The serrated neoplasia pathway: investigating the role of serrated polyps in colorectal cancer development

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Increased polyp detection using narrow-band imaging compared to high-resolution endoscopy in patients with hyperplastic polyposis syndrome

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SUMMARY

Background and study aims: Hyperplastic polyposis syndrome (HPS) is associated with colorectal cancer and is characterized by multiple hyperplastic polyps (HPs), sessile serrated adenomas (SSAs) and adenomas. Narrow-band imaging (NBI) may improve the detection of polyps in HPS. We aimed to compare polyp miss-rates of NBI compared to high-resolution endoscopy (HRE).

Patients and Methods: This was a single center, randomized cross-over study in which consecutive HPS patients underwent tandem colonoscopy with HRE and NBI, in randomized order with removal of all detected polyps.

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. In 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.

Conclusion: NBI significantly reduces polyp miss-rates in HPS patients. We recommend using either NBI or chromoendoscopy 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 strongly suggest that serrated polyps are lesions which may lead to CRC with BRAF and CPG-island methylator phenotype (CIMP).[16-20] In addition, clinicohistological reports supporting a serrated neoplasia pathway include CRCs in close vicinity of large hyperplastic polyps [21,22] and CRCs identified in serrated polyps [23-25]. Therefore, serrated polyps seem to represent direct premalignant lesions. SSAs have even been recommended to be managed as conventional adenomas.[26] Serrated polyps in HPS however, have been shown to have even higher numbers of BRAF mutations and CIMP compared to sporadic serrated polyps.[20,27] Moreover, HPS patients have far more serrated polyps than people in the general population. This may (in part) explain the increased risk of CRC in HPS patients. Numerous HPS patients with CRC arising in a serrated polyp have been reported.[23] Thus, detection and removal of serrated polyps seems necessary to prevent CRC in patients with HPS.
In HPS patients however, SSAs and HPs are generally small and flat.[28-30] These features are associated with polyp miss-rates of up to 26% using standard colonoscopy.[31-33] Improved detection of these polyps by using advanced endoscopic techniques seems therefore desirable. Chromoendoscopy has previously been shown to improve the detection of small and flat lesions, specifically HPs, in patients undergoing surveillance colonoscopy.[32-36] 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.[37,38] The aim of this randomized trial was to compare NBI and HRE for the detection of polyps 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 is 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] However, 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. [26,39-41] 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 (100×). 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 cross-over study design with randomized order. Consecutive patients underwent tandem colonoscopy with HRE and NBI by the same endoscopist and the order of these techniques was randomized (figure 1). After informed consent, block randomization was performed by a single investigator by opening sealed opaque envelopes (containing notes with ‘HRE’ or ‘NBI’ in a 1:1 ratio) once the cecum was reached.
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 (>500 NBI colonoscopies).

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.[42] 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 and Paris classification 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. It was not possible to blind the endoscopist to the imaging intervention, and, logistically, it was not possible to have a different endoscopist perform the second examination.
Histopathology

Resection specimens were evaluated by an expert GI pathologist (SvE) who was blinded for endoscopic technique. 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.[19,26,43] As previously described by Torlakovic et al, SSAs were defined by architectural distortion with irregular dilated crypts, including dilatation of the base of the crypts that often have a boot, L or inverted T shape, serration including at the base of the crypts and abnormal proliferation and maturation with mature goblet or foveolar cells at the base of the crypts.[44]

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. Additional exploratory sub-analyses were performed regarding polyp location, -size and -shape.

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%-confidence interval to represent the strength of the association. Histopathology of each polyp served as reference standard. The STARD statements were used for reporting diagnostic test accuracy.[45] In addition the CONSORT statements were used for reporting this randomized controlled trial.[46]
Previous research comparing NBI and HRE for adenoma detection showed a 3.3-fold increase in detection of HPs with NBI.[47] 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%.[31] 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.[48]

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

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

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 58, SSA in 5 and conventional adenoma in 7. Subsequent inspection with NBI added 44 polyps (mean 6.1mm; 2-20) of which 4 with normal histology, 29 HPs, 8 SSAs and 3 conventional adenomas. 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).

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-Ila, 0-Ilb, 0-Ila+c) and protruded (Paris 0-Ils, 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.
<table>
<thead>
<tr>
<th></th>
<th>HRE</th>
<th>NBI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall polyps</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First inspection, n</td>
<td>78</td>
<td>78</td>
<td>.741</td>
</tr>
<tr>
<td>Second inspection, n</td>
<td>44</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Miss-rate, % (95%-CI)</td>
<td>36 (28-45)</td>
<td>10 (5.5-19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Hyperplastic polyps</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First inspection, n</td>
<td>58</td>
<td>26</td>
<td>.181</td>
</tr>
<tr>
<td>Second inspection, n</td>
<td>29</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Miss-rate, % (95%-CI)</td>
<td>33 (24-44)</td>
<td>10 (3.6-26)</td>
<td>.017</td>
</tr>
<tr>
<td><strong>Sessile serrated adenomas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First inspection, n</td>
<td>5</td>
<td>25</td>
<td>.081</td>
</tr>
<tr>
<td>Second inspection, n</td>
<td>8</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Miss-rate, % (95%-CI)</td>
<td>62 (36-82)</td>
<td>14 (5.5-31)</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Adenomas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First inspection, n</td>
<td>7</td>
<td>14</td>
<td>.271</td>
</tr>
<tr>
<td>Second inspection, n</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Miss-rate, % (95%-CI)</td>
<td>30 (11-60)</td>
<td>0 (0-22)</td>
<td>.059</td>
</tr>
</tbody>
</table>

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.
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.

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.[47,49] Table 4 lists all randomized clinical trials comparing NBI with standard white-light endoscopy for the detection of HPs and non-adenomatous polyps. These studies showed that NBI was particularly of value for the detection of HPs.
Table 4: Randomized clinical trials comparing the detection of hyperplastic polyps between narrow-band imaging (NBI) and white light endoscopy (WLE). N, number of patients; RCT, Randomized controlled trial; n.a., not analyzed; n.s., not significant.

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 regarded as disappointing. However, whereas serrated polyps traditionally are considered to be harmless lesions, especially when they are small, recent molecular research in serrated polyps in HPS suggests these are high-risk lesions leading to CRC. [11,16,52,53] 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 relatively small serrated polyps (range: 4-16mm).[54] This supports our opinion 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. \cite{47,49,51,55} 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 (figure 2). Particularly these features may explain the higher miss-rate of serrated polyps by HRE.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{example_images.png}
\caption{Examples of detected flat sessile serrated adenomas imaged with high-resolution endoscopy (A + C) and corresponding images with narrow-band imaging (B+D).}
\end{figure}

Several remarks regarding this study must be made before making any firm recommendations 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.[56] However, in our study the endoscopist had already performed more than 500 colonoscopies with NBI, making a learning effect with regard to HRE unlikely. Secondly, 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). These numbers approximate the true (detected and undetected) number of baseline polyps in each group. 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 between HPS patients will easily lead to unequal numbers of polyps after randomization of only 22 patients. Due to this expected unequal distribution of baseline polyp numbers, we chose a cross-over study design which compares the percentage of missed polyps (i.e. polyp miss rates) with each modality independent of the total number of baseline polyps in each group instead of comparing the total number of detected polyps (i.e. detection rates). Contrary to polyp miss-rates, polyp detection rates are also dependent on the total number of baseline polyps present in each group. Detection rate analysis is therefore only possible when baseline polyp numbers are equal between groups. For this reason detection rate analysis in the setting of our study would have been unsuitable. If we would have compared polyp detection rates at first inspection, one would expect a bias in favour of the group with more baseline polyps. In our study that would have resulted in a bias in favour of HRE (n=122) and against NBI (n=87). This bias also explains the equal number of detected polyps at
first inspection with HRE and NBI while after second inspection polyp miss-rates with HRE were higher. Finally, this pilot study was performed by a single experienced endoscopist who was unblinded to the imaging intervention. Although comparison of investigation times between randomization groups (both >6 minutes per inspection) showed no significant differences at first and second inspection, a bias by the endoscopist in favour of NBI can not be excluded. Nevertheless, the significantly large difference in miss-rates between NBI and HRE for the detection of polyps in HPS warrants confirmation in a subsequent multi-centre study involving more patients and different endoscopists.

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 this surveillance strategy 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).[48] Differentiating these diminutive premalignant polyps from HPs with NBI by means of polyp colour differentiation (lighter than the surrounding mucosa is unsuspicious; darker than or the same as 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 the same as the surrounding mucosa may be sufficient for polyps of this size.

Previously randomized studies have shown that chromoendoscopy increases the detection of sporadic HPs in non-HPS patients compared to standard white-light endoscopy.[57-60] Our
study with NBI (“electronic chromoendoscopy”), which allows the endoscopist to switch between modalities at a switch of the button, showed similar results for the detection of serrated polyps in HPS patients. Although the value of chromoendoscopy in HPS has not formally been investigated, this cheap and readily available technique seems to be a valid alternative for the endoscopic surveillance of HPS patients.

In summary, this pilot study demonstrated that NBI is associated with a reduced polyp miss-rate when compared to HRE in patients with HPS. These findings suggest that all polyps in patients with HPS need to be resected during colonoscopic surveillance, which should be done using either NBI or chromoendoscopy.
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