Serrated polyps
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CHAPTER 5

CT-colonography versus colonoscopy for detection of high-risk sessile serrated polyps


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CHAPTER 5

ABSTRACT

Objectives
Sessile serrated polyps (SSPs) are suggested to be the precursors of 15–30% of all colorectal cancers (CRCs). Therefore, CRC screening modalities should also be designed to detect high-risk SSPs. We compared computed tomography colonography (CTC) with colonoscopy-based screening for the detection of high-risk SSPs in average-risk individuals.

Methods
Data from a randomized controlled trial that compared CTC with colonoscopy for population screening were used for the analysis. Individuals diagnosed at CTC with a lesion ≥10 mm in size were referred for colonoscopy. Individuals with only 6–9 mm lesions were offered surveillance CTC. This surveillance CTC was followed by a colonoscopy when a lesion ≥6 mm was detected. Yield of both was accumulated to mimic current American College of Radiology CTC referral strategy (referral of individuals with any lesion ≥6 mm). Per participant detection of ≥1 high-risk (dysplastic and/or ≥10 mm) SSP was compared with colonoscopy using multiple logistic regression analysis.

Results
In total, 8,844 individuals were invited to participate (in 2:1 allocation), of which 1,276 colonoscopy and 982 CTC invitees participated in the study. In the colonoscopy arm, 4.3% of individuals were diagnosed with ≥1 high-risk SSP, compared with 0.8% in the CTC arm (odds ratio (OR) 5.5; 95% confidence interval (CI) 2.6–11.6; P <0.001). In total, 3.1% of individuals in the colonoscopy arm were diagnosed with high-risk SSPs as most advanced lesion, compared with 0.4% in the CTC arm (OR 7.7; 95% CI 2.7–21.6; P <0.001). The current CTC strategy showed a marked lower detection for especially flat high-risk SSPs (17 vs. 0), high-risk SSP located in the proximal colon (32 vs. 1), and SSPs with dysplasia (30 vs. 1).

Conclusions
In a randomized controlled setting, the detection rate of high-risk SSPs was significantly higher with colonoscopy than CTC. These results might have implications for CTC as a CRC modality for opportunistic screening in average-risk adults.
INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality worldwide. CRC arises from precursor lesions in the course of many years, and detection and resection of these lesions can prevent CRC. Research from the last two decades has suggested that 15–30% of CRCs arise from serrated polyps, via the serrated neoplasia pathway, rather than from adenomas. This has caused a paradigm shift in CRC prevention strategies, as not only adenomas but also all premalignant serrated polyps should be detected and resected during colonoscopy. According to the most recent World Health Organization guideline, serrated polyps are subdivided into hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSPs) without dysplasia, SSPs with dysplasia, and traditional serrated adenomas (TSAs). This classification seems to be of importance, as not all serrated polyp subtypes possess an identical malignant potential. Mainly, SSPs have been associated with CRC, whereas distally located and/or smaller HPs are considered innocuous lesions. The US Multi-Society Task Force on Colorectal Cancer acknowledged that individuals with dysplastic and/or large (≥10 mm) SSPs have a high risk of developing CRC and should be managed comparable to patients with high-risk adenomas. Therefore, CRC screening strategies should not only be designed to detect high-risk adenomas and early CRC but should also be able to identify those individuals with dysplastic and/or large SSPs, referred to as high-risk SSPs.

Colonoscopy has been widely acknowledged as the reference standard to detect colonic polyps as well as CRC, while other modalities are also accepted as CRC screening techniques. In a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology, it was stated that computed tomography colonography (CTC) is the radiological examination of choice for CRC screening in average-risk adults aged 50 years and above. In the most recent European guideline, CTC is not recommended as a primary test for population screening. However, it may be proposed as a CRC screening test on an individual basis provided the screenee is adequately informed about test characteristics, benefits, and risks. Although a large number of studies have reported on the performance of CTC in the detection of high-risk adenomas and CRC, studies that assess the performance of CTC in the detection of high-risk SSPs are lacking to our knowledge. The aim of this study was to compare the performance of CTC with colonoscopy for the detection of large and/or dysplastic SSPs.

METHODS

Study design and population
This study has a post hoc design, using data from a randomized controlled trial that compared colonoscopy vs. CTC for population screening (COCOS-trial). This trial was performed in two academic hospitals in the Netherlands. In total, 8,844 patients from the greater Amsterdam and Rotterdam region...
were invited to participate in this study. Ethical approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). All participants gave their written informed consent.

Individuals were randomly allocated to colonoscopy or CTC (2:1 distribution) as method of primary screening for CRC. Individuals were randomized, stratified on age, gender, and socio-economic status. Screening-naive average-risk individuals, aged 50–75 years, were eligible to be included. Individuals who had undergone a complete colonic examination (colonoscopy, CTC, and/or double contrast barium enema) within 5 years before the invitation, who were under colonoscopic surveillance, and/or individuals with an end-stage disease were excluded from participation in the trial. Furthermore, individuals randomized to CTC were excluded in case of pregnancy, hyperthyroidism, iodine contrast medium allergy, or when they had been exposed to ionizing radiation for the purpose of research in the last 12 months. The overall design of this trial, as well as detailed information regarding the randomization procedure, has been described in detail previously.14,15

Procedures

All individuals were invited via postal mail between June 2009 and August 2010, by the regional comprehensive cancer centers. Invitation letters were accompanied by an invitation leaflet with further information regarding CTC or colonoscopy (depending on the allocated study arm). The information leaflets were approved by the Dutch Health Council and can be found in the web appendix of an earlier report.15 All invitees were offered a consultation with a nurse or a doctor before screening. The procedure, including potential harms and benefits, the general health status, and the informed consent were discussed during consultation.

CTC

Participants allocated to receive primary CTC screening were prepared with a reduced bowel preparation consisting of two times 50 ml iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnaysous-Bois, France) the day before the examination and one identical bottle 90 min before examination, accompanied by a low-fiber diet. Distension of the colon was achieved with an automatic carbon dioxide insufflator (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA). Directly before distension, 20 mg of hyoscine butylbromide was administrated intravenously as bowel relaxants or, if contraindicated, was substituted for 1 mg of glucagon hydrochloride intravenously. No medication was given if both agents were contraindicated. Each CTC was read within 2 weeks by three readers: one of the three experienced radiologists (≥800 examinations) and two of the four experienced radiological technologists, who all underwent an extensive and structured training program including 175 training cases and 25 test cases. A more detailed description of the CTC reading procedure was reported earlier.15 The readers were instructed to report all polyps ≥6 mm and ignore smaller polyps.

Follow-up advice after CTC depended on the size of the largest lesion. All individuals who were diagnosed with at least one large lesion at CTC (≥10 mm in size) were referred for a colonoscopy. All
individuals with a largest lesion sized 6–9 mm at CTC were recommended surveillance CTC. Individuals with three or more lesions of 6–9 mm were recommended surveillance CTC after 1.5 years, and individuals with one or two lesions of 6–9 mm were recommended surveillance CTC after 3 years. Individuals without lesions ≥6 mm did not receive follow-up. In case of any discrepancy in CTC reading by the three individual readers (one radiologist and two technologists for each CTC), the most stringent advice was pursued. Earlier research from our group showed that a reading strategy of three readers without consensus resulted in the most effective strategy considering diagnostic yield of CTC.

Individuals who were recommended surveillance after the initial CTC were offered surveillance CTC at one of both participating academic hospitals. The CTC procedure was identical as described above, except that all individuals who were diagnosed with at least one lesion ≥6 mm at surveillance CTC were referred for colonoscopy. Individuals who underwent surveillance CTC or colonoscopy before the advised surveillance interval were contacted for their informed consent to collect the outcome of the performed procedure.

**Colonoscopy**

All colonoscopies were executed according to the standard quality indicators. Pre-procedure bowel cleansing was obtained by a combination of 2 l of clear fluids and 2 l of hypertonic polyethylene glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands), accompanied by specific diet instructions. Colonoscopy was performed under conscious sedation using intravenous fentanyl (Bipharma, Weesp, The Netherlands) and midazolam (Dormicum, Actavis, Baarn, The Netherlands), dosed to the preference of the endoscopists, as well as the participant. Cecal intubation was confirmed by still images of the standard landmarks (ileocecal valve as well as the appendiceal orifice) and/or by intubation of the terminal ileum. Quality of bowel cleansing was evaluated using the validated Ottawa bowel preparation score. Colonoscopies were rescheduled in case of an inadequate bowel preparation. All detected polyps were immediately removed and obtained for histological assessment, irrespective of polyp location and/or optical polyp diagnosis. If resection of the detected polyp was not directly possible, biopsies were taken to enable histopathological assessment. Characteristics of all detected polyps were obtained during colonoscopy—i.e., size (measured compared with an open forceps of 7 mm), location (colonic segment), morphology (pedunculated (Paris Ip), sessile (Paris Is), flat (Paris Ila, Iib), or depressed (IIC)), and optical diagnosis (carcinomatous, adenomatous, hyperplastic).

**Histopathology**

All tissue samples were evaluated according to the Vienna criteria by one designated expert gastrointestinal pathologist per hospital. Adenomatous polyps were classified based on the presence of a villous component (tubular, tubulovillous, or villous) and on their severity of dysplasia (low-grade or high-grade). Serrated polyps were subdivided into HPs, SSPs without dysplasia, SSPs with dysplasia, or TSAs. Predominantly, a SSP was defined based on distortion of the crypts, as well as the presence of (hyper-)serration up to the base of the crypts. A TSA was predominantly defined based on the presence of...
of prominent serration, aberrant crypt formation, a distorted tubulovillous or villous configuration, and diffuse cytoplasmic eosinophilia. A high-risk adenoma was defined as an adenoma of at least 10 mm in size at colonoscopy, with at least a 25% villous component and/or with high-grade dysplasia. A high-risk SSP was defined as a SSP containing dysplasia and/or a SSP of at least 10 mm in size. An HP of at least 10 mm was regarded as a high-risk SSP, in agreement with the recent US guidelines.

Statistical analysis

The primary outcome measure of this study was the detection rate of ≥1 high-risk SSP for CTC as compared with colonoscopy as method for opportunistic screening in average-risk individuals. Because of imposed restrictions by the Dutch Health Council in the COCOS-trial only those individuals with a lesion ≥10 mm were initially referred for colonoscopy. Individuals with lesions 6–9 mm in size were offered surveillance CTC, followed by a colonoscopy in case a lesion ≥6 mm was detected at surveillance CTC. To mimic international referral guidelines (referral for colonoscopy in case of a polyp ≥6 mm detected at CT-colonography), the yield of initial CTC screening together with the yield of CTC surveillance for all individuals with a polyp 6–9 mm at initial CTC was aggregated and used to calculate the detection rate of CTC as screening strategy. Lesions detected in individuals in the CTC group who underwent a colonoscopy before the recommended CTC surveillance interval were also added to the detection rate of CTC screening.
Both the overall detection rate of all serrated polyp subtypes as well as the detection rate of all serrated polyp subtypes as most advanced lesion per individual was evaluated. CRCs as well as high-risk adenomas were considered as more advanced lesions than high-risk SSP, whereas all other adenomas were regarded as less advanced lesions. Low-risk SSPs as well as HPs were considered as less advanced lesions than any type of adenoma. Multiple logistic regression, adjusted for gender and age, was used to statistically compare the detection rate of colonoscopy vs. CTC-based screening. Difference was presented as odds ratio (OR) with 95% confidence interval (CI). A two-sided P-value <0.05 was considered significant in this study. Analyses were performed using SPSS statistics version 21 (Chicago, IL).

RESULTS

In total, 8,844 individuals aged 50–75 years were invited to participate, of which 2,920 were randomized to CTC and 5,924 to colonoscopy (Figure 1). Of the CTC invitees, 982 (34%) participated and were eligible for inclusion. Mean age of CTC participants was 60.3 years (s.d. 6.4) and 507 were male (52%). Of the colonoscopy invitees, 1,276 individuals (22%) participated and were eligible for inclusion in this study. Mean age of colonoscopy participants was 60.1 years (s.d. 6.2) and 652 were male (51%). Reasons for non-participation have been described in detail earlier.

Of the 982 individuals who underwent a CTC, 96 had at least one ≥10 mm polyp and were referred for colonoscopy, 104 had a largest polyp of 6–9 mm and were offered surveillance CTC, and 782 had no ≥6 mm polyps and therefore required no follow-up. Of the 104 individuals referred for surveillance, five died within the surveillance interval (four for other reasons than CRC and one unknown), 11 did not want to participate because of various reasons, and 10 already underwent a colonoscopy within the surveillance interval. As a result, 78 individuals underwent surveillance CTC at 3 years, of which 57 were referred for colonoscopy because of a colonic lesion ≥6 mm. Of these individuals, 50 underwent a colonoscopy in one of the participating academic centers, three underwent a colonoscopy in another hospital, and four did not want to participate (Figure 1). The data on all polyps collected in 96 initial colonoscopies and 63 surveillance colonoscopies in the CTC arm were compared with polyp data collected in 1,276 colonoscopies in the primary colonoscopy arm.

Detection rate of high-risk SSPs

In Table 1, the detection rate for colonoscopy as well as CTC as primary CRC screening modality in average-risk adults is presented. In the primary colonoscopy arm, 55 individuals (4.3%) were diagnosed with at least one high-risk SSP, compared with eight individuals (0.8%) in the CTC arm (P<0.001). This corresponds to an adjusted OR of 5.5 (95% CI 2.6–11.6) to detect at least one high-risk SSP for colonoscopy compared with CTC. In total, 39 individuals (3.1%) in the colonoscopy arm were diagnosed with at least one high-risk SSP as most advanced lesion, compared with four individuals...
(0.4%) in the CTC arm. This corresponds to a significantly higher detection rate for colonoscopy (P<0.001), with an adjusted OR to detect at least one high-risk SSP as most advanced lesion of 7.7 (95% CI 2.7–21.6).

**Characteristics of high-risk SSPs**

In Tables 2 and 3, the characteristics of all high-risk SSPs are presented, detected during the 1,276 primary colonoscopies and 159 colonoscopies after CTC, respectively. In the colonoscopy arm, 68 high-risk SSPs were detected: 43 (63%) SSPs ≥10 mm, eight (12%) SSPs with dysplasia of 6–9 mm, and 17 (25%) SSPs with dysplasia <6 mm. In total, 17 (25%) of these lesions were flat and 51 (75%) were sessile. Of all high-risk SSPs detected in the colonoscopy arm, 51 (75%) were detected in the proximal colon. In the CTC arm, nine high-risk SSPs were detected: eight SSPs ≥10 mm (89%) and one SSP with dysplasia <6 mm (11%). All detected high-risk SSPs were sessile and eight (89%) were located in the distal colon. In total, seven high-risk SSPs were detected during the initial CTC screening round, and two were detected after 3-year surveillance. In total, 6 of these lesions were identified at CTC and 3 were detected by coincidence during colonoscopy in individuals referred for a synchronous adenoma.

**DISCUSSION**

Our study shows that, in average-risk individuals aged 50 years and above, the detection rate of high-risk SSPs is significantly higher using colonoscopy compared with CTC as primary CRC screening modality, with an OR to detect at least one high-risk SSP of 5.5 (95% CI 2.6–11.6; P<0.001) overall and an OR to detect at least one high-risk SSP as most advanced lesion of 7.7 (95% CI 2.7–21.6; P<0.001). As compared with the findings in the colonoscopy arm, especially flat SSPs with dysplasia located in the proximal colon were often not detected with the current CTC strategy.
Table 2 | Histology of detected serrated polyps (per polyp analysis)

<table>
<thead>
<tr>
<th>Serrated polyps ≥10mm</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
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<tbody>
<tr>
<td>SSP with dysplasia</td>
<td>0 (0)</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td>SSP without dysplasia</td>
<td>8 (100)</td>
<td>38 (88.4)</td>
</tr>
<tr>
<td>TSA</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serrated polyps 6-9mm</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP with dysplasia</td>
<td>0 (0)</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>SSP without dysplasia</td>
<td>8 (30.8)</td>
<td>14 (17.5)</td>
</tr>
<tr>
<td>TSA</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>HP</td>
<td>18 (69.2)</td>
<td>58 (72.5)</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>80</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Serrated polyps &lt;6mm</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSP with dysplasia</td>
<td>1 (0.7)</td>
<td>17 (3.0)</td>
</tr>
<tr>
<td>SSP without dysplasia</td>
<td>18 (12.2)</td>
<td>42 (7.3)</td>
</tr>
<tr>
<td>TSA</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>HP</td>
<td>128 (87.1)</td>
<td>512 (89.5)</td>
</tr>
<tr>
<td>Total</td>
<td>147</td>
<td>572</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of serrated polyps</td>
<td>181</td>
<td>695</td>
</tr>
<tr>
<td>Total number of high-risk SSPs</td>
<td>9</td>
<td>68</td>
</tr>
</tbody>
</table>

SSP = sessile serrated adenoma/polyp; TSA = traditional serrated adenoma; HP = hyperplastic polyp

Table 3 | Morphology and location of detected high-risk sessile serrated adenomas/polyps (per polyp analysis)

<table>
<thead>
<tr>
<th>Morphology</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat</td>
<td>0 (0)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>Sessile</td>
<td>9 (100)</td>
<td>51 (75.0)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>CT-colonography; n(%)</th>
<th>Colonoscopy; n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecum</td>
<td>0 (0)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>1 (11.1)</td>
<td>23 (33.9)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>0 (0)</td>
<td>19 (27.9)</td>
</tr>
<tr>
<td>Descending colon</td>
<td>0 (0)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>8 (88.9)</td>
<td>16 (23.5)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>68</td>
</tr>
</tbody>
</table>

All available data were collected in a large prospective randomized controlled setting, and both colonoscopies as well as CTCs were performed according to the most up-to-date quality guidelines12,17. General colonoscopy quality was described in a previous study20. Yet, a number of limitations have to be acknowledged in this study. As mentioned before, the current US guideline recommends that every individual with a lesion ≥6 mm at CTC should be referred for colonoscopy11. However, because of imposed restrictions by the Dutch Health Council in the COCOS-trial only those individuals with a lesion ≥10 mm were initially referred for colonoscopy. Individuals with lesions 6–9 mm in size were offered surveillance CTC, followed by a colonoscopy in case of a lesion ≥6 mm detected at CTC. To mimic the current referral guideline, initial CTC screening and surveillance data of CTC followed by colonoscopy...
for all polyps ≥6 mm were aggregated in this study, imposing a potential risk for biased results. For this reason, the diagnostic yield in the setting of population-based screening was beyond the scope of this study, and we decided to restrict our conclusions to the main outcome parameter, the detection rate of high-risk SSPs per participating individual. Because of the extent of the detected difference and the underlying quality of this study, we believe that, irrespective of the potential bias, the external validity of our results is amply sufficient for the assessment of the primary outcome measure.

To our knowledge, no earlier studies have been performed that compared the detection rate of high-risk SSPs of CTC with colonoscopy as primary screening modalities in average-risk adults. Nevertheless, this study can be related to earlier findings in the literature. Of specific importance with regard to the detection of SSPs is the fact that these lesions tend to be small and inconspicuous lesions and have a sessile or flat morphology\(^{21}\). More advanced SSPs often do not tend to be larger than less advanced SSPs and do not differ in morphology\(^{22,23}\). For instance, Bouwens et al.\(^{22}\) showed that SSPs with dysplasia are as often 1–5 mm in size as SSPs without dysplasia. Furthermore, Rosty et al.\(^{23}\) showed that the mean polyp size of SSPs with invasive malignancy ranged from 8 to 11 mm. In line with these results, we showed that 37% of the high-risk SSPs detected in the colonoscopy arm were <10 mm, whereas 25% were 1–5 mm in size. In total, 75% of high-risk SSPs were sessile, whereas 25% were flat. These characteristics of high-risk SSPs might have largely contributed to the significantly lower detection of high-risk SSPs in the CTC arm, compared with the colonoscopy arm. First, because of the stepwise approach, referring only those individuals with a lesion ≥6 mm at CTC, a substantial number of 1–5 mm SSPs with dysplasia will have remained in situ with the CTC-based screening strategy. This threshold for referral is standard procedure in CTC practice, as the accuracy measures are low for 1–5 mm lesions\(^{24,25}\). Second, several studies suggested that the sensitivity of CTC for the detection of flat and/or 6–9 mm lesions might be suboptimal compared with colonoscopy, although these results widely differ\(^{26–29}\). In the largest multicenter CTC screening trial to date (n=2,600 individuals), the diagnostic accuracy of CTC was compared with colonoscopy for the detection of adenomas and CRC\(^{29}\). The sensitivity for the detection of lesions above 10 mm in diameter was 90%, whereas the sensitivity for the detection of lesions ≥6 mm dropped to 78%. Unfortunately, no sub-analysis was performed, stratified for polyp morphology. A recent retrospective study suggested that the sensitivity of CTC to detect flat adenomas ≥10 mm was 70.6%\(^{26}\). Another prospective study showed that the sensitivity of CTC for the detection of flat adenomas of ≥20 mm in size was only 32%\(^{27}\). In a large prospective study in one expert center, however, a sensitivity of 93.3% was reported for the detection of flat lesions ≥6 mm\(^{28}\). A third potential reason for a low detection rate of high-risk SSPs at CTC is the fact that serrated polyps tend to flatten during distention of the colon, described as the visual “disappearing phenomenon”\(^{30,31}\). As distension of the cecum and ascending colon is relatively the widest during CTC, which is also the most prevalent location of SSPs, this might explain why high-risk SSPs in the proximal colon were more often left undetected\(^{31}\). Although this phenomenon will also occur during colonoscopy, the overlying mucus cap of SSPs still supports their identification\(^{31}\). Because of this mucus cap surface contrast coating might also enable a better visualization of SSPs
with CTC\textsuperscript{34}. Contrast coating has been described as the phenomenon where the oral contrast adheres to the polyps’ surface, making it more susceptible for detection\textsuperscript{35}. Previous research showed that this was especially seen in flat polyps located in the proximal colon. Although the mechanism of this phenomenon remains speculative, the authors believe that the oral preparation including different agents is responsible\textsuperscript{34}. Therefore, a fourth explanation for the lower detection rate of serrated polyps with CTC could be the bowel preparation used in our study, consisting of only one iodinated agent.

The results from our study might have implications for the value of CTC as opportunistic screening modality for average-risk individuals. As mentioned before, The US Multi-Society Task Force on Colorectal Cancer acknowledged that individuals with high-risk SSPs should be managed similar to patients with high-risk adenomas\textsuperscript{9}. Implementation of these goals could decrease the overall diagnostic yield of CTC for the detection of its targeted lesions (CRCs + high-risk adenomas + high-risk SSPs). To gain more evidence for the performance of CTC in the detection of advanced neoplasia, including high-risk SSPs, large randomized controlled studies should be designed that, in contrary to the initial design of the current study, compare the yield of CTC with colonoscopy according to current international CTC referral guidelines\textsuperscript{11,12}. To enable a comparison of CTC vs. colonoscopy as modality for population-based screening, also the participation rate of both modalities should be taken into account. Earlier results from the original COCOS-trial have demonstrated a significant difference in participation between colonoscopy and CTC, in favor of CTC-based screening\textsuperscript{15}.

In conclusion, we demonstrated that the detection rate of high-risk SSPs is significantly lower for CTC-based screening when compared with colonoscopy, both regarding per patient detection, as well as regarding the detection of high-risk SSPs as most advanced lesion. This might have implications for the value of CTC as a primary CRC screening tool in opportunistic screening. Results from other large screening cohorts are needed to elaborate our findings and to determine the performance of CTC in the detection of advanced neoplasia, including high-risk SSPs, compared with the performance of colonoscopy, both in an opportunistic as well as a population-based screening setting taking into account other variables such as participation\textsuperscript{36}.
REFERENCES


