Colon Capsule Endoscopy for colonic surveillance

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Abstract:

Background: Resources used on surveillance colonoscopies are taking up an increasing proportion of colonoscopy capacity. Colon capsule endoscopy (CCE) is a promising technique for non-invasive investigation of the colon.

Aim: To investigate CCE as a possible filter in colonic surveillance with the primary outcome to reduce the number of colonoscopies.

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Method: Patients scheduled for follow-up colonoscopy were subjected to a primary CCE and only supplemental conventional endoscopy if significant pathology was detected or if the CCE examination was incomplete. Significant pathology was defined as more than two small polyps or one polyp >9 mm or any polyp in patients with hereditary non-polyposis colorectal cancer. Supplemental endoscopy was carried out to the extent needed to resect the detected polyps and investigate the parts of colon not sufficiently visualized by the capsule.

Results: A total of 180 patients were included. A complete CCE with no significant findings was found in 77 patients (43%). A complete colonoscopy was carried out in 67 patients (37%) and 36 patients (20%) underwent a sigmoidoscopy. In the 103 patients undergoing endoscopy, 59 patients (57%) had no adenomas detected, 33 patients (32%) had “low risk adenomas”, and 11 patients (11%) had “high risk adenomas”.

Conclusion: The introduction of CCE as filter test in colonic surveillance reduced colonoscopies by 43%, but implies leaving polyps untreated behind and is not cost-effective. The CCE completion rate must be improved.

What does this paper add to the literature?

This is the first study to date investigating the potential of colon capsule endoscopy as a filter test to colonoscopy in colonic surveillance. We find that it reduced the number of colonoscopies by 43%, but requires leaving small polyps untreated, and colon capsule completion rates must be improved.

Introduction:

Surveillance colonoscopies are taking up a large proportion of colonoscopy capacity. The two primary indications are personal history of colorectal adenomas or familial history of colorectal cancer (CRC). The rationale for surveillance is the increased risk of developing colorectal cancer within these groups [1, 2]. With the onset of colorectal cancer screening surveillance colonoscopies...
are expected to account for up to 50% of screening derived colonoscopies [3, 4]. As colonoscopy capacity is limited, means to achieve adequate surveillance and reduce demand for colonoscopy are sought for. Colon capsule endoscopy (CCE) is a minimally invasive technique for investigation of the colon. In a small study of 62 faecal test positive screening individuals Holleran et al. concluded that CCE could be a useful ‘filter test’ to colonoscopy and reduce colonoscopy demand by 71% [5]. Spada et al. published a review and meta-analyses of the diagnostic accuracy of the second generation CCE compared to colonoscopy in 2016 [6]. For polyps ≥ 10 mm, they found a per-patient sensitivity of 87% and a specificity of 95.3%. Since then two larger scale studies have been published finding similar results. Parodi et al. reported an 89% sensitivity and a 95% specificity for polyps ≥10 mm, and we found a CCE per-patient sensitivity and specificity for polyps ≥10 mm of 87% and 92% respectively. In complete CCE exams we found a sensitivity of 93% in detecting individuals at increased risk requiring colonoscopy for polyp removal, using a threshold of more than two polyps or at least one polyp >10 mm [7]. In this light, CCE seems a lenient method to function as a filter-test in colonic surveillance, in order to reduce the number of scheduled colonoscopies. The ability to accurately discriminate, between those requiring a colonoscopy and those who don’t, is of paramount importance if CCE is used as a filter test. To this date, all studies on the colon capsule have focused on the diagnostic accuracy of CCE compared to colonoscopy, performing blinded procedures. No trials have investigated the effect of CCE as an actual filter to an un-blinded colonoscopy.

The aim of this study was to investigate the short term clinical consequences of CCE as a filter test before an un-blinded surveillance colonoscopy, with the reduction in colonoscopies as the primary outcome.

**Material and methods:**

The patients included derive from a prospective randomized trial evaluating three different booster regimens for CCE. The primary endpoint was completion rate and no significant differences were found between the regimens used [8].

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Inclusion criteria were patients aged 18-70 years scheduled for surveillance colonoscopy between February 1\textsuperscript{st} 2017 and November 1\textsuperscript{st} 2017. Another inclusion criterion was at least one additional colonoscopy planned within the next five years regardless of the result of the current investigation. Exclusion criteria were a history of previous bowel resection, known gastrointestinal strictures, inflammatory bowel disease, renal insufficiency, implanted electronic devices, pregnancy, breast feeding, allergy towards active preparation and booster substances and familial adenomatous polyposis. Participants were prepared with a two liter split dose polyethylene glycol preparation, swallowed the PillCam Colon II (Medtronic, USA) and received one of the three booster regimens. The CCE video recordings were read by trained personnel (Corporate Health\textsuperscript{®}, Hamburg, Germany). The reports contained the information on extent of colon visualized, grade of bowel cleanliness 1-4\textsuperscript{[9]} and any suspicious lesions were documented by still images together with the estimated location (right, transverse, left colon and rectum). The size of polyps was measured in mm. Analyses of the video recordings were done using the Rapid Reader\textsuperscript{®} software (Given Imaging, Israel). All participants with either inadequate bowel cleansing or incomplete video due to slow transit underwent supplemental endoscopy to investigate the parts of the colon not visualized by CCE. Participants with hereditary non-polyposis colorectal cancer (HNPCC) who had any polyp found on CCE were referred for therapeutic endoscopy. All other participants were only referred for endoscopy if there were more than two polyps irrespective of the size or one polyp > 9 mm. The endoscopists were aware of the CCE findings and endoscopies were carried out to the extent necessary to retrieve the suspected findings and to investigate the parts of colon not sufficiently visualized by the capsule.

The CCE examination was regarded as complete, when achieving a complete video recording of the colon and rectum with adequate cleansing (grade ≥ 2). Clinical outcome parameters included the number of participants referred for endoscopy after CCE, the polyp findings and risk stratification according to the European Society of Gastroenterology guidelines [3]. We compared the polyp findings in CCE and colonoscopy in the patients who had a complete CCE and underwent full...
colonoscopy. The polyp findings in CCE and colonoscopy were matched using a best-fit first approach matching polyps within a 50% size range of the CCE and colonoscopy measure, and a location in the same or adjacent colonic segment (right, transverse, left colon and rectum). Polyps reported on CCE, but not found by colonoscopy, were regarded as false negative for colonoscopy. Polyps found by colonoscopy, not found by CCE, were regarded as false negative for CCE. Thus, the standard used here to determine colonoscopy and CCE per-polyp sensitivity in patients undergoing both investigations was the sum of matched and unmatched polyps in both investigations.

Proportions are reported with 95% confidence intervals and compared using chi-squared test. A p-value of <0.05 was considered statistically significant. STATA 15 (Texas, USA) was used for analysis.

Results:

A total of 180 patients were included. Mean age was 59 years and 52% were males. The indication for surveillance and time since last colonoscopy is shown in Table 1. Patients with surveillance due to familial history of colorectal cancer accounted for 41%, and 59% had surveillance due to a personal history of adenomas. The majority (90.5%) had their last colonoscopy within 3 years. The CCE excretion rate was 70.6% and adequate cleansing rate was 92.2%, resulting in a complete examination rate for CCE of 66.7%. The polyp detection rate in complete CCE exams was 69%.

The flow of patients according to the study protocol is shown in Figure 1. A total of 77 patients (42.8%) had a complete CCE with less than three polyps <10 mm. They were scheduled for their next follow-up. The remaining 103 patients (57.2%) with either a complete CCE with findings above the threshold (N=43, 23.9%) or an incomplete CCE (N=60, 33.3%) underwent conventional endoscopy in order to remove detected polyps or for diagnostic purposes. Of those, 36 (20%) underwent sigmoidoscopy, 65 (36.1%) underwent colonoscopy and two patients (1.1%) were referred for endoscopic mucosal resection due to larger lesions.
Table 2 lists the findings of the subsequent conventional endoscopy. The polyp detection rate was 55.3 % and the adenoma detection rate 42.7 %. Fifty-nine patients (57.3%) had no adenomas detected, 33 patients (32.0 %) as “low risk” and 11 patients (10.7 %) as “high risk”.

Table 3 summarizes the 29 patients who had a complete CCE and a full colonoscopy. Sixty polyps were matched between CCE and colonoscopy. CCE detected an additional 60 polyps and colonoscopy detected an additional 16 polyps that could not be matched between the two exams. The resulting per-polyp sensitivity was 88 % (95%CI: 82.8-93.6) for CCE and 56% (47.6-64.2) for colonoscopy (p<0.0001) when regarding all polyps found in both examinations to be true positive findings. Out of the 60 polyps detected by CCE, not matched by colonoscopy, 13 were ≥10 mm. The images of these polyps are shown in figure 2. All 16 polyps found by colonoscopy not matched with CCE were sub-centimeter polyps, 9 were hyperplastic polyps, 7 were tubular adenomas with low grade dysplasia.

Discussion:

The use of CCE as a filter in colonic surveillance comes with several challenges. Firstly, we found a CCE complete examination rate of 66.7%, resulting in one third of the patients having to undergo an additional examination for diagnostic purposes. Secondly, the polyp detection rate of 69% in complete examinations indicate a high rate of polyps in this group, but only half of the polyps detected in CCE in the patients referred for colonoscopy could be found and removed. In a recent trial on colorectal cancer screening patients we found a higher polyp detection rate of 86% in complete exams, and a similar trend of CCE reporting more polyps than colonoscopy [10].

We found that, using a cut-off of no more than two small (<10 mm) polyps (no polyps at all for HNPCC patients), 42.8 % needed no further investigation at the current surveillance and were scheduled for their next follow-up within one to five years. An additional 20 % could be completed with a sigmoidoscopy and only 37.2 % required a full colonoscopy. Still, only 10.7% of patients
undergoing endoscopy had high risk findings. It indicates that due to the low yield nature of colonoscopic surveillance, the potential of filtering patients using CCE is substantial, but it implies leaving small polyps untreated until the subsequent follow-up. Whether the approach of leaving small polyps behind is safe or not, is debatable, and the knowledge is scarce. In a recent review [11] of 9 studies, 721 patients and 1034 diminutive or small adenomas, 6% progressed to advanced adenomas over time. Disregarding diminutive and small polyps is currently practiced with CT colonography in most countries. With the known high polyp miss rate by colonoscopy [12], higher sensitivity of CCE [10], low incidence of advanced neoplasia in small polyps and the slow growth rate of small polyps [13, 14], the risk of this approach compared to current practice seems negligible, if not favorable. Especially in this surveillance setting where most patients have undergone colonoscopy within the last 3 years and are expected to undergo another within the next five years.

Results from this trial, when the next surveillance has been done, will help to shed light on the risk of leaving polyps behind.

In all previous trials comparing CCE and colonoscopy, any polyps that could not be confirmed by colonoscopy was regarded as false positive for CCE. Sometimes, due to multiple passages and reporting of the same polyp several times, this will also be the case. But, as has been shown, colonoscopy may also miss polyps. In this trial, colonoscopists were not blinded to the CCE report, thus given a better opportunity to find the polyps reported in CCE. Still, in the 29 patients undergoing two complete investigations, 60 polyps reported in CCE could not be found. When all polyps found by both methods are regarded as true, this leads to a superior sensitivity of CCE compared to colonoscopy. This is a very small population for testing diagnostic accuracy, and it is probably an overestimation. It illustrates the statistical significance of how the gold standard is defined, but also the clinical dilemma involved when using CCE as a filter, and not being able to account for all detected polyps at the subsequent colonoscopy.
Another important issue regarding the implementation of CCE into clinical practice is the workload associated with the procedure and its cost-effectiveness. Currently, an investigator needs approximately one hour to evaluate the video and devise the report. This time is longer than what is needed with most colonoscopies. Further, with only one marketed solution, the price of the hardware remains high, and the total costs of the procedure is approximately twice that of a colonoscopy. Clearly, as of yet, the CCE procedure is not cost-effective, but this may change with more solutions being marketed and the development of artificial intelligence for video analyses.

Currently our research unit is developing machine learning algorithms for assessment of bowel cleansing [15], polyp recognition and polyp localization (papers submitted).

The CCE completion rate using low volume and low risk preparations and booster compounds remain to be improved before CCE can be implemented into clinical practice as a diagnostic alternative to CT-colonography and colonoscopy. Even if the procedure can be improved, there remain clinical issues regarding the need to leave polyps behind when using CCE as a filter, but also when the polyps cannot be found at the subsequent colonoscopy. If other non-invasive testing such as faecal or blood tests can increase accuracy they may prove to be more feasible as filter tests to colonoscopy.

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Disclosures:

This study group has been supported by Medtronic. No investigator has received personal benefits.

References:

14. Wilson AI, Saunders BP. New paradigms in polypectomy: resect and discard, diagnose and

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Table 1: Demographic results

<table>
<thead>
<tr>
<th>Median Age, years</th>
<th>59</th>
</tr>
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<tbody>
<tr>
<td>Gender, % males</td>
<td>52</td>
</tr>
</tbody>
</table>

**Indication for surveillance, N (%)**

- Familial history of colorectal cancer: 74 (41.1)
- Previous neoplastic findings in colorectal cancer screening: 62 (34.4)
- Previous neoplastic findings in colonoscopy due to symptoms: 44 (24.4)

**Time since last colonoscopy, N (%):**

<table>
<thead>
<tr>
<th>Time</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52 (28.9)</td>
<td>53 (29.4)</td>
<td>58 (32.2)</td>
<td>6 (3.3)</td>
<td>11 (6.1)</td>
</tr>
</tbody>
</table>

Table 2: Endoscopic findings and outcome according to adenoma risk stratification

| Conventional Endoscopy, N (%) | 103 (57.2) |
| Polyp detection rate, N (%)   | 57 (55.3)  |
| Adenoma detection rate, N (%) | 44 (42.7)  |

**Risk Stratification*, N (%):**

| No adenomas   | 59 (57.3) |
| Low risk adenomas | 33 (32.0) |
| High risk adenomas | 11 (10.7) |

*Risk stratification according to the European guidelines for colorectal cancer screening*
Table 3: Colon capsule endoscopy (CCE) and colonoscopy (OC) agreement (in the 29 patients with complete CCE and full colonoscopy)

<table>
<thead>
<tr>
<th></th>
<th>Polyps found, N</th>
<th>Unmatched polyps, N</th>
<th>Matched polyps*, N</th>
<th>Total polyps^, N</th>
<th>Per polyp sensitivity, % (95% CI~)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCE</strong></td>
<td>120</td>
<td>60</td>
<td>60</td>
<td>136</td>
<td>88% (82.8-93.6)</td>
</tr>
<tr>
<td><strong>OC</strong></td>
<td>76</td>
<td>16</td>
<td></td>
<td></td>
<td>56% (47.6-64.2)</td>
</tr>
</tbody>
</table>

*Polyps in CCE and OC within a size range of 50% and in same or adjacent colonic section (right, transverse, left colon) were considered a match. ^Sum of matched and unmatched polyps in CCE and OC. ~CI: Confidence Interval

Figure 1: Study flowchart of investigations
Figure 2: Images of the thirteen polyps ≥10 mm that were detected by colon capsule endoscopy, but not retrieved by colonoscopy.