The role of endoscopic imaging for an improved diagnosis of colorectal neoplasia
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CHAPTER 4
Clinical evaluation of endoscopic tri-modal imaging for the detection and differentiation of colonic polyps

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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. Genetic alterations in the mucosa lead to the formation of adenomas, that take a varying time span to progress into CRC. This time span provides an opportunity for detection and removal of adenomas by colonoscopy, thereby preventing their progression into CRC. Periodic removal of all adenomas is estimated to reduce the CRC incidence by 76-90%. Recent reports demonstrated that patients under close colonoscopic surveillance still develop CRC. This may be explained by either rapid progression of adenomas, or by the fact that colonoscopy is not infallible for the detection of adenomas. A systematic review of back-to-back colonoscopies demonstrated that 15-32% of adenomas were overlooked. 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.

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. 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. Concerning the detection of adenomas, NBI has failed to demonstrate an increased yield compared to high resolution endoscopy (HRE) in two randomized studies. For the differentiation of neoplastic from non-neoplastic lesions, however, NBI has an accuracy comparable to CE.

Autofluorescence imaging (AFI) is another novel technique which might improve the detection of adenomas. During AFI, blue light is used for illumination of the mucosa, which leads to fluorescent light emission of colonic tissue. 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.

Endoscopic tri-modal imaging (ETMI) integrates AFI, NBI and HRE into one system. 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). 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).

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-
endoscopic tri-modal imaging for colonic polyps

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. 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. 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. 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.

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 ($\alpha$-error 0.05 and $\beta$-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.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>AFI first (n=50)</td>
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<tr>
<td>Male n (%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Mean age - yrs (SD)</td>
<td>50 (15)</td>
</tr>
<tr>
<td>Median interval to previous endoscopy - yrs (IQR)</td>
<td>2.0 (0.4-2.4)</td>
</tr>
<tr>
<td>Indication for colonoscopy n (%)</td>
<td></td>
</tr>
<tr>
<td>- History of neoplasia</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>- HNPCC</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Genetic mutation positive</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Amsterdam criteria positive</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>- Family history of CRC</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Good colon preparation n (%)</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>Excellent colon preparation n (%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Entire procedural time – min (SD)</td>
<td>55 (26)</td>
</tr>
</tbody>
</table>

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 *adenoma 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 \( \geq 10 \text{mm} \), 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 \( \geq 10 \text{mm} \), none of which were detected during the second inspection. Location and macroscopic appearance of adenomas were not associated with the miss-rate.

<table>
<thead>
<tr>
<th>NBI Classification</th>
<th>Final histopathology</th>
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<tbody>
<tr>
<td></td>
<td>Adenoma</td>
<td>Non-neoplastic</td>
<td></td>
</tr>
<tr>
<td>Kudo type III-V</td>
<td>79</td>
<td>35</td>
<td>114 PPV 69.3%</td>
</tr>
<tr>
<td>Kudo type I-II</td>
<td>9</td>
<td>83</td>
<td>92 NPV 90.2%</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>118</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Sensitivity 89.8%</td>
<td>Specificity 70.3%</td>
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</tr>
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</table>

*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. Chromoendoscopy has shown to improve both the detection and differentiation of colonic polyps. 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. 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. 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. Studies using CE as second examination technique have shown miss-rates as high as 79%. 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. 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. 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. 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. 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. 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.
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 SSA25-31, 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

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.


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.