaluated. In particular, comparisons between AFI and CE may be very interesting.

Since the combined use of AFI and NBI in endoscopic tri-modal imaging has shown to further improve the diagnostic accuracy with respect to differentiating neoplasia from non-neoplastic lesions, the algorithm combining AFI- and NBI-information needs further validation. The comparison between this algorithm and the promising confocal laser endomicroscopy (which is in fact in-vivo histopathology) could lead to interesting results.

Conclusion

This thesis has shown that advanced endoscopic imaging techniques are more and more used in general colonoscopic practice and are frequently objective of scientific research. By critically appraising the literature we have summarized the current level of evidence for using these techniques and we have provided recommendations regarding which study design is the most efficient and valid for evaluating these techniques. These recommendations may be useful for future endoscopic research.

By our own clinical studies we demonstrated that the use of endoscopic imaging techniques is feasible during colonoscopy among patients who are under surveillance for polyps as well as for UC-associated neoplasia. In particular, the combined use of AFI and NBI in 'endoscopic tri-modal imaging' appears easy-to-learn and has shown promising results regarding an improved detection of UC-associated neoplasia as well as an improved differentiation of neoplastic and non-neoplastic mucosa. Since we were the first to demonstrate these advantages of 'endoscopic tri-modal imaging' in relatively small studies, additional research is necessary to confirm our findings in a broader and general clinical setting.

As NBI is currently becoming commercially available worldwide, we want to make a last special note on this technique. The sole use of NBI appears to fall short with respect to improving the detection of neoplastic polyps and UC-associated neoplasia, but seems valuable for differentiating polyps in daily practice. Colonoscopists should be aware of the learning curve of NBI for this purpose and should take notice of the level of risk that patients harbour of having premalignant lesions when using NBI for differentiation. Among patients with hyperplastic polyposis syndrome however, NBI may be better than standard colonoscopy for detecting polyps but needs further confirmation in larger trials.

Samenvatting en toekomstperspectief

Samenvatting

De afdeling Maag- Darm- en Leverziekten van het Academisch Medisch Centrum te Amsterdam is al jaren geïnteresseerd in nieuwe endoscopische imaging technieken. Dit proefschrift omvat het recente wetenschappelijke onderzoek van onze afdeling betreffende nieuwe endoscopische imaging technieken in het colon. De doelen van ons onderzoek waren het verkrijgen van wetenschappelijk bewijs voor het aan- of afraden van het gebruik van endoscopische imaging technieken in het colon voor de dagelijkse praktijk en het verschaffen van een methodologisch kader voor toekomstig onderzoek op dit gebied.

In hoofdstuk 1 van dit proefschrift, geschreven in het begin van het jaar 2007, is het wetenschappelijk bewijs over het gebruik van colonoscopische imaging technieken tot dat moment samengevat. Het wetenschappelijk bewijs was destijds beperkt tot studies over chromo-endoscopie (CE). Sinds de erkenning van het bestaan van vlakke colonlaesies in de westerse wereld heeft men veel onderzoek gedaan naar het verbeteren van de opsporing van deze subtiele laesies die overigens een hoger risico bevatten voor maligne ontaarding. Chromo-endoscopie leek een goede techniek met betrekking tot het verbeteren van de opsporing van deze laesies, vooral in patiënten met colitis ulcerosa (CU). Narrow-band imaging (NBI) en autofluorescentie imaging (AFI) waren op dat moment niet gestructureerd onderzocht, wat een aanbeveling voor hun gebruik in de dagelijkse praktijk in de weg stond. Als we echter kritisch de studies beoordeelden die gunstige uitkomsten lieten zien voor CE, dan vonden we dat de CE procedures alleen door zeer ervaren endoscopisten uitgevoerd waren en dat de endoscopietijden langer waren voor CE. Deze twee factoren kunnen als confounder hebben gewerkt in de resultaten. Toch leek CE geschikt voor implementatie in surveillanceprogramma's voor hoogrisico groepen (zoals patiënten met CU), maar het arbeidsintensieve en tijdrovende karakter van deze techniek hebben ervoor gezorgd dat CE nog niet wijdverspreid gebruikt wordt.

Aangezien NBI commercieel beschikbaar werd gedurende de uitvoering van de studies in dit proefschrift werd er veel onderzoek verricht naar deze techniek. Ondanks de theoretische overeenkomsten tussen NBI en CE liet onze systematische review in hoofdstuk 2 zien dat NBI niet tot een verbeterde opsporing van sporadische adenomen of dysplasie in het kader van CU leidde. Met betrekking tot het endoscopisch onderscheiden van dysplastische en niet-dysplastische laesies, lieten de gepoolde data van diagnostische accuratessestudies wel zien dat NBI een vergelijkbare accuratesse heeft als CE. Met een sensitiviteit van 92% en een specificiteit van 86% lijkt NBI potentieel te hebben voor routinematig gebruik in de dagelijkse praktijk voor het differentiëren tussen 'onschuldige' hyperplastische poliepen en premaligne adenomen.

Toen we de bestaande literatuur over de rol van endoscopische imaging technieken voor het opsporen van premaligne laesies in het colon kritisch beoordeelden, vonden we dat er zeer verschillende studieopzetten en statistische analyses gebruikt werden ondanks vergelijkbare doelstellingen. Ondanks het feit dat endoscopische imaging technieken diagnostische tests zijn en daarom door middel van een klassieke 'diagnostische accuratesse' studieopzet onderzocht lijken te moeten worden, i.e. het vergelijken van testresultaten met een gouden standaard, bestaat er geen goede gouden standaard voor de evaluatie van een coloscopische techniek met betrekking tot het opsporen van poliepen. Daarom hebben we in hoofdstuk 3 de meest gebruikte studie-

opzetten geëvalueerd en vooral gelet op hun validiteit en efficiëntie. De parallel gerandomiseerde studieopzet is de meest gebruikte en zonder bias, maar de power van deze studieopzet bleek teleurstellend laag te zijn. Daarom zouden onderzoekers van endoscopie technieken zorgvuldig moeten overwegen of ze niet een cross-over studieopzet kunnen gebruiken omdat deze opzet een veel grotere power heeft. Echter moet men zich dan wel realiseren dat een dergelijke cross-over studie veel bewerkelijker is voor zowel patiënten als onderzoekers. Welke studieopzet uiteindelijk ook gekozen wordt, mogelijke confounders (zoals geslacht, ras, leeftijd, indicatie voor coloscopie, ervaring van de endoscopist, mate van darmvoorbereiding, proceduretijd, en type gebruikte endoscoop) moeten in ieder geval gerapporteerd worden.

Onze eigen gerandomiseerde cross-over studie die beschreven is in hoofdstuk 4 was de eerste die 'endoscopic tri-modal imaging' onderzocht voor het diagnosticeren van poliepen. Met betrekking tot de opsporing van adenomen bleek AFI 20% van de aanwezige adenomen te missen en hoge-resolutie endoscopie (HRE) 29%. Men kan zich afvragen of het feit, dat dit verschil niet statistisch significant was, komt door de (te) kleine steekproefgrootte van de studie. Als het verschil van 9% als klinisch relevant wordt beschouwd, is aanvullend wetenschappelijk onderzoek noodzakelijk om de werkelijke waarde van AFI verder uit te zoeken. Als secundaire uitkomst vonden we dat NBI betreffende het differentiëren tussen dysplastische en niet-dysplastische poliepen een sensitiviteit, specificiteit en algemene accuratesse had van achtereenvolgens 90%, 70% en 79%, met een negatief voorspellende waarde van 90%. Deze getallen lijken te laag voor routinematig gebruik van NBI in de dagelijkse praktijk. Echter, wij ontdekten een algoritme, dat gebruik maakte van zowel de bevindingen van AFI als NBI, met een hypothetische sensitiviteit, specificiteit en accuratesse van 98%, 74% en 84%, en een negatief voorspellende waarde van 98%. Dit algoritme werd tijdens de analyse van onze data ontdekt en was gedefinieerd als: alle AFI-paarse en AFI-onduidelijk gekleurde laesies met een Kudo pitpatroon III-V tijdens NBI werden beschouwd als dysplastisch, terwijl alle AFI-groene en AFI-onduidelijke laesies met een Kudo pitpatroon I-II beschouwd werden als niet-dysplastisch.

Dit algoritme werd vervolgens onderzocht in een studie waarin poliepfoto's werden geëvalueerd in hoofdstuk 5. Foto's van poliepen die gemaakt waren met AFI en NBI werden beoordeeld door zowel ervaren (met betrekking tot het gebruik van imaging technieken) als onervaren endoscopisten. Uit deze studie bleken ervaren endoscopisten een betere inter-observer overeenstemming te hebben voor NBI (κ=0.77) dan voor AFI (κ=0.33). Onervaren endoscopisten hadden echter een betere overeenstemming voor AFI (κ=0.58) dan voor NBI (κ=0.33). Deze resultaten suggereren dat endoscopisten zonder ervaring met endoscopische imaging technieken makkelijker overeenstemming bereiken over AFI-kleur dan over de ingewikkelde Kudo classificatie. Een opvallende bevinding was dat het simultaan presenteren van de AFI- en NBI-poliepfoto's ertoe leidde dat de inter-observer overeenstemming onder onervaren endoscopisten beter werd en dat in het algemeen de specificiteit significant verbeterde. Het lijkt erop dat de combinatie van AFI en NBI een synergistisch effect heeft op een verbeterde differentiatie tussen dysplastische en niet-dysplastische laesies. Het eerdergenoemde algoritme werd wederom toegepast en leidde tot een significant betere accuratesse (85%) vergeleken met het gebruik van AFI (74-77%) of NBI (63-70%) alleen. Dit onderscheid werd bevestigd in een tweede deel van de studie onder 6 onervaren endoscopisten uit 5 perifere ziekenhuizen. Deze onervaren endoscopisten hadden slechts

een korte training gehad van 17 voorbeeldfoto's en hadden daarmee al een 'gemiddelde' inter-observer overeenstemming (κ==0.53). Hun sensitiviteit, specificiteit en accuratesse waren 96%, 69% and 80% die zeer behoorlijk zijn voor gebruik in de dagelijkse praktijk.

In hoofdstuk 6 beschreven we het gebruik van HRE, AFI and NBI voor het differentiëren tussen verschillende soorten poliepen bij patiënten met een hyperplastische polyposis syndroom (HPS). Deze studie liet zien dat de diagnostische accuratesse van AFI en NBI onvoldoende hoog waren voor het onderscheiden van sessiele geserreerde adenomen (SSA) en hyperplastische poliepen (accuratesse 55% met een bovengrens van het 95%-betrouwbaarheidsinterval van 68% op zijn best). Het differentiëren tussen conventionele adenomen en geserreerde poliepen was daarentegen wel goed mogelijk door middel van zowel het Kudo pit patroon als de 'vascular pattern intensity' met NBI. Uiteindelijk bleek de combinatie van 'proximale locatie in het colon' en 'grootte ≥3mm' de meest accurate variabele te zijn voor het differentiëren tussen SSA's en hyperplastische poliepen (accuratesse slechts 76%). Daarom was onze conclusie dat 'endoscopic tri-modal imaging' onvoldoende accuraat lijkt voor het onderscheiden van verschillende soorten poliepen in patiënten met HPS.

Betreffende het opsporen van poliepen in patiënten met HPS hebben we een gerandomiseerde cross-over studie verricht waarin we het percentage gemiste poliepen vergeleken tussen NBI en HRE. Deze studie is beschreven in hoofdstuk 7, waarin tijdens NBI 10% van de poliepen gemist bleek te worden versus 36% tijdens HRE (odds ratio 0.21; 95%-BI: 0.094-0.45). Deze studie liet zien dat NBI vooral van waarde bleek voor het opsporen van vlakke SSA's. Het feit dat geserreerde poliepen tijdens NBI licht aankleuren en daarmee een verhoogd contrast geven met de omgevende normale mucosa kan verklaren waarom het percentage gemiste geserreerde poliepen tijdens NBI lager was. Daarom raden wij aan om NBI als eerste keuze te gebruiken voor coloscopie bij patiënten met HPS. Voor de differentiatie tussen hyperplastische poliepen, SSA's en conventionele adenomen bleek NBI wederom onvoldoende in deze studie. De bereikte accuratesse was slechts 65%, wat verre van bruikbaar is.

In hoofdstuk 8 presenteerden we onze data van een retrospectieve studie naar de opbrengst en klinische waarde van random biopten die genomen werden tijdens coloscopische surveillance van patiënten met colitis ulcerosa (CU) in een tijdsbestek van 10 jaar in het Academisch Medisch Centrum te Amsterdam. De opbrengst van random biopten was 16% van alle dysplastische gebieden in het colon, 5.7% van alle coloscopieën met gevonden dysplasie, en 7.5% van alle patiënten met dysplasie. Dus, 84% van alle dysplastische gebieden in het colon kon zichtbaar worden gemaakt tijdens conventionele coloscopie. Daarbovenop bleek dat bij slechts 1 van de 167 patiënten (0.6%) die een surveillance coloscopie onderging een relevante verandering in het klinische beleid was doorgevoerd door het vinden van een positief (dysplastisch) random biopt. Aangezien de dysplasieopbrengst van random biopten beperkt was en ze weinig klinische consequenties hadden, stellen wij voor om random biopten achterwege te laten tijdens surveillance van CU patiënten en de hierdoor gewonnen tijd te gebruiken voor CE van het gehele colon.

Hoofdstuk 9 beschreef de eerste gerandomiseerde cross-over studie waarin prototype NBI (eerste generatie systeem) werd vergeleken met conventionele coloscopie voor het opsporen van dysplasie in patiënten met CU. De studie toonde aan dat met NBI tweemaal zoveel verdachte laesies werden gevonden en dus meer gerichte biopten werden genomen. Dit leidde echter niet

tot een verbeterde opsporing van dysplasie. Zowel NBI als conventionele coloscopie miste ongeveer een derde van alle patiënten met dysplasie dat de lage sensitiviteit van beide methoden weerspiegelt. Alleen het achtereenvolgende gebruik van beide technieken kon 11 van de 12 patiënten met dysplasie detecteren.

In hoofdstuk 10 beschreven we het gebruik van 'endoscopic tri-modal imaging' in patiënten met CU. Patiënten werden gerandomiseerd in een cross-over studieopzet voor AFI of HRE en de resultaten wezen uit dat het percentage gemiste dysplasieën 0% was voor AFI versus 50% voor HRE (p=0.036). Ook in deze studie was de opbrengst van random biopten laag (0.1% van de biopten). Het feit dat alle dysplasieën paars verkleurd waren tijdens AFI en dat random biopten geen extra patiënten met dysplasie opspoorde, onderstreept de vraag of random biopten nog wel nodig zijn als AFI een normaalogend 'groen' colonslijmvlies laat zien. Als tweede uitkomst werd de diagnostische accuratesse van NBI voor het onderscheiden van dysplastische en niet-dysplastische mucosa vastgesteld. Wederom waren de sensitiviteit en specificiteit teleurstellend met waarden van achtereenvolgens 75% en 81%. Het al eerder genoemde algoritme dat gebruik maakt van de combinatie van AFI en NBI had wederom een betere sensitiviteit van 100% en specificiteit van 77%. We concluderen dat 'endoscopic tri-modal imaging' een veelbelovende techniek is voor CU surveillance.

In hoofdstuk 11 werd een nieuwe generatie NBI systeem (met een verbeterde helderheid van het endoscopielicht en een ander filter voor het lichtspectrum) vergeleken met 'high-definition' endoscopie (HDE) in patiënten met CU. Wederom bleek NBI suboptimaal te zijn door slechts 81% van de dysplasieën op te sporen versus 69% door HDE (p=0.727). De teleurstellende resultaten kunnen verklaard worden door het feit dat NBI een donker beeld geeft, evenals door het feit dat de 'high-definition' technologie kleine verschillen tussen NBI en HDE op zou kunnen heffen. Als tweede doelstelling van de studie werd de diagnostische accuratesse van NBI voor het differentiëren van dysplasie en niet-dysplastische mucosa vastgesteld. Zowel de Kudo classificatie als het 'vascular pattern intensity' waren onvoldoende accuraat met een sensitiviteit van achtereenvolgens 76% en 80%, en een specificiteit van 66% en 72%. We concluderen dat NBI zowel de detectie van dysplasie als de differentiatie tussen dysplastische en niet-dysplastische mucosa niet kon verbeteren.

Aangezien endoscopische confocale laser endomicroscopie (eCLE) in de gepubliceerde literatuur een goede kandidaat lijkt te zijn voor een accurate differentiatie tussen dysplastisch en niet-dysplastisch epitheel in patiënten met CU, hebben we een studie verricht naar de uitvoerbaarheid en diagnostische accuratesse van CLE door middel van een systeem dat gebruik maakt van een probe (pCLE). Deze studie is beschreven in hoofdstuk 12 en liet zien dat de techniek goed uitvoerbaar is tijden CU surveillance, ook al werd de coloscopietijd significant verlengd tijdens onze eerste ervaring met pCLE. Technische verbeteringen lijken noodzakelijk om microscopiebeelden van hogere kwaliteit te verkrijgen en een toename van onze ervaring met pCLE zal moeten uitwijzen of een verbeterde handvaardigheid tot een beter gebruiksgemak leidt. De gemaakt pCLE beelden werden achteraf door twee endoscopisten gebruikt om een diagnose te stellen. De diagnostische accuratesse (sensitiviteit 65%; specificiteit 82%) en de inter-observer overeenstemming over de diagnose (κ=0.47; volledige overeenstemming in 83%) waren voldoende hoog aangezien het onze eerste ervaring betrof en aangezien de beelden geblindeerd beoordeeld waren. De bruikbaarheid van pCLE schiet op dit moment echter nog wel tekort als we deze vergelijken met HDE en NBI.

Toekomst perspectief

Chromo-endoscopie

Ondanks het feit dat CE veelbelovende resultaten liet zien in enkele gerandomiseerde studies met betrekking tot het opsporen van adenomen en CU-geassocieerde dysplasie, blijft deze techniek bewerkelijk, afhankelijk van de endoscopist, en vinden sommigen de techniek gebruikersonvriendelijk. Verder leidden methodologische tekortkomingen en gebrek aan studies uit de algemene praktijk er toe dat de techniek niet wijdverspreid is geraakt of is opgenomen in richtlijnen. Toekomstig onderzoek zal zich daarom moeten richten op het gebruik van CE in de algemene praktijk (rekening houdend met de tijd en kosten die de techniek met zich meebrengt) en op training van minder ervaren endoscopisten. Direct vergelijkend onderzoek tussen CE en andere endoscopische imaging technieken die beschikbaar zijn met een druk op een toets (e.g. NBI, AFI) is nog nooit verricht en zou zeer interessant zijn voor toekomstig onderzoek. Ten slotte is tot op heden onbekend welke kleurstof (methyleenblauw of indigokarmijn) de voorkeur verdient voor gebruik tijdens CE. Toekomstig onderzoek zou moeten trachten een antwoord op deze vraag te geven.

Narrow-band imaging

Tot dusverre lijkt NBI niet tot een betere opsporing van adenomen of CU-geassocieerde dysplasie te leiden in vergelijking met standaard, hoge-resolutie of high-definition wit licht endoscopie. Toekomstig onderzoek zou zich moeten focussen op de vergelijking tussen CE en HDE en/of NBI voor deze doeleinden. Bij patiënten met HPS leek NBI echter wel meer geserreerde poliepen op te sporen dan HRE. Het gebruik van NBI bij deze patiënten zou dus kunnen voorkomen dat er intervalkankers ontstaan tussen twee coloscopieën in. Toekomstig onderzoek zou onze resultaten moeten bevestigen, wat tot praktische aanbevelingen kan leiden voor deze patiëntengroep.

Met betrekking tot het differentiëren tussen dysplastische en niet-dysplastische poliepen lijkt NBI een voldoende hoge diagnostische accuratesse te hebben zoals blijkt uit onze systematische review. Deze techniek kan volgens ons routinematig gebruikt worden voor dit doeleinde binnen laagrisicopatiënten (e.g. screening voor dikke darm kanker), aangezien de negatief voorspellende waarde van NBI bij deze patiënten hoog zal zijn. Aangezien de negatief voorspellende waarde echter lager zal zijn bij de beoordeling van grote poliepen en bij hoogrisico groepen, zal toekomstig onderzoek moeten uitwijzen of de accuratesse van NBI voldoende hoog is voor routinematig gebruik in deze subgroepen. Aangezien NBI momenteel wijd verspreid wordt over de wereld, zal onderzoek zich moeten richten op het definiëren van een leercurve voor NBI voor het gebruik ervan om onderscheid te kunnen maken tussen dysplastische en niet-dysplastische poliepen. Daarnaast moeten we ons ten doel stellen om slechts één gevalideerd en accuraat classificatiesysteem te gebruiken aangezien tot op heden teveel verschillende systemen gebruikt zijn (e.g. Kudo classificatie, 'vascular pattern intensity').

Autofluorescentie imaging

Daar waar NBI het niet lukte om tot een verbeterende opsporing van adenomen en CU-geassocieerde dysplasie te leiden, lijkt AFI gunstigere resultaten te geven. Ondanks het feit

dat de relatieve winst in het opsporen van adenomen laag is, lijken onze resultaten en die van anderen voldoende gunstig te zijn om het nut van deze techniek verder uit te diepen. Vooral onder patiënten met CU vonden we dat AFI gunstige resultaten boekte en in deze patiëntengroep zal deze techniek dan ook zeker verder geëvalueerd moeten worden. Een vergelijking tussen AFI en CE lijkt daarbij in het bijzonder van belang.

Aangezien het gecombineerd gebruik van AFI en NBI in 'endoscopic tri-modal imaging' de diagnostische accuratesse voor het onderscheiden van verschillende soorten poliepen lijkt te verhogen in onze studies, zal het door ons gebruikte algoritme verder gevalideerd moeten worden in wetenschappelijk onderzoek. De vergelijking tussen 'endoscopic tri-modal imaging' en confocale laser endomicroscopie (wat in feite pathologie in-vivo is) zal tot interessante resultaten leiden.

Conclusie

Dit proefschrift laat zien dat nieuwe imaging technieken steeds vaker worden gebruikt in de dagelijkse coloscopiepraktijk en frequent onderwerp zijn van wetenschappelijke studies. Door de huidige literatuur kritisch te beoordelen hebben we de huidige 'level of evidence' samengevat en een voorstel gedaan voor welke studieopzet het meest geschikt en efficiëntst is voor toekomstig endoscopisch onderzoek.

In ons eigen klinische onderzoek hebben we aangetoond dat nieuwe imaging technieken tijdens coloscopie goed toepasbaar zijn voor zowel patiënten die surveillance ondergaan voor adenomen als voor CU. Het gecombineerd gebruik van AFI en NBI in 'endoscopic tri-modal imaging' lijkt in het bijzonder gemakkelijk te leren en lijkt voornamelijk tot een verbeterde opsporing te leiden van CU-geassocieerde dysplasie en een verbeterde differentiatie tussen dysplastische en niet-dysplastische mucosa. Echter, aangezien wij de eersten zijn die deze voordelen van 'endoscopic tri-modal imaging' hebben aangetoond in relatief kleine studies, is aanvullend wetenschappelijk onderzoek nodig om onze bevindingen te bevestigen in een bredere en meer algemene setting.

Aangezien NBI zich hedendaags snel verspreid over de wereld zullen we een laatste opmerking plaatsen over het gebruik van deze techniek. Narrow-band imaging lijkt tekort te schieten met betrekking tot het verbeteren van het opsporen van adenomen en dysplasie in het kader van CU. Het gebruik van standaard coloscopie lijkt hiervoor voldoende. Echter, voor het opsporen van poliepen bij patiënten met een hyperplastische polyposis syndroom lijkt NBI wel beter te zijn dan standaard coloscopie. Toekomstig onderzoek in grotere studies zal onze resultaten in deze patiëntengroep moeten bevestigen. Voor het endoscopisch onderscheiden van verschillende soorten poliepen in de dagelijkse praktijk lijkt NBI wel voldoende accuraat te zijn. Endoscopisten moeten zich wel realiseren dat er een leercurve is voor dit doeleinde van NBI, en moeten rekening houden met de voorafkans op het hebben van premaligne afwijkingen bij de patiënt alvorens ze deze techniek hiervoor toepassen.

Dankwoord

Dankwoord

En aan het einde van de rit is er dan het dankwoord, wellicht het meest gelezen deel van ieder proefschrift. Heel veel mensen hebben op hun eigen manier een steentje bijgedragen aan de totstandkoming van dit werk en wil ik daarom persoonlijk bedanken.

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Curriculum vitae

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Frank van den Broek werd geboren op 28 september 1978 te Venray als zoon van Piet van den Broek en Getruida van der Wouw. Na het succesvol afronden van gymnasium β aan het Raayland College te Venray, begon hij in 1996 aan de opleiding geneeskunde in het Universitair Medisch Centrum St. Radboud te Nijmegen. Tijdens zijn opleiding deed hij wetenschappelijk onderzoek naar de diagnostiek van appendicitis acuta bij kinderen in het Academisch Medisch Centrum te Amsterdam onder leiding van Prof. Dr. D.C. Aronson. Na het behalen van zijn artsexamen in november 2002 was hij werkzaam als arts-assistent chirurgie in het St. Lucas Andreas ziekenhuis te Amsterdam, het Westfriesgasthuis te Hoorn en het VU medisch centrum te Amsterdam. Vanaf april 2006 verrichte hij wetenschappelijk onderzoek op de afdeling Maag-, Darm- en Leverziekten in het Academisch Medisch Centrum te Amsterdam onder leiding van Prof. Dr. P. Fockens, hetgeen uiteindelijk resulteerde in dit proefschrift. Sinds juli 2009 is hij werkzaam als arts in opleiding tot chirurg in het Kennemer Gasthuis te Haarlem (opleider: Dr. H. Rijna) en het VU medisch centrum te Amsterdam (opleider: Prof. Dr. J.A. Rauwerda). Hij woont samen met Iris Ketel sinds 1999.