Cap cuff–assisted colonoscopy versus standard colonoscopy for adenoma detection: a randomized back-to-back study

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Running title
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N. Gennarelli: acquisition of data; analysis and interpretation of the data; drafting of the article; final approval of the article
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S. Siciliano: acquisition of data; analysis and interpretation of the data; drafting of the article; final approval of the article
B. Manzo: acquisition of data; analysis and interpretation of the data; drafting of the article; final approval of the article
G. Cassese: acquisition of data; analysis and interpretation of the data; drafting of the article; final approval of the article
G. Luglio: critical revision of the article for important intellectual content; final approval of the article

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ABSTRACT

Background and Aims EndoCuff is a disposable device applied to standard colonoscopes to improve mucosal visualization. Randomized parallel trials have shown that EndoCuff increases the adenoma detection rate (ADR). The primary aim of this study was to compare the ADR between EndoCuff-assisted colonoscopies (EAC) and standard colonoscopies (SC) within a randomized back-to-back trial.

Methods This is a single-center randomized crossover study (NCT02374515) involving adult patients undergoing screening, surveillance or diagnostic colonoscopy. Participants received back-to-back SC and EAC in a random order, performed by the same endoscopist. All polyps were excised, but only those proven at histology to be adenomas were considered for analysis.

Results From February 2015 to March 2016, 288 patients were enrolled and 274 were included in the per-protocol analysis. Compared with SC, EAC increased the ADR (29.6% vs 26.3%, p<0.01) and the number of diagnosed adenomas (176 vs 129, p<0.01), particularly in the left (73 vs 46, p<0.01) and right sides of the colon (83 vs 63, p<0.01). EAC increased the detection of adenomas smaller than 5 mm (129 vs 84, p<0.01), but no difference was found with regard to larger lesions. In 7.3% of patients, findings of EC shortened the surveillance interval determined by SC findings. EndoCuff caused 7 mucosal erosions (2.5% of patients) requiring a mucosal adrenaline injection in one case.

Conclusion The use of EndoCuff increases the number of identified adenomas, primarily small adenomas in the left and right sides of the colon. This increases the ADR and allows a better definition of the surveillance program.

KEY WORDS: adenoma detection rate; colonoscopy; Endocuff-assisted colonoscopy

Introduction

Colonoscopy prevents colorectal cancer (CRC) by identifying and removing adenomas\(^1\). Nonetheless, colonoscopy is an imperfect prevention tool, as confirmed by the occurrence of interval CRCs after negative colonoscopies\(^2\). Most of these cancers develop from adenomas missed during the examination\(^3\)\(^-\)\(^5\). Back-to-back studies have estimated the adenoma miss rate to be about 20\%\(^6\)\(^-\)\(^7\). One of the causes of overlooked adenomas is the incomplete visualization of mucosa. It is estimated that about 10\% of the internal colonic surface falls outside the field of
view of standard colonoscopes. This happens mostly in correspondence of flexures and folds and most of the missed lesions are indeed located in these blind areas.

In order to improve mucosal visualization, a number of devices have been proposed. Endoscopes with a large field of view, of up to 330°, and auxiliary-probes allowing a back view have been made available, but both represent a costly investment. Disposable devices have also been conceived. These tools mainly consist of plastic devices which are applied to the tip of standard colonoscopes. Due to their shape, these devices stretch the mucosa and flatten colonic folds during the scope withdrawal, thus improving the inspection of these areas.

EndoCuff is a disposable device which has on its external circumference a double row of flexible finger-like projections oriented backward. Randomized parallel trials have shown that compared to standard colonoscopies, EndoCuff improves the adenoma detection rate (ADR) and increases the number of detected adenomas. Nonetheless, parallel trials have some limits and randomized cross-over studies with back-to-back examinations are advocated to evaluate new endoscopic techniques. The diagnostic advantages of EndoCuff have not been investigated with this sort of study to date.

The primary aim of this study was therefore to compare the ADR between EndoCuff-assisted colonoscopies (EAC) and standard colonoscopies (SC) within a randomized back-to-back trial. The number of detected adenomas and consequent changes in the surveillance program, the time needed for cecal intubation and adverse events were also compared.

Methods

Study design and patients

This is a single-center randomized crossover study. Between February 2015 and March 2016, all consecutive patients undergoing a screening, surveillance or diagnostic colonoscopy at our center were screened for eligibility. Patients were considered not eligible in the case of age <18 or >80 years, pregnancy, known or suspected inflammatory bowel disease, bowel stricture, or acute inflammation.

Participants received back-to-back tandem colonoscopies with and without the use of the EndoCuff (Arc Medical Design, Leeds, England) device according to a randomized cross-over design without removal of polyps. A computer-generated sequence randomly allocated blocks of eight patients to receive, with a 1:1 ratio, either standard colonoscopy (SC) or EndoCuff-assisted colonoscopy (EAC), immediately followed by the other procedure (Figure 1). Doctors screening and informing patients for trial participation were blinded to the block size. After receiving appropriate consent from the patient, a trained doctor opened the envelope.
containing the allocation card. Patients were not blinded to the randomization group. This trial was approved by the “Federico II” University of Naples Institutional Review board (internal reference number, 230/14) and was registered with clinicaltrials.gov (NCT02374515). Written informed consent was obtained from all participants. The study was implemented and reported on according to the CONSORT statement, applicable to randomized cross-over studies, and to the available recommendations specific to this type of design.

Endoscopic procedures

All patients underwent colonoscopy preparation using a polyethylene glycol-based solution. Colonoscopies were performed with patients in conscious sedation obtained administering intravenous midazolam. All procedures were carried-out by four experienced endoscopists (G.D.P., N.G., S.S., and F.M.), each having performed more than 1,000 standard colonoscopies and at least 20 EACs. The procedures were performed using an Olympus CF-HQ190 or a CF TYPE Q180AL/I colonoscope, both with a 170° field of view. According to the randomization group, the endoscope was equipped or not with the device and was advanced to the cecum, where a photograph showing the ileocecal valve and/or the appendiceal orifice was taken. The scope was then slowly retrieved and the mucosa carefully inspected during a withdrawal time of at least 6 minutes. An inversion view in the rectum was obtained for all patients. The second procedure was performed by the same endoscopist using the same colonoscope after having either removed or added EndoCuff. The quality of bowel preparation was graded according to the Boston Bowel Preparation Scale (BBPS). Patients were excluded from the trial in the case of a BBPS score ≤ 5. Lesions detected during the first procedure were left in situ, to be removed at the end of the second procedure. According to the location, lesions were classified as belonging to the right side (cecum-ascending-hepatic flexure), transvers, and left (rectum, sigmoid, descending, splenic flexure) side of the colon. Both the time needed to reach the cecum and the withdrawal time were recorded. The time needed for polypectomies was deducted from the total withdrawal time. In the case of an inability to detect the lesion during the second procedure, a third procedure was carried out on the same day using the first technique. Any polypoid lesion was excised. Nonetheless, only lesions proven to be adenomatous at histology were considered in the analysis.

Outcomes

The primary outcome was the adenoma detection rate (ADR). Secondary outcomes were the number of detected adenomas, the adenoma miss rate (AMR), the rate of false-negative procedures at first-pass, the cecal intubation time, and changes on the surveillance interval time. Subset analyses were performed according to the size and location of adenomas.
Statistical analysis and sample size

The study had a 2x2 crossover design that was uniform in sequences and periods. The sample size required to show a 10% increase in the ADR by EACs, considering a 2% false negative EAC in patients with positive SC, was 274 patients. This calculation was based considering an \( \alpha \) of 0.01 and a power of 0.90. Patients were therefore enrolled in the trial until at least 137 were assessable for the Per-Protocol analysis in each group. The per-protocol analysis included all patients in whom the cecum was reached in both procedures. Patients were excluded from the analysis in the case of poor bowel preparation or when the cecum was not reached.

Categorical data were presented as frequency counts and associated rates were presented as percentages. In the case of symmetric distribution, data were presented as mean and standard deviations, whereas in the case of skewed distributions data were presented as medians and ranges. The crossover analysis of outcomes of paired back-to-back procedures was conducted using a generalized linear mixed model (GLMM). Rates and 95% confidence intervals (95% CI) were computed according to Schouten et al.\textsuperscript{22} Period effects were considered negligible in view of the design uniformity. Although lesions detected during the first pass were not removed, the examiner performing the second procedure was aware of the results of the first procedure and the risk of a carry-over effect between the 2 procedures was therefore present. Hence, the presence of a carryover effect was searched for by a GLMM. Paired variables were compared through McNemar test in the case of categorical data, whereas continuous variables were compared by the paired T-test or by a paired Wilcoxon signed-rank test. In the case of unpaired variables, comparisons were made by means of Pearson \( \chi^2 \) test, T-test and the Wilcoxon-Mann-Whitney test according to the type and distribution of variables.

A \( P \) value equal to or less than 0.01 was considered to be statistically significant for all tests. Statistical analyses were performed using the statistical computing environment R (R Foundation for Statistical Computing, Vienna, Austria).
Results

Study population

Between February 2015 and March 2016, 2453 patients underwent colonoscopy at our center. Of these, 2184 met the inclusion criteria and were therefore considered for enrolment in the study. After receiving appropriate information, 288 patients (13.1%) finally consented to participate and were randomly assigned to the SC first group or EAC first group. Of these, 274 patients (137 in each group) completed the study and were included in the final per-protocol analysis (Figure 2). The two groups were balanced in terms of age (p=0.652), gender (p=0.904), indication for colonoscopy (p=0.819), BPPS (p=0.407) and the endoscopist performing the procedures (p=0.977) (Table 1). A total of 285 polypoid lesions were excised and 188 (65.9%) turned out to be adenomas at histology and were eventually considered for the final analysis.

Adenoma detection rate

In the SC first group, adenomas were found in 39 patients on the first pass (ADR 28.5%, Table 2). The following EACs detected adenomas in additional four patients (ADR 31.3%). In the EAC first group, the first-pass ADR was 27.7%, as adenomas were found in 38 patients. SC did not identify any further patient with adenoma, but was negative in five patients with positive EACs (ADR 24.1%). The presence of a carry-over effect was excluded (p=0.49); this means that the results of second procedures were not significantly influenced by those of first procedures. The overall results are shown in Table 3. EAC increased the ADR (29.6% vs 26.3%) by 3.28 (95% CI, 1.17-5.39; p=0.003) percentage points.

Number of adenomas and adenoma miss rate.

In the SC first group, 71 adenomas were detected on the first pass. During the second pass, EAC identified a further 30 adenomas missed by SC (AMR of 29.7%). The characteristics of missed adenomas are shown in Table 4. During the second pass, however, EAC missed 11 adenomas previously detected. Hence, EAC determined a net adenoma increase rate of 21.1% (n= 19).

In the EAC first group, 86 adenomas were detected during the first pass. The following SC identified 58 adenomas, of which only one was missed on the first pass (AMR 1.1%). Overall, EAC detected a greater number of adenomas than SC (176 vs 129, p<0.001).

Compared with SC, EAC identified more adenomas smaller than 5 mm in diameter (129 vs 84, p<0.001, Table 3). Conversely, there was no difference in the detection of adenomas with diameters between 5 and 10 mm (35 vs 29, p=0.0568) and advanced adenomas (>10mm: 12 vs 16,
According to the location, EAC significantly increased the number of detected adenomas in the left (73 vs 46, \(p=0.009\)) and right (83 vs 63, \(p=0.001\)) sides of the colon (Table 3).

**Impact on surveillance program**

Considering U.S. guidelines on CRC screening and surveillance\(^2\), the EAC results shortened the surveillance interval time suggested by the SC results in 20 patients (7.3%). On the contrary, the SC results shortened the surveillance interval time suggested by the EAC results in 1.4% of patients. In the SC first group, the second pass shortened the surveillance interval in 10 patients (7.3%), whereas in the EAC first group this occurred only once (0.7%).

Considering the European guidelines for colonoscopic surveillance after adenoma removal\(^2\), EAC shortened the surveillance interval time in 18 patients (6.6%), whereas SC did this in four patients (1.4%). In the SC first group the second pass shortened the surveillance interval in nine patients (6.5%), whereas in the EAC first group this occurred only once (0.7%). Table 5 shows in more detail the impact of the different procedures on the surveillance interval.

**Cecal intubation and times**

Considering the intention-to-treat population, there was no difference in the rate of cecal intubation (\(p=0.561\)). The cecal intubation time (CIT) was shorter during EACs (-29.6 seconds; 95% CI, -40.1 to -19.1; \(p<0.001\)). This difference emerged mostly during the second procedures (Table 6). There was no difference in the withdrawal time between SC and EAC (\(p=0.06\), Table 6).

**Safety of Endo-cuff assisted procedures**

A total of nine adverse events occurred in nine patients during 274 EACs (3.3%). In 2 cases (0.7%), EndoCuff undocked from the colonoscope during withdrawal. In both cases, the event was promptly recognized and the device was uneventfully recovered. In 7 cases (2.5%) the device caused mucosal erosions. The resulting bleeding spontaneously resolved in 6 cases during the observation, whereas in 1 case a mucosal adrenalin injection was required.

**Discussion**

This is the first back-to-back trial investigating the advantages of using EndoCuff. Compared to SC, EAC was found to increase the ADR and the number of identified adenomas, thus allowing a more accurate definition of the surveillance interval.

ADR is considered the main indicator of colonoscopy quality and the main predictor of interval cancer\(^2\). Compared with SC, in this study EAC determined an absolute increase of the ADR of 3.28 percentage points (29.6% vs 26.3%). This result falls in the middle of the range of
results reported by the randomized parallel trials conducted to date. Van Doorn et al\textsuperscript{16} found that EAC did not improve ADR, although their trial was underpowered because the ADR was a secondary endpoint. Conversely, Biecker et al\textsuperscript{15} and Floer et al\textsuperscript{14} found that EAC increased the ADR by 8 and 14.7 percentage points, respectively. Both trials were carried out by the same research group and were mostly conducted in the same hospital setting; nonetheless, the results significantly differed from each other. This might be perhaps the consequence of the parallel design of their trials, where results suffer from noise due to an imbalance in arms, which might occur despite randomization\textsuperscript{17}. In addition, all randomized trials conducted so far have used both 140° and 170° colonoscopies, but none reported if the arms (SC and EAC) were balanced for the type of colonoscope used\textsuperscript{14–16}. If not, this might have acted as a further and important confounding factor.

In the present study, the EAC significantly increased the number of identified adenomas by about 36% (176 vs 129 detected by SC). This resulted in a significantly higher mean number of detected adenomas per patient (0.64 vs 0.47), a further indicator of the quality of colonoscopy\textsuperscript{25}. In particular, EAC improved the detection of small adenomas (<5 mm), as had already been found by van Doorn et al\textsuperscript{16}. Conversely, in our hands, EAC had no impact on the detection of advanced lesions (>10 mm), in contrast with Floer et al.\textsuperscript{14} Indeed, in our study EAC surprisingly missed 4 advanced lesions detected by SC. The reason behind this is not immediately clear. It is difficult to believe that EndoCuff improves the detection of diminutive adenomas and worsens the detection of larger ones. A post-hoc analysis showed that these adenomas were missed in 3 patients having multiple advanced adenomas. Hence, it is possible that the “one and done” phenomenon might have played a role in these cases\textsuperscript{26}. However, advanced adenomas were less than 10% of adenomas found in our trial. This subgroup analysis might consequently be underpowered and the real impact of EAC on the detection of advanced lesions needs to be verified on larger samples, even to reduce statistical noise.

In the present study, EAC improved the ADR primarily enhancing the detection of diminutive adenomas. These adenomas rarely show high-risk features (ie, villous elements or high grade dysplasia)\textsuperscript{27} and progress very slow into cancer\textsuperscript{28}. Hence, it is reasonably questioned whether such “enhanced-ADR” really contributes to the prevention of interval cancers\textsuperscript{29}. On the other hand, even in a standard setting of SC, the ADR is mainly determined by diminutive adenomas, which are the majority of adenomas detected\textsuperscript{30}. Nevertheless, ADR has emerged as predictor of interval cancer and indicator of colonoscopy quality\textsuperscript{2}. Indeed, patients with multiple diminutive adenomas are at higher risk of developing advanced adenomas CRC and consequently benefit of a stricter surveillance, as suggested by guidelines on surveillance after gold screening and polypectomy\textsuperscript{23,24,31}. The back-to-back design of the present study allowed us
to analyze how the use of EndoCuff affected the definition of surveillance timing, which might play a central role in reducing the risk of interval cancers. EAC shortened the surveillance interval suggested by SC in about 7% of patients, whereas SC shortened the surveillance interval time recommended by the EAC results in about 1% of cases.

The clinical impact of the abovementioned findings, beyond the statistical significance, needs to be discussed. A 3.28% absolute increase in ADR implies that compared to SC, EAC identifies an additional patient with adenoma every 31 colonoscopies (number needed to treat = 1/0.0328). It is estimated that a 1% absolute increase in the ADR corresponds to a 3% decrease in the risk of interval CRC\(^3\). In the light of our findings, using EndoCuff would result in a 10% decrease of this risk. In addition, EndoCuff ensures a more correct definition of the surveillance interval in 5.9% and 5.2% of patients, considering U.S. and E.U. guidelines, respectively. This means that, compared to SC, EAC determinates a more correct interval of surveillance in one patient every 17 and 19 colonoscopies.

In light of these results, the cost of the improvements achieved by EAC can be analysed. Considering that each device has a cost of 30€, avoiding one false-negative SC is achieved at a cost of 930€. Achieving the correction of one wrong surveillance interval suggested by SC has instead a cost of 510€ and 570€, considering U.S. and E.U. guidelines, respectively\(^23,24,31\).

This study has several strong points. First, a randomized crossover design without removal of polyps was adopted\(^17\). This design avoids the noise present in parallel trials due to imbalances in arms\(^17\). In addition, back-to-back examinations allow for the analysis of the characteristics of lesions missed by one technique and detected by the other\(^17\). Furthermore, leaving in situ lesions on the first pass enables a paired analysis between the two procedures to be undertaken. Indeed, each patient acts as his own control, thus reducing potential confounding factors and allowing further analysis (eg, effect on surveillance). The outcomes analysis was based on the histological examination, as only lesions diagnosed as adenomas were considered. All endoscopists had more than 10 years of experience each, performing at least 500 colonoscopies per year. As counterproof, the good quality of colonoscopies was verified by an ADR of above 25% in the course of SC\(^32\). Hence, the above reported advantages of EndoCuff were seen in the hands of experienced endoscopists. Therefore, it is possible that the diagnostic yield conferred by EndoCuff could be even greater in the practice of less-expert endoscopists.

Some limitations of this study need to be mentioned. This study was conducted on a mixed population of patients undergoing a screening, surveillance, or diagnostic colonoscopy, which makes our findings applicable to daily practice. However, the diagnostic yield of the EAC within each of these categories of patients has not been explored. Indeed, the prevalence of
adenomas among patients varies according to the indication for colonoscopy. Whether the diagnostic profit of EndoCuff might change according to the indication, needs to be estimated by further studies tailored to specific categories of patients. The same endoscopist performed both procedures, which immediately followed each other. This implies that the examiner of the second procedure was aware of the findings of the first. The significant effort of the endoscopist to recover during the second procedure lesions already detected during the first pass might have created a non-realistic condition. The possible carryover effect between the procedures, which however would have been equally present in both groups, was excluded by a tailored statistical analysis. In addition, alternatives were impracticable. Delaying in time the 2 procedures was considered not feasible, both in terms of hours (e.g., double sedation) and days (e.g., double-bowel preparation, loss of working days, and high risk of drop out). A different examiner performing the second procedure would have introduced bias in terms of scoping technique. A further limitation is that the endoscopists were not blinded for the presence or absence of EndoCuff and this might have influenced their efforts to look for lesions. However, we did not find a significant difference in the withdrawal time. The BBPS was recorded only during the first procedures and no difference was found between the groups (Table 1). As consequence of cleaning and rising during the first procedure, it is possible that the BBPS might have improved at the time of the second procedures, thus favoring the adenoma detection. Nevertheless, it can be rationally supposed that this happened in both groups, thus favouring both SC and EAC performed on the second pass. Hence, the improvement of BBPS during the second procedures should not have acted as confounding factor.

A novel version of the device is now available, EndoCuff Vision. This version differs from the one used in this study because it has a single row of finger-like projections. It is likely that this improvement will reduce the rate of mucosal erosions, although robust data are not available yet. The docking mechanism of EndoCuff Vision has instead mainly remained unchanged compared with the previous version. Although we experienced 2 uneventful episodes of device dislocation (0.7%), we believe that careful positioning of the device and avoidance of lubricants on the tip of endoscope are sufficient to guarantee a tight fit along the procedure. A pilot study has shown greater improvements in ADR with EndoCuff Vision compared with the previous version, but these data need to be confirmed by larger studies. A multicenter parallel randomized trial is currently ongoing to detect the accuracy of EndoCuff Vision.

In conclusion, in this back-to-back study, the use of EndoCuff permitted to identify more small adenomas than standard colonoscopy, thus increasing the ADR and allowing a more correct definition of the surveillance interval. Further studies are needed to evaluate the
diagnostic yield of EndoCuff within specific categories of patients according to the indication for colonoscopy. In addition, dedicated economic analysis would be useful to quantify the cost/benefit ratio, primarily in comparison with other techniques (eg, full-spectrum endoscopy). Finally, the ultimate goal in this field of research is the prevention of interval carcinomas. Nonetheless, current studies are looking to intermediate endpoints, such as ADR. Long-term follow-up results of randomized parallel trials are needed to verify whether or not EndoCuff really lowers the occurrence of interval cancers.

References


**Table 1.** Characteristics of patients by randomization group (Per-Protocol population)

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy first $n = 137$</th>
<th>EndoCuff colonoscopy first $n = 137$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> $^a$</td>
<td>55.7 ± 12.31</td>
<td>55.06 ± 12.58</td>
<td>0.652</td>
</tr>
<tr>
<td><strong>Gender (F)</strong></td>
<td>65 (47.4%)</td>
<td>66 (48.2%)</td>
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<tr>
<td><strong>Indication for colonoscopy</strong></td>
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<td>0.819</td>
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<tr>
<td>Surveillance</td>
<td>62 (45.2%)</td>
<td>57 (41.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Screening</td>
<td>29 (21.2%)</td>
<td>32 (23.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>46 (33.6%)</td>
<td>48 (35%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>BBPS</strong></td>
<td>7.18 ± 0.97</td>
<td>7.08 ± 1.06</td>
<td>0.407</td>
</tr>
</tbody>
</table>

*BBPS, Boston Bowel Preparation Scale*

$^a$Data are presented as mean and standard deviation
Table 2. Adenoma detected, by randomization group (per-protocol population)

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy first ( n = 137 )</th>
<th>EndoCuff colonoscopy first ( n = 137 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with at least one adenoma detected (ADR)</strong></td>
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</tr>
<tr>
<td>First procedure</td>
<td>39 (28.5%)</td>
<td>38 (27.7%)</td>
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<tr>
<td>Second procedure</td>
<td>43 (31.3%)</td>
<td>33 (24.1%)</td>
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<tr>
<td><strong>False negative first procedures, ( n ) (%)</strong></td>
<td>4 (2.9%)</td>
<td>0</td>
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<tr>
<td><strong>Adenomas detected, ( n )</strong></td>
<td></td>
<td></td>
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<tr>
<td>First procedure</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Second procedure</td>
<td>90</td>
<td>58</td>
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<tr>
<td><strong>Adenomas detected by dimension, ( n )</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First procedure</td>
<td>41</td>
<td>66</td>
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<td>Second procedure</td>
<td>63</td>
<td>43</td>
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<tr>
<td>5-10 mm</td>
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<td>Second procedure</td>
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<td>&gt;10 mm</td>
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<td>First procedure</td>
<td>13</td>
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<td>Second procedure</td>
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<td><strong>Adenomas detected by location</strong></td>
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<td>Right side of colon</td>
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<td>First procedure</td>
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<td>Second procedure</td>
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<tr>
<td>Transverse colon</td>
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</tr>
<tr>
<td>First procedure</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Second procedure</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Left side of colon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First procedure</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>Second procedure</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>
Table 3. Adenoma detected, overall results

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy</th>
<th>EndoCuff colonoscopy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adenoma (ADR)</td>
<td>72 (26.3%)</td>
<td>81(29.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adenoma detected, n</td>
<td>129</td>
<td>176</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adenoma detected, by dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>84</td>
<td>129</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-10 mm</td>
<td>29</td>
<td>35</td>
<td>0.056</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>16</td>
<td>12</td>
<td>0.317</td>
</tr>
<tr>
<td>Adenoma detected, by location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side of colon</td>
<td>63</td>
<td>83</td>
<td>0.002</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>20</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Left side of colon</td>
<td>46</td>
<td>73</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Table 4. Adenoma missed, by randomization group (Per-Protocol population)

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy first n = 137</th>
<th>EndoCuff colonoscopy first n = 137</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adenomas detected (n)</td>
<td>101</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Adenoma missed on the first pass, (AMR)</td>
<td>30 (29.7%)</td>
<td>1 (0.01%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adenoma missed on the first pass, by dimension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5 mm</td>
<td>25 (83.3%)</td>
<td>1 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>5-10 mm</td>
<td>3 (10%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>2 (6.7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adenoma missed on the first pass, by location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right side of colon</td>
<td>14 (46.7%)</td>
<td>1 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left side of colon</td>
<td>16 (53.3%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AMR, adenoma missed rate
Table 5. Impact on surveillance interval

<table>
<thead>
<tr>
<th></th>
<th>US guidelines</th>
<th>EU guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC shortened SI compared to EAC</td>
<td>4 pts (1.4%)</td>
<td>4 pts (1.4%)</td>
</tr>
<tr>
<td></td>
<td>- 4pts from 5-years to 3-years</td>
<td>- 1pt from Routine to 1-year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 3 pts from Routine to 3-years</td>
</tr>
<tr>
<td>EAC shortened SI compared with SC</td>
<td>20 pts (7.3%)</td>
<td>18 pts (6.6%)</td>
</tr>
<tr>
<td></td>
<td>- 4pts from 10-years to 3-years</td>
<td>- 1pt from Routine to 1-year</td>
</tr>
<tr>
<td></td>
<td>- 3pts from 10-years to 5-years</td>
<td>- 16 pts from Routine to 3-years</td>
</tr>
<tr>
<td></td>
<td>- 13 pts from 5-years to 3-year</td>
<td>- 1 pt from 3-years to 1-year</td>
</tr>
</tbody>
</table>

SC standard colonoscopy, SI surveillance interval, EAC EndoCuff-assisted colonoscopy
Table 6. Cecal intubation time

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy</th>
<th>EndoCuff colonoscopy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal intubation time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First pass</td>
<td>300 [85-599]</td>
<td>300 [54-640]</td>
<td>0.881</td>
</tr>
<tr>
<td>Second Pass</td>
<td>330 [86-780]</td>
<td>276 [51-600]</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall</td>
<td>320 [85-780]</td>
<td>300 [51-640]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Withdrawal time</td>
<td>402 [332-469]</td>
<td>391 [355-474]</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Time is reported in seconds.
Figure 1. Study design
SC Standard colonoscopy, EAC EndoCuff assisted colonoscopy

Figure 2. CONSORT diagram
SC Standard colonoscopy, EAC EndoCuff assisted colonoscopy
Randomization

SC first group

1st procedure
Polyps not removed

2nd procedure
Removal of all polyps

EAC first group

SC

EAC

EAC
Patients assessed for eligibility (n=2453)

- Not meeting inclusion criteria (n=269)
- Declined to participate (n=1896)

Randomized (n=288)

Allocated to SC first (n=144)
- Discontinued (n=7)
- Poor bowel preparation (n=5)
- Cecum not reached (n=2)

Included in the per-protocol analysis (n=137)

Allocated to EC first (n=144)
- Discontinued (n=7)
- Poor bowel preparation (n=6)
- Cecum not reached (n=1)

Included in the per-protocol analysis (n=137)
Acronyms

ADR: adenoma detection rate
EAC: Endocuff-assisted colonoscopy
SC: standard colonoscopy
AMR: Adenoma miss rate