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GASTROINTESTINAL

Computer tomography colonography participation and yield in patients under surveillance for 6-9 mm polyps in a population-based screening trial

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Abstract

Purpose Surveillance CT colonography (CTC) is a viable option for 6-9 mm polyps at CTC screening for colorectal cancer. We established participation and diagnostic yield of surveillance and determined overall yield of CTC screening.

Material and methods In an invitational CTC screening trial 82 of 982 participants harboured 6-9 mm polyps as the largest lesion(s) for which surveillance CTC was advised. Only participants with one or more lesion(s) ≥6 mm at surveillance CTC were offered colonoscopy (OC); 13 had undergone preliminary OC. The surveillance CTC yield was defined as the number of participants with advanced neoplasia in the 82 surveillance participants, and was added to the primary screening yield.

Results Sixty-five of 82 participants were eligible for surveillance CTC of which 56 (86.2 %) participated. Advanced neoplasia was diagnosed in 15/56 participants (26.8 %) and 9/13 (69.2 %) with preliminary OC. Total surveillance yield was 24/82 (29.3 %). No carcinomas were detected. Adding surveillance results to initial screening CTC yield significantly increased the advanced neoplasia yield per 100 CTC participants (6.1 to 8.6; $p<0.001$) and per 100 invitees (2.1 to 2.9; $p<0.001$).

Conclusion Surveillance CTC for 6-9 mm polyps has a substantial yield of advanced adenomas and significantly increased the CTC yield in population screening.

Key Points

- *The participation rate in surveillance CT colonography (CTC) is 86 %.*
- *Advanced adenoma prevalence in a 6-9 mm CTC surveillance population is high.*
- *Surveillance CTC significantly increases the yield of population screening by CTC.*
- *Surveillance CTC for 6-9 mm polyps is a safe strategy.*
- *Surveillance CTC is unlikely to yield new important extracolonic findings.*

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Keywords Colonography, computed tomographic/methods · Mass screening/methods · Colorectal neoplasms/diagnosis · Colonic polyps · Patient participation

Introduction

Colorectal cancer (CRC) screening with computed tomography colonography (CTC) is aimed at detecting individuals with CRC and significant polyps (advanced neoplasia). As the size of a polyp correlates with advanced histology, for CTC this selection is based on lesion size [1]. Large polyps (≥10 mm) should be removed by polypectomy and diminutive lesions (<6 mm) can be ignored. Debate remains regarding the management of small (6-9 mm) polyps [2]. Despite the low probability of harbouring advanced histology (3 %–6.6 % in an asymptomatic primary screening population) [1, 3], European and US colorectal cancer screening guidelines advise to refer all patients with ≥6 mm polyps for optical colonoscopy (OC), a policy that is primarily based on expert opinion until further evidence is available [4–6]. Surveillance CTC might be a viable alternative, but there is great need for data on CTC surveillance studies to determine the strength of a CTC surveillance strategy [7, 8].

Recently, a population-based screening trial was performed in which the participation rate and yield of OC and CTC as primary CRC screening modalities were compared in 8844 invitees after randomisation (COCOS trial) [8]. It was shown that with higher participation in the CTC group, and higher yield in the OC group, CTC and OC have similar yields for advanced neoplasia per invitee. However, in that trial only CTC participants with lesions ≥10 mm were referred for OC. CTC participants with a largest lesion ranged between 6-9 mm were recommended for a surveillance CTC. The yield of this surveillance population might give further direction to the discussion about the management of patients with small polyps. In addition, a provisional yield of CTC screening was reported [8]. For a definite yield of screening with CTC, the yield of surveillance CTC should be included.

We performed a prospective surveillance study in those individuals with only small (6-9 mm) polyps in the aforementioned trial. We determined the yield of surveillance CTC for advanced neoplasia as well as the total yield of CTC screening in the COCOS trial. In addition, the surveillance participation rate and the number of new relevant (E3 or E4) extracolonic findings were determined [9].

Material and methods

Study design

In a previous randomized controlled trial (RCT) participation and diagnostic yield of OC and CTC in an invitational population-based screening program of individuals aged 50-75 years was compared [8]. The overall design of the trial has been described in detail previously [10]. In that population screening trial 2920 out of 8844 trial invitees individuals were invited for CTC (others for OC) of which 982 participated (Fig. 1). All participants with only polyps measuring 6-9 mm (n=82) were advised to undergo a surveillance CTC after 1.5 or 3 years (with ≥3 or <3 polyps, respectively).

This trial was registered in the Dutch Trial Register (NTR3549). Ethics approval from the Dutch Health Council (2009/03WBO, The Hague, the Netherlands) was obtained for this trial, including surveillance CTC. Patients had already given their written informed consent to be contacted for follow-up studies and consented to this study.

Participants

Patients were contacted by postal mail. Patients with surveillance advice who were willing to undergo surveillance CTC were included, unless they underwent a CTC or OC in the time between the initial screening CTC and their invitation for surveillance CTC. In that case, findings of those examinations were requested and included in the yield analysis. Medical history and medication use were documented.

CTC

CTC scan protocol, preparation, and reading strategy were deliberately kept identical to the initial CTC [8]. The preparation consisted of two times 50 mL of iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnaysous-Bois, France) on the day before the examination [11]. Another 50 mL was given 1.5 hour prior to the examination (total 150 mL) and a low-fibre diet was followed for one day. Colonic distention was obtained by automatic carbon dioxide insufflation (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA) after intravenous 20 mg hyoscine butylbromide (if contraindicated, 1 mg glucagon hydrochloride intravenously). Supine and prone position CT images were obtained on two 64-slice CT scanners (Brilliance, Philips Healthcare, Best, the Netherlands; SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany, with 64 x 0.625 mm detector-rows, slice thickness 0.9 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 25 reference mAs (for Brilliance) and 128 x 0.6 mm detector-rows, slice thickness 1.0 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 16 reference mAs (for SOMATOM Sensation).

All CTCs were evaluated within two weeks after the exam by one experienced abdominal radiologist (CYN, abdominal radiologist since 19 years, 14 years of CTC experience including approximately 2000 CTCs) as this reading strategy was also used for the COCOS trial. Images were read in primary 2D (window setting 1500, -250 HU) with 3D read (supine and

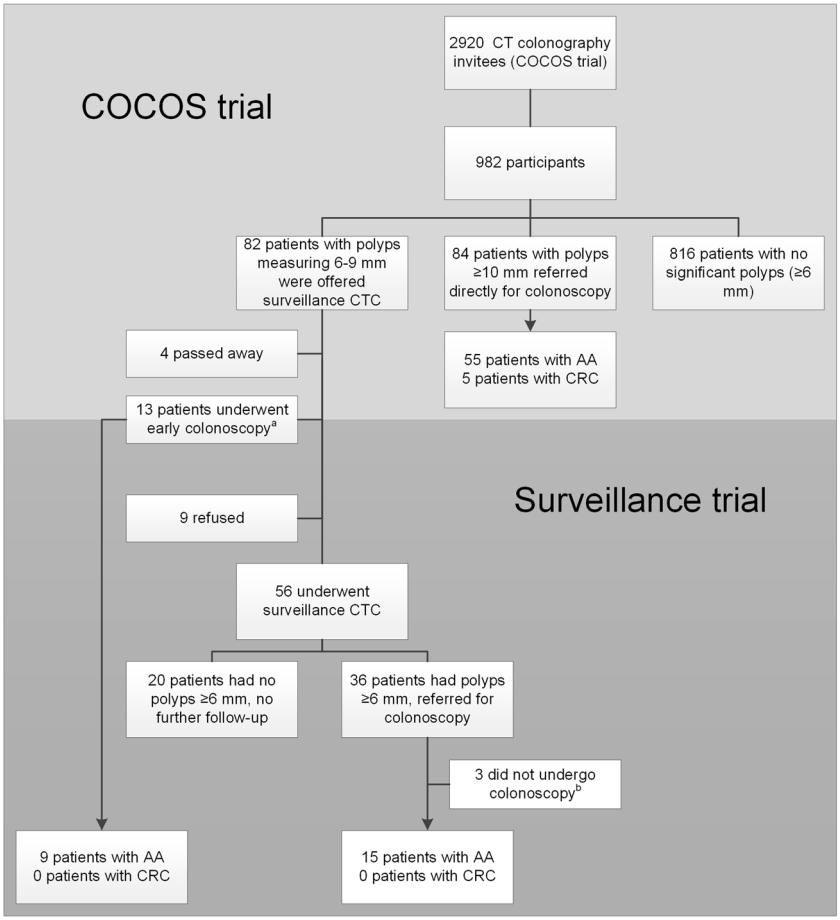

Fig. 1 Participation and outcome of CTC patients in the COCOS trial including surveillance CTC. [a]had OC prior to surveillance invitation, OC findings were used for our analyses. [b]2 refused (repeat) OC, 1 is still to be performed. AA=advanced adenoma, CRC=colorectal cancer

prone) for problem solving. Following this strategy, a secondary computer-aided detection (CAD) reading was performed using a commercial CAD system (ColonCAD, Philips Healthcare). The observer was not blinded to the findings of the initial COCOS CTC and performed polyp matching [12]. Maximum linear diameter, morphology (flat, sessile, pedunculated or tumour) and location (caecum, ascending, transverse, descending, sigmoid or rectum) were noted. Extracolonic organs and findings were examined by one of two radiologists using the C-RADS classification [CYN and MT (MT, abdominal radiologist since 14 years)] [9].

For the sole purpose of determining definite polyp regression, the surveillance CTCs were retrospectively also evaluated by two of four experienced readers. We did not use their evaluations for yield calculations.

Follow-up after a positive test result

OC was indicated for all participants with at least one polyp measuring ≥6 mm at surveillance CTC. Polyps smaller than 6 mm were ignored because of the very low prevalence of malignancy in these lesions [1, 13].

Approximately ten weeks after a positive surveillance CTC, an OC was performed by experienced endoscopists (see Appendix 1) [14]. Segmental unblinding of CTC findings was performed by a research nurse or research fellow. Detected lesions were described and removed for histopathological examination. Lesions were classified by two expert gastrointestinal pathologists (same as in initial trial, MVDV and KB as hyperplastic polyp, serrated adenoma, adenoma or carcinoma (Vienna classification) [15]. Advanced adenoma was defined as an adenoma that is ≥10 mm and/or has more than 25 % villous component and/or high grade dysplasia [16]. For determination of lesion size, measurements at OC were used. Advanced neoplasia was defined as either an advanced adenoma or invasive colorectal cancer. As serrated adenomas ≥10 mm were not classified as advanced adenomas in the original COCOS trial, we described them separately.

Statistical analysis

Descriptive analysis of patients, polyps and extracolonic findings were presented. Participation rate was defined as the number of participants undergoing the surveillance CTC relative to the total number of patients invited to undergo surveillance CTC. Diagnostic surveillance yield was defined as the number of patients with an advanced neoplasia in our surveillance population of 82 patients, which was a combined

yield of individuals that underwent surveillance CTC and of individuals that underwent a preliminary OC.

The overall diagnostic yield of CTC in the population-based trial was defined as the number of patients detected with advanced neoplasia relative to all participants and relative to all invitees of the initial trial. A McNemar test for paired observations (in 982 participants and in 2920 invitees) was used to calculate differences between initial yield and overall yield including surveillance CTC. The *P*-values less than 0.05 were deemed significant.

The scope of this paper was not to present an in-depth per-polyp analyses with change in size during the surveillance interval, as within the framework of CTC screening for CRC the per-patient results are considered the primary end-point.

We used SPSS for Windows, version 19, for all the analyses.

Results

Participation

Between February 2011 and May 2014 the 82 individuals (mean age 66.0 (SD 6.8); 56 % (46/82) male) with 6-9 mm polyps at initial screening CTC were approached for surveillance CTC (Fig. 1). Of these, four individuals died (Table 1). Thirteen underwent OC prior to invitation (Table 1), seven of which because they participated in a study parallel to the initial trial on the optimal reading strategy for CTC, comparing the yield of a radiologist to that of two radiologic technologists ($n=7$) [17]. In these seven individuals OC was performed because one of the technologists measured the polyp as ≥10 mm, in contrast to the radiologist measurement of 6-9 mm. We did use the OC findings of those 13 individuals with a preliminary OC for our yield calculations. In total, 65 of 82 individuals were invited, of which 56 (86.2 %) participated in surveillance CTC (all non-participation reasons are summarized in table 1). Mean surveillance interval was 3.4 years (SD 0.43; range 2.0-4.6). All three individuals with 1.5-year surveillance advice were excluded (one died and two were coping with another illness).

Yield of surveillance CTC

At CTC surveillance, in 17 patients were no polyps detected and in three patients only a <6 mm polyp was detected. These 20 (36 %) of 56 participants required therefore no further follow-up examinations. After retrospective evaluation of these 17 surveillance CTCs with no polyps by two experienced readers, polyp regression was suggested in ten patients (Appendix 2). Thirty-six (64 %) of 56 participants had polyps ≥6 mm, of which 24 with 6-9 mm polyps and 12 with at least one ≥10 mm polyp, and were referred for OC. All referrals were based on polyps corresponding to the 6-9 mm polyps on the initial CTC. Until now, 34 of 36 participants underwent an OC, mean time interval between CTC and OC of 10.7 weeks (SD 6.2; range 3.4-25.3). Two patients refused OC, and in one patient OC was stopped prior to completion due to a large number of polyps that required removal, and the participant refused repeat OC (because of concomitant health problems) (Table 1). In these three participants the polyp was detected at CTC was therefore not removed. In one participant no lesions were detected during OC.

Of all 56 patients participating in surveillance CTC, 15 (26.8 %) had advanced adenomas (Fig. 1). No colorectal cancers were detected. The positive predictive value (PPV) for advanced neoplasia of surveillance CTC on a per-patient level was 45 % (15/33) (95 % CI 0.15-0.76). The PPV for matched polyps on a per-patient level, regardless of histology, was 97 % (32/33) (95 % CI 0.91-1.03). Included was the use of

Table 1 Reasons for non-participation in surveillance CTC or in the advised OC after a positive test result

Reason	Surveillance CTC	OC
Died*	4	–
I have undergone a colonoscopy since the initial CTC		
because of referral advise in context of CTC reading strategy study [17]	7	–
because of worries about the presence of polyps detected at primary screening CTC	4	–
because of bowel related complaints	2	–
I am coping with another illness	5	2
I am too old	–	1
After a negative FIT I see no reason to participate	1	–
General physician does not think it is necessary and I agree	1	–
Own contribution of insurance policy is too high	1	–
Non-respondence	1	–
Total number of non-participants	**26**	**3**

*2 of lung cancer, 1 of complicated perforated diverticulitis, 1 unknown cause

Table 2 Characteristics of 32 advanced adenomas

	Resulting from surveillance CTC	Resulting from preliminary OC
Size		
≥10 mm	19 (90 %)	10 (91 %)
6-9 mm	2 (10 %)	1 (9 %)
<6 mm	0	0
Histology		
Villous	0	1 (9 %)
Tubulovillous	6 (29 %)	4 (36 %)
Tubular	15 (71 %)	6 (55 %)
Dysplasia		
High-grade dysplasia	0	0
Low-grade dysplasia	21 (100 %)	11 (100 %)
Total	**21**	**11**

CAD, which had resulted in one additional OC with an advanced neoplasia.

Yield of preliminary OC

In 13 individuals with an OC prior to invitation, mean time between index CTC and preliminary OC was 54.0 weeks (SD 43.8, range 3.9-137.0) (see for a detailed timeframe Appendix 3). Of these, nine had advanced adenomas (in all seven individuals referred for OC based on technologists advise, in one because of bowel complaints and in one because of worries about the presence of small polyps) (Fig. 1).

Yield of entire surveillance population

The per-patient yield for advanced neoplasia of our total surveillance population was 29.3 (24/82). Tables 2 and 3 summarize the characteristics of all detected adenomas and serrated lesions (see also Appendix 4). In total, 32 advanced adenomas were detected, of which 29 (91 %) were at least 10 mm, 11 (34 %) contained 25 % or more a villous component and none contained high-grade dysplasia. The other 117 neoplastic lesions included 100 tubular adenomas and 17 serrated lesions. Two patients had a large (5 and 3.5 cm) rectal carpet lesion at OC. One was under surveillance for this lesion which measured 6-9 mm at the initial CTC; OC and polypectomy revealed a sessile polyp with tubular histology. The other had undergone an OC prior to invitation (because of complaints) showing a carpet (flat) lesion with tubulovillous histology, which was not noted on the initial CTC (interval lesion).

Overall yield of screening with CTC

At initial screening, 60 CTC participants were found with at least one advanced neoplasia out of all 982 CTC participants

Table 3 Morphology and location of detected adenomas and serrated lesions

Morphology of detected adenomas	
Advanced adenomas	**32**
Flat	5 (16 %)
Sessile	13 (41 %)
Pedunculated	13 (41 %)
Missing	1 (3 %)
Non-advanced adenomas	**100**
Flat	17 (17 %)
Sessile	64 (64 %)
Pedunculated	12 (12 %)
Missing	7 (7 %)
Serrated lesions	**17**
Flat	1 (6 %)
Sessile	15 (88 %)
Pedunculated	1 (6 %)
Missing	0
Location of detected adenomas	
Advanced adenomas	**32**
Rectosigmoid	15 (47 %)
Proximal[a]	17 (53 %)
Non-advanced adenomas	**100**
Rectosigmoid	13 (13 %)
Proximal[a]	84 (84 %)
Missing	3 (3 %)
Serrated lesions	**17**
Rectosigmoid	9 (53 %)
Proximal[a]	7 (41 %)
Missing	1 (6 %)

Data are n(%)

[a] Proximal is defined as descending colon, transverse colon, ascending colon or caecum (as Atkin [Atkin Lancet 2010])

Table 4 Most advanced lesion per participant and per invitee for primary and surveillance CT colonography

	Yield per 100 participants			Yield per 100 invitees		
	COCOS population (n=982)	COCOS population including surveillance CTC (n=982)	p Value	COCOS population (n=2920)	COCOS population including surveillance CTC (n=2920)	p Value
Colorectal cancer (n)	0.5 (5)	0.5 (5)	ns	0.2 (5)	0.2 (5)	ns
Advanced adenoma (n)	5.6 (55)	8.0 (79)	<0.001	1.9 (55)	2.7 (79)	<0.001
≥10 mm	5.4 (53)	7.6 (75)	<0.001	1.8 (53)	2.6 (75)	<0.001
Non-advanced adenoma (n)	1.2 (12)	3.2 (31)	<0.001	0.4 (12)	1.1 (31)	<0.001
Serrated adenoma (n)	0.2 (2)	0.4 (4)	ns	0.1 (2)	0.1 (4)	ns
Hyperplastic polyp (n)	0.3 (3)	0.4 (4)	ns	0.1 (3)	0.1 (4)	ns
Advanced neoplasia (n)	**6.1 (60)**	**8.6 (84)**	**<0.001**	**2.1 (60)**	**2.9 (84)**	**<0.001**
≥10 mm	**5.9 (58)**	**8.1 (80)**	**<0.001**	**2.0 (58)**	**2.7 (80)**	**<0.001**

Note - Numbers in brackets are the actual number of individuals

Ns=not significant

(Table 4) [8]. Adding the 24 surveillance participants with at least one advanced neoplasia, the proportion of CTC participants with at least one advanced neoplasia significantly increased to 84 of 982 participants (p<0.001). The overall yield per 100 CTC participants increased from 6.1 to 8.6 (p<0.001) and relative to those invited for CTC screening, we found an increased yield from 2.1 to 2.9 advanced neoplasia per 100 CTC invitees (p<0.001).

Extracolonic findings

Potentially important findings (C-RADS E3 or E4) were found in 4 (7.1 %) of 56 participants. One finding (1.8 %) was new with respect to the initial CTC and required no further handling after assessment by the general physician (E4; collapsed osteoporotic vertebrae). One finding (1.8 %) was increased in size at surveillance CTC and required the scheduled appointment at the urologist to be brought forward (E4, growth of multiple angiomyolipomas).

Adverse events

No serious adverse events occurred during surveillance CTC or subsequent OC. One individual with an OC and polypectomy of a 20 mm pedunculated sigmoid polyp in a different hospital prior to invitation returned after 11 days with a perforation.

Discussion

The surveillance yield for advanced neoplasia was 29.3 % (24/82). No CRC or high-grade dysplasia was detected, suggesting a safe surveillance strategy. Inclusion of the surveillance yield of 82 patients under surveillance for 6-9 mm polyps led to a significant increase in yield of population-based CTC screening for advanced neoplasia, both per 100 CTC participants (from 6.1 to 8.6; p<0.001) and per 100 invitees (from 2.1 to 2.9; p<0.001) [8]. The surveillance participation rate was high (86.2 %) while new important extracolonic findings were rarely detected (1.8 %).

To our knowledge, there has not been a previous study reporting on the yield and participation of surveillance CTC in the setting of an invitation-based CRC screening program. One article has been published describing the findings of a 6-9 mm surveillance cohort of a non-invitational primary screening population of 303 patients [18]. In that surveillance population of 303 patients with 6-9 mm polyps, 24 advanced neoplasms resided in 23 patients (yield 7.6 % (23/303)) (email correspondence PJ Pickhardt, MD; date: 19 July 2014). A possible explanation for our higher diagnostic yield is that we referred all patients with ≥6 mm polyps for OC and obtained histopathological verification of all lesions. Instead, that study referred only individuals with polyps with ≥1 mm increase in size thereby excluding stable or decreasing size ≥6 mm polyps and leaving a group of individuals (n=143) for ongoing CTC surveillance. Also, they did not present data from patients who withdrew prior to surveillance CTC, for our study inclusion of this data resulted in an additional nine patients with advanced adenomas. The participation rate in both studies was comparable (80 % versus 86 %).

The high yield in our CTC surveillance population showed that the earlier reported initial yield of screening with CTC has been underestimated [8]. Whether the nine advanced adenomas resulting from the preliminary OCs were more likely part of the initial COCOS yield or the surveillance yield is debatable per-patient given the variety in time point of the OCs (Appendix 3). In addition, by including the seven patients with advanced adenomas which were measured ≥10 mm by one of the

technologists in the surveillance yield, one might be compensating for initial misclassification by the radiologist. However, overall yield was not affected by this and is, therefore, probably the most representative outcome of screening for CRC with CTC.

When interpreting this overall yield one should realize that progression in growth and/or transformation from tubular to tubulovillous histology could have taken place during the surveillance interval, probably leading to a larger number of advanced adenomas. A side-by-side comparison with the initial OC yield is therefore not possible. However, in this surveillance population all referrals for OC were for polyps already present at initial screening CTC. We believe this justifies our strategy to add the surveillance results to the initial CTC screening results leading to a significant increase in overall yield per 100 participants and per 100 invitees. As surveillance CTC for 6-9 mm polyps is a viable option in CRC screening, this surveillance yield must be taken into account when deciding on a proper screening strategy.

Debate remains regarding the policy for 6-9 mm polyps. Supportive for referral at ≥6 mm is the considerable yield of participants with advanced adenomas in our surveillance population (29.3 %). On the other hand, most advanced adenomas were ≥10 mm and referral at ≥10 mm with continuing CTC surveillance for 6-9 mm polyps would have led to a decreased number of OCs and a substantial increase of PPV for advanced neoplasia (from 45 % to 75 %). Similar to another surveillance CTC study, no interval CRC's were detected and none versus only one advanced adenoma with high-grade dysplasia in their study, suggesting a safe strategy [18]. A sigmoidoscopy surveillance study for <10 mm polyps also concluded that surveillance for 6-9 mm polyps was safe [19]. In an older population other health issues like life expectance have to be taken into account when advising a certain screening procedure. In our population the four deceased and one severely ill invitee probably had benefit from this non-aggressive follow-up strategy. However, the true efficacy and safety of surveillance for 6-9 mm polyps awaits a study that incorporates multiple CTC follow-up studies over a longer interval.

Extracolonic findings have been mentioned as a potential advantage as well as a disadvantage of CTC [4, 20]. To our knowledge, there is no data on extracolonic findings in surveillance populations after initial CTC screening. As expected, the prevalence of potentially important extracolonic findings that precipitate additional diagnostic follow-up testing in our surveillance population is lower than in a primary CTC screening population (1.8 % versus 4.4 % – 11 %), as the course of time and/or previous additional investigations have proven some findings to be benign or treatment has taken place [7, 8, 21–23].

Our study has some limitations. The trial from which this surveillance population originated was powered for comparing the participation rate of CTC versus OC screening and not for evaluating CTC surveillance [10]. However, for determining the overall yield of CTC in screening (including surveillance) the study population is sizeable (2920 invitees and 982 participants). Further, the present surveillance population was already large enough to demonstrate a significant increase in yield of CTC screening. We found a relatively low PPV (45 %) when only considering advanced neoplasia at OC as a true positive result, especially in comparison to the initial trial (PPV 71 %). This is due to our different cut-off value for which participants were referred for OC (now ≥6 mm instead of ≥10 mm). This different cut-off value was used to learn more about small polyps' histology in surveillance. The PPV for ≥6 mm polyps was very good (97 %), corresponding to a large study investigating PPV for CTC detected polyps [24]. Twenty participants had no ≥6 mm polyps at surveillance CTC, which could be explained by polyp regression [18], a false-positive initial CT or a false-negative surveillance CT. No OCs were performed in participants with a negative CTC, nor did we take the observations of other readers into account. This was done for consistency purposes, as to make overall yield calculations with the original COCOS trial possible. Furthermore, determining accuracy was not the purpose of this study. We did not classify serrated lesions as advanced adenomas because of previous defined histopathology criteria in the initial trial [8]. However, growing evidence shows the malignant potential and the importance of these lesions [25, 26]. Including ≥10 mm serrated lesions as advanced adenomas would have increased the diagnostic yield to 31 % (25/82) [27].

The substantial yield in the CTC surveillance population resulted in a significantly higher diagnostic yield of primary CTC screening than previously has been reported [8]. We were able to provide further insights into diagnostic yield, participation, and new important extracolonic findings in surveillance CTC, all of which should be taken into account when deciding on a proper management strategy for patients with 6-9 mm polyps detected at primary CRC screening.

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One of the authors has significant statistical expertise. Institutional Review Board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study.

This study was a follow-up study of the COCOS-trial (COlonoscopy or COlonography for Screening), a population-based CRC screening RCT performed in the Netherlands (published in Lancet Oncology 2012;13:55-64).

Methodology: prospective, cross sectional study, multicenter study.

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Appendix 1

Detailed explanation of OC procedure. OCs were performed by experienced endoscopists (gastroenterologist, gastroenterology resident or a trained gastroenterologist nurse) according to the standard quality indicators defined by the Society of Gastointestinal Endoscopy [14]. For bowel preparation, 2 L of polyethylene electrolyte glycol solution (Moviprep, Norgine bv, Amsterdam, the Netherlands) was used together with 2 L of transparent fluid, and a low-fibre diet for 2 days. Conscious sedation (midazolam, Dormicum; Roche, Basel, Switzerland) and analgesics (fentanyl, Fentanyl-Janssen; Janssen Pharmaceuticals, Beerse, Belgium) were given intravenously at the discretion of the participant and the endoscopist. Hyoscine butylbromide was given intravenously at the start of withdrawal of the endoscope to reduce colonic motility if needed. During the withdrawal of the endoscope, starting from the caecum, segmental unblinding was performed by a research nurse or research fellow (CTN, TNB, IV). Of all detected lesions, morphology, location, macroscopic aspect and size (measured with open forceps) were noted. If possible, all detected lesions were removed during the same procedure.

Appendix 2

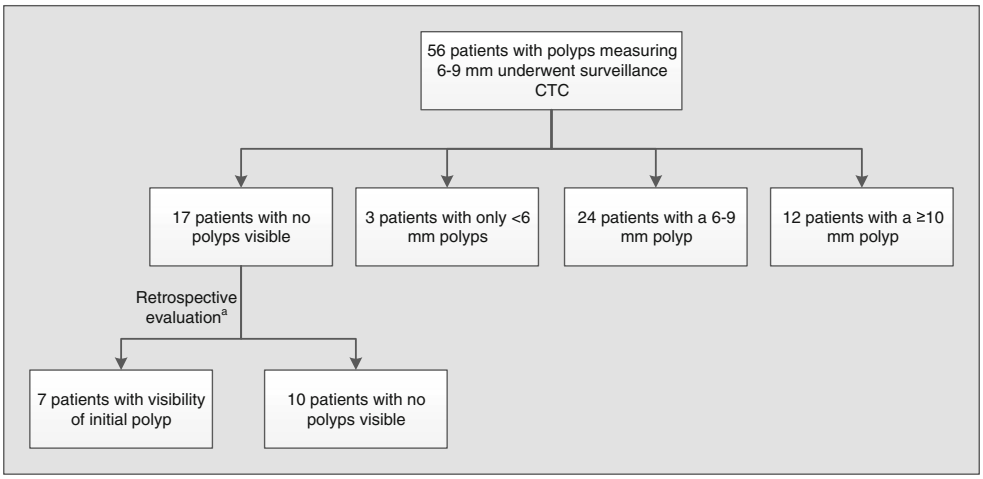

Fig. 2 Evolution of 6–9 mm polyps in surveillance patients on CTC reflected by the most advanced lesion per patient. [a]retrospective evaluation of the surveillance CTC by two of four experienced observers

Appendix 3

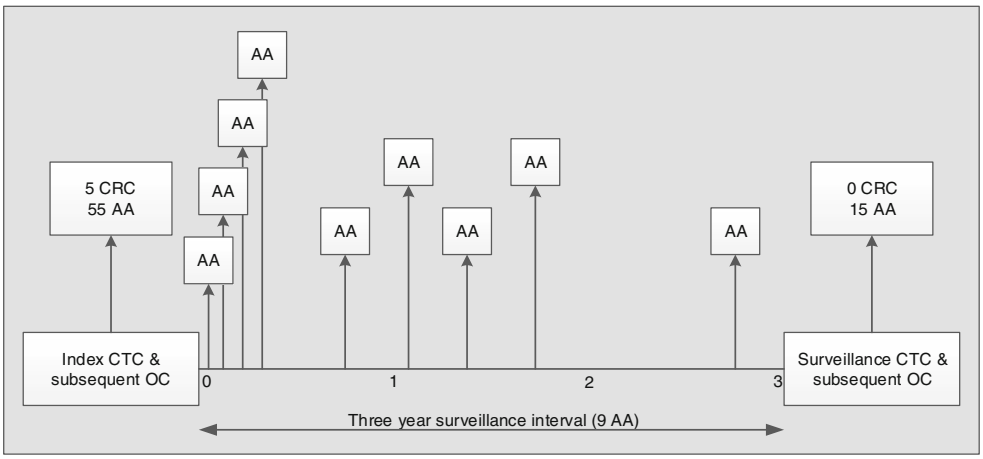

Fig. 3 Timeframe of nine patients with an advanced adenoma at preliminary OC prior to the invitation for surveillance CTC

Appendix 4

Table 5 Histology of 132 detected adenomas

Adenomas ≥10 mm	
Villous	1 (3 %)
Tubulovillous	7 (24 %)
Tubular	21 (72 %)
Total	29
Adenomas 6-9 mm	
Villous	0
Tubulovillous	3 (7 %)
Tubular	41 (93 %)
Total	44
Adenomas <6 mm	
Villous	0
Tubulovillous	0
Tubular	59 (100 %)
Total	59
General	
Total number of adenomas	100
Total number of advanced adenomas	32

Data are n (%)

None of the adenomas contained high-grade dysplasia

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