The role of endoscopic imaging for an improved diagnosis of colorectal neoplasia
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CHAPTER 1
Review article: New developments in colonic imaging

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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.\textsuperscript{1, 2} Most CRC’s are preceded by premalignant adenomas, providing an opportunity for early detection and removal of these precursor lesions.\textsuperscript{3} Colonic clearing of adenomas reduces the incidence of CRC by approximately 80%.\textsuperscript{4, 5} However, recent reports have shown that some patients under close colonoscopic surveillance still develop CRC at short intervals.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14-18} Therefore, most guidelines recommend taking random biopsies in addition to targeted biopsies of suspicious lesions.\textsuperscript{19-21} Despite this aggressive approach neoplasia is still frequently being missed, leading to interval cancers between successive surveillance colonoscopies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, 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. 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. 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. 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. 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. 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. In the first study 165 patients with UC were randomly assigned to undergo surveillance with either methylene blue CE or SC. 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. 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. Hurlstone et al performed a prospective study in 350 UC patients making use of dye spraying in a targeted fashion. 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. 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. 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 auto fluorescence (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. 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. 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. Fluorescence point spectroscopy proved to be highly accurate for discriminating neoplastic and non-neoplastic mucosa, but was not feasible for broad field surveillance. 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. Recently, video endoscopic auto fluorescence 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. 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 auto fluorescence imaging (AFI) for colonic adenoma detection. Two randomized studies have been performed which were reported in abstract form only. 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. 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. 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 fibre-optic AFI (Xillix) in the second. 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.
Neoplasia associated with UC

The use of AFI for surveillance of patients with UC has been investigated in two studies, both reported as abstracts. 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. 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. 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 colo-
noscopic surveillance in UC. Whether this technique will grow into clinical practice depends on
results of prospective studies, which are being performed.
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new developments in colonic imaging


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