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


