The role of endoscopic imaging for an improved diagnosis of colorectal neoplasia
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CHAPTER 9
Narrow band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis

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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). 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. 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. However, endoscopic detection of early neoplasia is difficult in patients with UC because these lesions may be subtle or even grossly invisible. Therefore, surveillance guidelines recommend that in addition to targeted biopsies from suspicious lesions, 2-4 random biopsies should be taken every 10cm of colon. 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.

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. Chromoendoscopy has been shown to improve the detection of neoplasia compared to conventional colonoscopy in patients with ulcerative colitis. 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. 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.

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 pancolitis, disease duration ≥8 years and inactive disease assessed by the Modified Truelove Witts...
Severity Index (MTWSI ≤ 2). 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 reliably 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 (\( \alpha \)) 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.
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.

<table>
<thead>
<tr>
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<th>NBI colonoscopy</th>
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<tr>
<td>Number of false positive lesions</td>
<td>43</td>
<td>16</td>
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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).
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. 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.

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. 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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