CT colonography in faecal occult blood test positives

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CT colonography is a non-invasive imaging technique to visualise the colon. The colon is insufflated with CO2 or air and a CT-scan of the abdomen is performed. The performance of CT colonography is nearly equal to that of colonoscopy in the detection of large colonic polyps and carcinomas.

This thesis describes the performance of CT colonography in a faecal occult blood test positive screening population. The detection of polyps and carcinomas by CT colonography and the effectiveness of CT colonography as a triage technique for colonoscopy indication were evaluated. Different iodine based bowel preparation schemes were tested in the individuals.

Furthermore this thesis describes a learning curve in CT colonography reading by novice CT colonography readers, an evaluation of a 2D versus a 3D reading paradigm and an inventory of CT colonography radiation doses among different research institutions.
CT COLONOGRAPHY IN FAECAL OCCULT BLOOD TEST POSITIVES
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ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 20 april 2010, te 14.00 uur

door

Marjolein Henrieke Liedenbaum

geboren te Terneuzen
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Faculteit der Geneeskunde
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td><strong>Two different doses of iodinated fecal tagging agent for CT colonography: evaluation of tagging quality, homogeneity, patient acceptance and diagnostic accuracy</strong> <em>Eur Rad 2009 DOI 10.1007/s00330-009-1570-8</em></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td><strong>Low-fiber diet in CT colonography bowel preparation: influence on image quality, patient acceptance and polyp detection</strong> <em>Accepted AJR AM J Roentgenol</em></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td><strong>Reducing the oral contrast dose in CT colonography: Evaluation of faecal tagging quality and patient acceptance</strong> <em>Submitted</em></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td><strong>Using CT colonography as triage technique for colorectal cancer in a FOBT positive screening population</strong> <em>GUT 2009 58:1242-1249</em></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td><strong>CT colonography for detection of colorectal neoplasia in a FOBT positive screening population</strong> <em>Abdom Imaging 2009 DOI: 10.1007/s00261-009-9586-8</em></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>111</td>
</tr>
<tr>
<td><strong>Radiation dose in CT colonography-trends in time and differences between daily practice and screening protocols</strong> <em>Eur Radial 2008 18:2222-30</em></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>129</td>
</tr>
<tr>
<td><strong>Evaluation of a standardized CT colonography training program in novice readers</strong> <em>Submitted</em></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 9
Primary uncleansed 2D versus primary electronically cleansed 3D in limited bowel preparation CT-colonography. Is there a difference for novices and expert readers?
Eur Radiol 2009 19:1939-50

Chapter 10
CT colonography polyp matching: differences between experienced readers.
Eur Radiol 2009 19:1723–1730

Chapter 11
Summary of findings and implications

Chapter 12
Samenvatting van bevindingen en implicaties
Dankwoord
Curriculum Vitae
Publications
Introduction and outline of the thesis
Cancer of the large bowel is the second leading cause of cancer death in the Netherlands.\(^1\) In nearly 6\% of all persons in the Netherlands a colorectal carcinoma develops during their life-time. Currently, almost half of these persons die from this disease within five years. One of the main reasons for this high mortality rate is that the disease usually only becomes symptomatic when it is in an advanced stage. Only 10\% of the patients with advanced stage colorectal carcinoma with distant metastasis, is still alive 5 years after the diagnosis has been made.\(^2\) This compares to 90\% of patients with colorectal carcinomas with the least advanced stage, where disease is confined to the bowel only. Therefore an early detection of the colorectal carcinoma can lower mortality. Colorectal carcinoma can also be prevented by removing its main precursor, the adenomatous polyp.\(^3\)\(^5\) Population screening to detect carcinomas and adenomas, enabling an early removal of the adenomas, can reduce colorectal cancer mortality.

In the next paragraphs a short overview is presented of the anatomy and pathology of the colon, the possible screening options for colorectal cancer, the principles of computed tomography colonography (CT colonography; also named virtual colonoscopy) and an outline of this thesis.

### Anatomy & pathology of the colon

The colon is the last part of our intestinal canal. Its main function is the absorption of water and salts from the faeces. The ileocaecal valve separates the small bowel (ileum) from the colon. Six colonic segments are distinguished: the caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum (see fig. 1).

From the normal inner lining of the colon (mucosa), polypoid structures (colorectal polyps) can arise. Most of the colorectal cancers (95\%) are believed to develop from these colorectal polyps after several genetic alterations.\(^6\)\(^,\)\(^7\) Histologically, polyps can be classified as neoplastic (adenomas) or nonneoplastic polyps.\(^8\) Nonneoplastic polyps have no malignant potential and include hyperplastic polyps (except a specific subtype with a serrated histology)\(^9\)\(^,\)\(^10\) and inflammatory polyps. Neoplastic polyps or adenomas have the potential to develop into a malignant tumor.\(^7\) The development from an adenoma to a colorectal carcinoma is probably 5 to 15 years.\(^11\) Not all adenomas will eventually develop into a colorectal carcinoma. Predominantly the adenomas with high grade dysplasia, a villous histology or those with a diameter larger than 10 mm have a greater chance to develop into a malignancy. This type of adenomas are classified as advanced.
adenomas. In fig. 2 a pedunculated and sessile polyp are shown, both with zones of carcinomatous cells.

![Fig. 2 Drawing of a pedunculated and sessile polyp. All dark areas represent zones of carcinoma. Zone B and C show invasion into the submucosa of the bowel wall and are therefore called invasive carcinomas.](http://www.cancer.gov/)

**SCREENING ON COLORECTAL CARCINOMA**

In several countries population screening programs for colorectal cancer have been started. The goal of cancer screening is to reduce mortality from this disease through early detection of cancer and its precursors, preventing or limiting the development of advanced disease. A number of tests are available for colorectal cancer screening. These screening tests are grouped into those that primarily detect cancer early and those that can detect cancer early as well as adenomatous polyps.

The first category, tests that detect cancer early, comprises the stool tests: the guiac faecal occult blood test (G-FOBT), the immunochemical faecal occult blood test (I-FOBT) and the DNA stool tests. The G-FOBT detects blood in the stool through pseudoperoxidase activity of haeme of haemoglobin, while immunochemical-based tests react to human globin. The advantage of the FOBT as a screening test is that it is a very cheap and simple test and therefore suitable for population screening. It has been demonstrated that G-FOBT significantly reduces disease-related mortality and is cost effective. Disadvantages are a low sensitivity and a high number of false positives (a PPV of less than 50% for carcinomas and adenomas). Therefore a large part of the FOBT positive participants will receive an unnecessary colonoscopy with subsequent burden and risks on complications. A test performed in FOBT positives that can triage only the positives with relevant lesions that need colonoscopy could avoid those unnecessary examinations.
The second category consists of tests that do not only detect colorectal carcinomas, but also adenomatous polyps. To this category of tests belong the sigmoidoscopy, colonoscopy, double contrast barium enema (DCBE) and CT colonography. A major advantage of colonoscopy that it is not only a diagnostic test but that polypectomy and biopsy can be performed in one examination. All other tests need a colonoscopy as a second procedure. Disadvantages are that colonoscopy is an invasive test that requires extensive bowel preparation, its performance depends on the skills of the endoscopist and colonoscopy is not a perfect reference standard, 2% of adenomas ≥10mm and 13% of adenomas between 6 and 9mm are missed. A fairly new imaging technique of the colon is CT colonography. This technique is described in the paragraphs hereafter.

CT COLONOGRAPHY (VIRTUAL COLONOSCOPY)
In 1983 the first article was published on computerized radiology of the colon. Until 1996 this new technique remained relatively undeveloped. Vining was the first to publish an article on Virtual Endoscopy after this period. From that time the technique has developed enormously and a large amount of research has been performed in this field. Several studies have been performed to evaluate the accuracy of adenoma and carcinoma detection in symptomatic, surveillance and screening patients. Furthermore developments have been made to reduce the radiation dose and bowel preparation.

Technique of CT colonography
CT colonography is performed on a multislice CT scanner (MSCT), preferentially 16-slice or more MSCT. A small collimation can then be used which makes small polyps more easy to detect, while scanning times can be short (5-10 seconds for 64-slice scanners). Most recent studies used a collimation of 1 mm and a tube current of 50 mAs or less when no intravenous contrast agent was administered. To distend the colon prior to scanning, air or preferably CO₂ has to be insufflated. An automated insufflator, instead of manual insufflation, can be used to for a pressure controlled inflow of CO₂. For an optimal examination, scans have to be made in two positions, the supine and the prone position. When distension in one part of the colon is not optimal or a polyp is covered by faeces, the other position might help visualizing this colonic part.

Bowel preparation
For optimal imaging of the colon, the colon should be cleansed using laxative agents, or residual faeces has to be 'tagged' with an oral contrast agent. Recent studies have shown that using an oral contrast agent only gives good results regarding image quality and polyp detection. The two types of oral contrast agent that are used for tagging are iodine and barium. Barium mixes well with solid stool particles and does not cause diarrhoea. A disadvantage is that barium mixes badly with aqueous solutions resulting in a more difficult interpretation of images. Iodine on the other hand mixes well with liquid stools and a homogeneous mixing can be obtained. Because most iodine contrast agents are hyperosmotic, patients will have diarrhoea after ingestion.
Chapter 1 | Introduction

Accuracy of CT colonography
CT colonography can be considered as a good alternative to colonoscopy in case of similar sensitivity and specificity in the detection of polyps and carcinomas. Two large meta-analyses have evaluated the accuracy of CT colonography. The per-patient sensitivity of CT colonography for the detection of colorectal carcinomas was 96%, for polyps ≥10mm this was 85-93% and for polyps between 6 and 9 mm 70-86%. These were predominantly studies in symptomatic patients. Two recent studies that used CT colonography as a population screening tool for colorectal cancer, showed that the detection of colorectal neoplasia at CT colonography was nearly equal to that of colonoscopy. Kim et al. found that in two equally sized groups of patients the number of detected colorectal neoplasms was similar; 123 advanced neoplasms were found in the CT colonography group and 121 in the colonoscopy group. Johnson et al. evaluated the accuracy of CT colonography in a screening population and found a per-patient sensitivity of 90% for the detection of adenomas and carcinomas ≥10mm and a specificity of 86%. Up till now no randomized trial for screening with CT colonography has been performed and the effects on mortality reduction are not clear yet. One study has assessed the accuracy of CT colonography in FOBT positives (no screening participants). A high sensitivity of 87% for detection of advanced neoplasia was found.

Extracolonic findings
Although a CT colonography is primarily performed for inspection of the colon, extracolonic structures such as the kidneys, liver and the aorta are also displayed. A consensus proposal has been published that classifies extracolonic findings in an E-RADS scoring system. E4 findings are highly important findings that need intervention. In a systematic review it was found that 14% of all patients that received a CT colonography had extracolonic findings that needed follow-up, while Pickhardt et al. found a prevalence of 7.2% relevant lesions in screening participants. Studies that evaluated the costs of extracolonic findings also reported different results on cost-effectiveness, some in favour of CT colonography and others not.

Radiation dose
An issue that is often debated when CT colonography is considered as screening option for colorectal carcinoma is the risk on radiation induced cancer. Hall and Brenner calculated that the lifetime cancer risk induced by a CT colonography in a 50 year old patient is 0.14%. Numerous comments were made on these calculations, for example that a linear no-threshold hypothesis was used which means that every minimal radiation dose could induce cancer. When BEIR VII data on health risks from exposure from low level radiation are used, a CT colonography with a 3 mSv effective dose results in a risk of 0.01-0.02% for a 50 year old and 0.006-0.008% for a 75 year old. Currently, efforts are being made to reduce the radiation dose for CT colonography as much as possible.

Reading methods and experience
Two different reading methods exist for reading a CT colonography examination; a primary 2D read with 3D images for verification or a primary 3D read using 2D for verification. Several studies have been performed to test which reading method is most effective. It
however appeared in most studies that there was no difference in sensitivity when using the primary 2D versus the primary 3D method.\textsuperscript{42-44} In a study of Pickhardt et al. experienced readers performed significantly better in 3D reading.\textsuperscript{45} An additional tool to improve the detection of polyps by a reader is the use of Computer Aided Detection (CAD). This software algorithm automatically detects polyps by identifying voxels along the wall of the colon and measuring the shape index of the wall to classify the wall locally into polypoid and nonpolypoid (i.e. normal) areas.\textsuperscript{46,47} Previous studies have shown that especially inexperienced readers benefited from the use of CAD software and their sensitivity was significantly increased.\textsuperscript{48-51} CAD used by experienced readers does not seem to result in a higher sensitivity.\textsuperscript{50,52} The amount of experience in reading CT colonographies to become an expert reader with a high sensitivity and specificity is not clear. It has been shown that after a training course with 50 CT colonographies a reader does not obtain an accuracy equal to an experienced reader.\textsuperscript{53,54} Training does improve the accuracy of a reader, but the necessary amount of training cases to become an expert reader has not been established yet.

**OUTLINE OF THE THESIS**

This thesis focuses on the performance of CT colonography in FOBT positive screening participants. Several aspects such as the accuracy, bowel preparation, participation rate, patient acceptance, learning curves and reading methods were analysed.

In order to obtain a good image quality and an optimal level of polyp detection, the bowel preparation used for CT colonography needs to be of good quality. In chapters 2 to 4, three studies on bowel preparation are described. The participants of all prospective studies presented in this thesis received an iodine tagging agent only and no laxatives. This has advantages for patient compliance and patient acceptance when compared to an extensive cathartic preparation. In chapter 2 we compared a two-day preparation scheme with iodine tagging to a one-day preparation scheme aiming to find the most optimal scheme regarding patient acceptance and image quality. In chapter 3 the use of an additional low-fibre diet one day before the CT colonography examination was evaluated. Our purpose was to find out if a low-fibre diet is necessary to use in a bowel preparation for CT colonography. In the last chapter on bowel preparation, chapter 4, three very minimal iodine bowel preparations were studied. The subjective and quantitative image quality, the patient acceptance of the preparations and polyp detection were evaluated.

In chapters 5 and 6 the results of a large CT colonography triage study are described. Positive FOBT screening participants were asked to undergo a CT colonography before colonoscopy. In chapter 5 we evaluated the effectiveness of CT colonography as a triage method after FOBT. The positive and negative predictive values of CT colonography, the number of extracolonic findings, the patient acceptance and the participation rate are presented. Furthermore we calculated the sensitivity and specificity of adenoma and carcinoma detection in chapter 6.
When CT colonography is used in a population screening setting it is important to minimize the radiation dose in order to lower the risk of obtaining radiation induced cancer. In chapter 7 we made an extensive inventory of used radiation doses among all institutions that perform CT colonography for research purposes. The median radiation doses of CT colonographies performed for daily practice and screening purposes were calculated.

When reading CT colonography images it is important to have sufficient experience. This experience can be acquired by following a dedicated training. It was however unclear up till now how many CT colonographies should be examined before reaching an adequate level of experience. In chapter 8 the learning curves of CT colonography reading in novice readers were evaluated. The reading method, primary 2D or primary 3D viewing, might influence the accuracy in novice and experienced readers. The accuracy of different readers performing primary 2D versus primary 3D reading was evaluated in chapter 9.

Chapter 10 we describe a study on matching of polyps found at CT colonography with polyps found at colonoscopy by expert readers. In all studies that evaluate the accuracy of CT colonography compared to colonoscopy, a matching procedure is performed. When this procedure is performed differently by CT colonography readers, this will have influence on the outcomes of accuracy. The purpose of the study in this chapter was to evaluate if differences in matching between expert readers exist.

In chapter 11 and 12 we provide a summary, general discussion and implications for patient care and future research.
Chapter 1 | Introduction

References

CT colonography with minimal bowel preparation: evaluation of tagging quality, patient acceptance and diagnostic accuracy in two iodine-based preparation schemes

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Eur Radiol
DOI 10.1007/s00330-009-1570-8
ABSTRACT

Purpose: The aim of this study was to compare a 1-day with a 2-day iodine bowel preparation for CT colonography in a positive faecal occult blood test (FOBT) screening population.

Materials and methods: One hundred consecutive patients underwent CT colonography and colonoscopy with segmental unblinding. The first 50 patients (group 1) ingested 7*50 ml iodinated contrast starting 2 days before CT colonography. The latter 50 patients (group 2) ingested 4*50 ml iodinated contrast starting 1 day before CT colonography. Per colonic segment measurements of residual stool attenuation and homogeneity were performed, and a subjective evaluation of tagging quality (grade 1–5) was done. Independently, two reviewers performed polyp and carcinoma detection.

Results: The tagging density was 638 and 618 HU (p=0.458) and homogeneity 91 and 86 HU for groups 1 and 2, respectively (p=0.145). The tagging quality was graded 5 (excellent) in 90% of all segments in group 1 and 91% in group 2 (p=0.749). Mean per-polyp sensitivity for lesions ≥10 mm was 86% in group 1 and 97% in group 2 (p=0.355). Patient burden from diarrhoea significantly decreased for patients in group 2.

Conclusions: One-day preparation with meglumine ioxithalamate results in an improved patient acceptability compared with 2-day preparation and has a comparable, excellent image quality and good diagnostic performance.
INTRODUCTION

Computed tomography (CT) colonography (CT colonography) is an accurate method for detection of polyps and carcinomas in the colon and rectum, and can be considered a less burdensome examination compared with colonoscopy.\(^1,2\) Recent studies have shown that faecal tagging only, i.e., without laxatives, is sufficient for bowel preparation.\(^3-8\)

Importantly, high diagnostic accuracy is found in studies that use such a limited bowel preparation for CT colonography.\(^4,6,7\)

Tagging for CT colonography can be performed with barium- or iodine-based contrast agents. Barium suspensions do not dissolve in liquids and are therefore more efficient at tagging only solid stools.\(^8\) Non-ionic and ionic iodine-based agents dissolve in aqueous solutions, but can result in fluid shifts into the bowel lumen that generate soft stools and diarrhoea.\(^5\) Zalis et al. compared barium and iodine contrast medium preparations and found improved discomfort scores and readability in the patient group that had ingested an iodine tagging agent.\(^10\) Other studies also used iodine tagging in different amounts and often with use of additional laxatives.\(^3,11,12\) A complicated scheme for ingestion of laxatives and tagging agents can however be difficult to follow for a patient, which can lead to incompliance.\(^13\) Therefore, we aim to have a simple bowel preparation scheme, with ingestion of the oral contrast medium only.

By increasing the amount of iodine contrast medium the stool will soften, which improves the image readability. Presently, no consensus exists on the amount of contrast medium and the number of preparation days needed for optimal tagging. An earlier study showed that a 1-day preparation with iodine contrast medium only might be sufficient to tag the faeces.\(^12\) However, patient groups were small, which makes it difficult to draw conclusions regarding accuracy of polyp detection, and therefore a larger study is needed to substantiate these findings.

The aim of the present study was to compare the use of a 1-day versus a 2-day iodine-based bowel preparation for CT colonography in two patient groups by evaluating the patient acceptance, quality of the bowel preparation, homogeneity of tagged bowel contents and the accuracy of polyp detection.

MATERIALS AND METHODS

Between June 2006 and May 2007 a cohort of 10,000 patients between 50 and 75 years old received a faecal occult blood test (FOBT), either guaiac (Hemoccult II) or immunochemical (OC-Sensor), at home.\(^14\) In total 302 patients who were willing to undergo CT colonography before colonoscopy were included in a CT colonography trial, which was previously reported.\(^15\) Of these 302 patients, 100 consecutive patients that received a CT colonography in the Amsterdam region were included in this bowel preparation study. Exclusion criteria for FOBT positives were: persons unable to give informed consent, terminal illness, severe psychiatric symptoms, colonoscopy
or an FOBT in the previous 2 years, examinations with radiation exposure in the last 12 months, previous contrast medium reaction, hyperthyroidism and pregnancy. The study was approved by the review board of the institution, and all participating patients gave informed consent.

**CT colonography examination**

*Bowel preparation*

All patients received a high-osmolar ionic monomer contrast medium (meglumine-ioxithalamate, 300 mg I/ml, Telebrix Gastro; Guerbert, Cedex, France). The first 50 consecutive patients received in total 350 ml Telebrix (preparation 1, 2-day preparation) and the following 50 consecutive patients received 200 ml Telebrix (preparation 2, 1-day preparation). The contrast medium was given without any additional fluid, but patients were allowed to drink the bottles of Telebrix mixed with syrup or water, for example. Furthermore, they were instructed to drink additional glasses of water during the day. In addition, patients followed a low-fibre diet. In Table 1 both preparation schemes are displayed.

*CT colonography acquisition*

CT was performed on a 64-slice CT system (Brilliance, Philips Medical Systems, Best, The Netherlands) at a slice collimation of 64×0.625 mm, pitch 1.2, slice thickness 0.9 mm, rotation time 0.4 s, a tube voltage of 120 kV and a reference mAs of 40 with dose modulation. A muscle relaxant, 20 mg of butylscopolamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany), or, when contraindicated, 1 mg of glucagon hydrochloride (Glucagen; Novo-Nordisk, Bagsvaerd, Denmark), was injected before insufflation of the colon. When these were both contraindicated, no muscle relaxant was injected. A balloon-tipped rectal catheter was inserted to insufflate approximately 3 l of CO2 gas into the colon, using an automated insufflator (Bracco, PROTOCO2l insufflator, New York, USA).

**Table 1** Bowel preparation scheme for the two preparations

<table>
<thead>
<tr>
<th>Two days before CT colonography</th>
<th>One day before CT colonography</th>
<th>Day CT colonography</th>
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<tbody>
<tr>
<td><strong>Preparation 1</strong></td>
<td>-3 * 50 ml Telebrix during each meal</td>
<td>-3 * 50 ml Telebrix during each meal</td>
</tr>
<tr>
<td></td>
<td>-low-fibre diet</td>
<td>-low-fibre diet</td>
</tr>
<tr>
<td><strong>Preparation 2</strong></td>
<td>-no diet restrictions</td>
<td>-3 * 50 ml Telebrix during each meal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-low-fibre diet</td>
</tr>
</tbody>
</table>
Evaluation of image quality
Images were read on a Philips workstation (View Forum v5.2, Philips Medical Systems) in 2D setting in a supine position only. The quality of tagging was assessed according to a rating scale\textsuperscript{10} by two observers: MHL, a radiology research fellow, with previous experience of 350 CT colonography readings, and CIBFG, a radiology fellow, with no previous experience with CT colonography reading, who received training on how to identify the appropriate bowel segment and how to evaluate homogeneity. The reading of the second observer was used to test observer agreement. The amount of faeces per colonic segment,\textsuperscript{16} the consistency of the residual faeces and the colonic distension were scored by the first observer on different rating scales (see Table 2). Assessments were performed after inclusion of all 100 patients. The patient study numbers were blinded so that the observers were not aware of the type of bowel preparation.

Table 2 Rating scales for the subjective scores on quality of bowel preparation and the colonic distension

<table>
<thead>
<tr>
<th>Scale</th>
<th>Consistency of residual faeces</th>
<th>Amount of faeces per segment</th>
<th>Quality of tagging (average grade for one whole segment)</th>
<th>Colonic distension</th>
</tr>
</thead>
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<tr>
<td></td>
<td>1. liquid residual faeces</td>
<td>1. 0% of the lumen filled with residual faeces</td>
<td>1. non-interpretable images, untagged faeces and artefacts</td>
<td>1. very poor distension; colon lumen cannot be identified</td>
</tr>
<tr>
<td></td>
<td>2. liquid and solid residual faeces</td>
<td>2. &lt; 25% of the lumen is filled with residual faeces</td>
<td>2. poor interpretation, large amount of non-opacified faeces</td>
<td>2. poorly distended; partly collapsed colon</td>
</tr>
<tr>
<td></td>
<td>3. solid residual faeces</td>
<td>3. 25-50% of the lumen is filled with residual faeces</td>
<td>3. moderate preparation, moderate amounts of non-opacified faeces</td>
<td>3. sufficient distension; suboptimal distended colon, but the colon lumen is properly visible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. ≥50% is filled with residual faeces</td>
<td>4. good preparation, small amounts of non-opacified faeces</td>
<td>4. well distended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5. excellent preparation, no non-opacified faeces</td>
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The homogeneity of the residual faeces was assessed by quantitative measurement by a second, independent observer [CIBFG, a radiology fellow who received training on how to perform region of interest (ROI) measurements]. Density (HU values) and homogeneity (SD values) of the tagged faeces were measured in all six colonic segments per patient. Slices were randomly selected by using a computer program (Windows Excel 2003, Microsoft) that produced six slice numbers for one CT colonography. These were correlated to the six colonic segments by the observer. When after the first randomisation a segment was not included, subsequent randomisations followed until all segments were measured. Per segment a specific ROI was drawn in the faeces to measure the attenuation (mean HU) and SD. See Fig. 1 for an example of an ROI drawing.
Polyp detection at CT colonography

Images were read by two experienced readers (AHdV, previous experience 400 CT colonographies with colonoscopic verification and MHL, with 250) in a primary 2D setting, standard window level 1,500 and window width −250, with 3D problem solving and a second read in 3D fly through. All lesions were marked and measured at 2D MPR. Of each position (prone and supine) the reading times were noted for reading primary 2D axial slices and the 3D fly-through second reading.

Colonoscopy

Within approximately 2 weeks (range: 1 to 22 days) of CT colonography, colonoscopy was performed. Bowel preparation for colonoscopy consisted of 4 l polyethylene glycol electrolyte solution (KleanPrep; Helsinn Birex Pharmaceuticals, Dublin, Ireland) and a clear liquid diet starting the evening before colonoscopy. Experienced colonoscopists performed optical colonoscopy with a standard colonoscope (Olympus, Tokyo, Japan). Sedation, analgesics and/or a muscle-relaxant was used in all patients. According to the technique of segmental unblinding, the findings of the CT colonography were revealed to the colonoscopist after completing the examination of one segment. Polyp size was estimated by an opened biopsy forceps (8 mm) or by a linear measure probe (Olympus America). The histology of the lesion biopsies was classified as normal, hyperplastic, adenoma (type: serrated, tubular, tubulo-villous or villous and degree of dysplasia) or carcinoma according to the Vienna classification.

Patient compliance and acceptance

Patient experience of bowel preparation was evaluated by standardised questionnaires before the CT colonography and colonoscopy, and a mailed questionnaire 5 weeks after the colonoscopy. Patients were asked in the questionnaire before the CT colonography examination about their normal defecation pattern and how burdensome they found the overall CT colonography bowel preparation, and answered on a 5-point scale: 1= no discomfort, 2= mild, 3= moderate, 4= severe or 5= extremely burdensome. Furthermore, they were asked if they had diarrhoea and how burdensome this was (assessed on a similar 5-point scale). Five weeks after the colonoscopy examination, patients were asked which examination or preparation they found most burdensome. The questionnaires had been used in previous studies on acceptance of CT colonography.
Statistical analysis
No power calculation was performed, because we had no indication about the difference in homogeneity of the faeces in patients that would receive the 1-day versus the 2-day preparation. We estimated that a sample size of 50 patients per group should be sufficient to give insight into the quality of bowel preparation with an iodine tagging agent. Age and sex distribution between the groups were tested using the Mann-Whitney and the chi-squared test respectively.

We estimated interobserver agreement for the quality of tagging by calculating weighted kappa statistics with corresponding 95% confidence intervals and by calculating the total number of concordant cases. The kappa values were interpreted as follows: <0.20 poor agreement; 0.21–0.40, fair; 0.41–0.60 moderate; 0.61–0.80, good; 0.81–1.00, excellent.

For the analysis of the amount of faecal residue, the quality of tagging, the colonic distension and the consistency of residual stool per segment, we applied ordinal regression analysis using generalised estimating equations (GEE) to revise the data clustering and dependency.19 This was done because more than one segment per patient was used. For comparison of the HU values (density) and SD values (homogeneity), the independent samples t-test was used to obtain means and standard deviation and to identify differences between the two groups. For overall analysis, a linear regression analysis was applied using GEE to revise the data clustering and dependency, and estimates of means with corresponding standard error were obtained.

For comparison of the reading times the independent samples t-test was used to identify differences between the two groups. For comparison of the different outcomes on the patient questionnaires, we performed an ordinal regression analysis.

CT colonography polyps were considered as true positive if the colonoscopy polyp was within one adjacent segment, if the estimated polyp size was within 50% of the colonoscopic measurement and if the morphology closely resembled the corresponding polyp seen on the videotaped colonoscopy. A per-polyp analysis was done resulting in a sensitivity and false-positive rate per observer and per patient analysis resulting in a per-patient sensitivity and specificity. Results are given in two size categories: lesions of 6 mm and larger (medium) and lesions of 10 mm and larger (large). Lesions were categorised by size on the basis of the colonoscopic measurements, and the false positives were categorised according to the size measured at CT colonography. Only polyps with a possible pre-malignant histology (adenomatous or hyperplasia) and carcinomas were considered true lesions. Differences between the two preparation groups for per polyp sensitivity, per patient sensitivity and specificity were tested using the chi-squared test.

Statistical analyses were performed using MedCalc version 9.4.2.0 for Windows to calculate agreement, SAS version 8.02 for Windows (SAS Institute) to perform the GEE analyses, and all other analyses were done with SPSS version 15.0.1 for Windows (SPSS). For all analysis, a p value of <0.05 indicated a significant difference between the two preparation groups.
RESULTS

Preparation group 1 consisted of 27 men and 23 women, group 2 of 30 men and 20 women ($p=0.545$). Median age in group 1 was 58 years (range 50–72) and in group 2, 62 years (50–75) ($p=0.002$). No adverse events occurred during the study. Nineteen patients were excluded; three patients were excluded because of hyperthyroidism, one because a previous allergic reaction to iodine intravenous contrast medium, nine had had a colonoscopy within 2 years, five had terminal illness and one had severe psychiatric symptoms.

Evaluation of image quality CT colonography

In group 1 the consistency of the residual faeces was liquid in 242 of a total of 285 segments (85%); for group 2 this was 258 out of 285 segments (91%). In both groups 15 segments contained no residual faeces. No significant differences were found in the consistency of the residual faeces among all segments of both groups ($p=0.122$). The subjective judgement on the homogeneity of the residual faeces was graded 5 (excellent) in 90% of all colon segments in the first preparation group and 91% in preparation group 2. When the quality of tagging per segment was compared between the two preparation groups, no differences in homogeneity were found ($p=0.749$). The results are summarised in Fig. 2. In Fig. 3 examples are given of different grades of preparation.

Agreement in the quality of tagging between both observers in the caecum, ascending colon, transverse colon, descending colon, sigmoid and rectum was 88%, 90%, 98%, 92%, 91% and 90%, respectively. Weighted kappa statistics were 0.603, 0.548, 0.660, 0.458, 0.467 and 0.469, respectively, for these segments.

For the amount of residual faeces per segment and per preparation group, we found no significant difference between the two groups ($p=0.599$). Seventy-two percent of the segments in group 1 and 69% of the segments in group 2 were filled with 0–25% of residual faeces. Regarding the distension, the ascending colon received the highest grade (grade 4) for all segments in groups 1 and 2. A better distension of the sigmoid was found in preparation group 1 compared with group 2 ($p=0.021$). For the other segments no significant differences were found, and overall no difference existed between both groups ($p=0.200$).

Density and homogeneity of tagging

The mean attenuation of the residual faeces in all segments was 638 HU (SD 121) for preparation 1 and 618 HU (SD 155) for preparation 2 ($p=0.456$; Table 3). The homogeneity, the SD of the attenuation in the ROI, was 91 HU (SD 22) for preparation group 1 and 86 HU (SD 18) for preparation group 2 ($p=0.148$; see Table 3). A better homogeneity in the transverse colon and descending colon was found in preparation group 2 ($p=0.006$ and $p=0.036$, respectively).
Chapter 2 | Comparison of two iodine bowel preparations for CT colonography

![Quality scale diagram](image)

**Fig. 2** Quality judgement of residual faeces for all colonic segments per preparation group (p=0.749).

1= non-interpretable images, untagged faeces and artefacts, 2= poor interpretation, large amount of non-opacified faeces, 3= moderate preparation, moderate amounts of non-opacified faeces, 4= good preparation, small amounts of non-opacified faeces, 5= excellent preparation no nonopacified faeces

**Patient preference**

Most patients, 69% in group 1 and 67% in group 2, indicated that the consistency of their normal faeces was hard and dry; no differences were found in the consistency of normal stools (p=0.062). The discomfort scores of the CT colonography bowel preparation of patients with preparations 1 and 2 are shown in Fig. 4. In group 1, 8% (4/50) rated the CT colonography bowel preparation as extremely burdensome compared with 2% (1/49) in group 2 (p=0.388). In group 1, six patients indicated that they did not take the total amount of 7 aliquots of 50 ml of Telebrix (one patient ingested only 3 aliquots, three patients only 5 aliquots and one patient 6 aliquots). In group 2 all patients took the full amount, resulting in better compliance than in group 1 (p=0.013). Diarrhoea was present in all patients of group 1; only two patients in group 2 reported that they did not have diarrhoea. In group 1, 26% (13/50) rated the diarrhoea as extremely burdensome compared with 15% (7/47) in group 2 (p=0.049; see Fig. 5 for discomfort scores of diarrhoea). When comparing both preparations and examinations in both groups 1 and 2, 67% found the colonoscopy bowel preparation the most burdensome aspect. See Fig. 6 for the results.

**Reading times**

Reading times of observers 1 and 2 were 15 min 46 s (SD 7 min 51 s) and 15 min 06 s (SD 6 min 44 s), respectively, in group 1 and 14 min 50 s (SD 3 min 17 s) and 12 min 56 s (SD 6 min 16 s) in group 2 (p=0.486 for observer 1 and p= 0.057 for observer 2).
Table 3 Results of the density and homogeneity measurements per segment and per preparation group

<table>
<thead>
<tr>
<th>Segment</th>
<th>Density (HU)</th>
<th>Homogeneity (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preparation 1</td>
<td>Preparation 2</td>
</tr>
<tr>
<td>Caecum</td>
<td>620</td>
<td>599</td>
</tr>
<tr>
<td>Ascending</td>
<td>624</td>
<td>591</td>
</tr>
<tr>
<td>Transverse</td>
<td>683</td>
<td>670</td>
</tr>
<tr>
<td>Descending</td>
<td>668</td>
<td>657</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>633</td>
<td>618</td>
</tr>
<tr>
<td>Rectum</td>
<td>583</td>
<td>564</td>
</tr>
<tr>
<td>Total</td>
<td>637</td>
<td>618</td>
</tr>
</tbody>
</table>

†Indicates a significant difference

Fig. 3 Examples of different grades of preparation. At the left axial images and at the right the sagittal images. White arrows indicate the faecal residues.  

a Excellent preparation (grade 5) in the caecum and ascending colon.  
b Moderate preparation (grade 3) in the caecum and ascending colon.  
c Non-interpretable preparation (grade 1) in the caecum and ascending colon.
**Colonoscopy**

In the first group 33 lesions of ≥10 mm, 31 adenomas and two carcinomas were identified at colonoscopy with segmental unblinding in 21 patients. In group 2, 33 lesions, of which
four were carcinomas and two hyperplastic lesions, were found in 27 patients in this size category. For the category of lesions ≥6 mm, 61 lesions (of which 4 were hyperplastic) in 34 patients and 68 lesions (of which 7 were hyperplastic) in 40 patients were found in groups 1 and 2, respectively.

**Polyp detection at CT colonography**
In Table 4 results are given for the per polyp sensitivity for reviewers 1 and 2 for both preparation groups and size categories. The mean sensitivity for lesions of ≥10 mm was 86% in group 1 and 97% for group 2 (p=0.355). The mean sensitivity for lesions of ≥6 mm was 76% in group 1 and 90% for group 2 (p=0.052). When considering adenomas and carcinomas ≥10 mm only, the mean sensitivity was also 86% in group 1 and 97% in group 2 (p=0.360). For adenomas and carcinomas ≥6 mm the mean sensitivity was 78% in group 1 and 88% in group 2 (p=0.157).

**Table 4** Per polyp sensitivity for observers 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Preparation 1</th>
<th>Preparation 2</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observer 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥10mm</td>
<td>85% (73-97)</td>
<td>97% (91-100)</td>
<td>p=0.197</td>
</tr>
<tr>
<td>lesions ≥6mm</td>
<td>75% (65-86)</td>
<td>87% (79-95)</td>
<td>p=0.098</td>
</tr>
<tr>
<td><strong>Observer 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥10mm</td>
<td>88% (77-99)</td>
<td>97% (91-100)</td>
<td>p=0.355</td>
</tr>
<tr>
<td>lesions ≥6mm</td>
<td>77% (66-88)</td>
<td>93% (86-99)</td>
<td>p=0.013</td>
</tr>
</tbody>
</table>

Table 5 shows the results of the FP rate in both size categories and for both observers. The per patient sensitivity is given in Table 6. The mean sensitivity in group 1 was 90% for lesions ≥10 mm and in group 2 96% (p=0.574). The sensitivity for lesions ≥6 mm in group 1 was 84%, and in group 2 it was 98% with a significant difference for observer 1. No differences in per patient specificity between the two preparation groups were found.

**Table 5** Total number of FPs per observer

<table>
<thead>
<tr>
<th></th>
<th>Preparation 1</th>
<th>Preparation 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observer 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥10mm</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>lesions ≥6mm</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td><strong>Observer 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥10mm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>lesions ≥6mm</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 6 Per patient sensitivity per observer

<table>
<thead>
<tr>
<th>Observer</th>
<th>Preparation 1</th>
<th>Preparation 2</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Observer 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥ 10 mm</td>
<td>90% (78-100)</td>
<td>96% (89-100)</td>
<td>p=0.574</td>
</tr>
<tr>
<td>lesions ≥ 6 mm</td>
<td>82% (70-95)</td>
<td>98% (93-100)</td>
<td>p=0.043</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesions ≥ 10 mm</td>
<td>90% (78-100)</td>
<td>96% (89-100)</td>
<td>p=0.574</td>
</tr>
<tr>
<td>lesions ≥ 6 mm</td>
<td>85% (73-97)</td>
<td>98% (93-100)</td>
<td>p=0.088</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In this study we compared a 1-day with a 2-day tagging only preparation scheme for CT colonography using a high-osmolar iodine contrast medium (meglumine-ioxithalamate) and a low-fibre diet. The most important results were that the image quality and polyp detection were comparable in the two groups. Tagging quality was given high scores in both groups, and ROI measurements of homogeneity and density were nearly equal; even a significantly better homogeneity in the transverse and descending colon in group 2 was found (thus, the 1-day preparation group). Furthermore, the burden of diarrhoea was decreased in the second group.

In our institution nowadays the 1-day preparation scheme is used for routine clinical practice. In this study we used a high-osmolar ionic contrast medium because this agent causes a fluid consistency of the faeces that mixes well with the iodine contrast medium and thus homogeneous tagging can be obtained. The fluid consistency is useful because image readability improves when properly tagged fluid faeces shift if the patient turns from the supine to the prone position. Furthermore, the high density and good homogeneity that were obtained are probably important for improved polyp detection. A previous study showed that with a tagged material density of 480 HU or higher at a tube current of 40 mAs, the sensitivity for polyp detection is optimal.

When a cleansing algorithm is used to digitally subtract residual faeces a good homogeneity is necessary. In both preparation groups in our study the density was more than 600 HU, and the homogeneity (SD) was less than 100 HU. Compared to earlier studies these are comparable results. In the study of Zalis et al. who tested two iodine preparations that started 48 h before scanning, tagging density was 500 to 550 HU, and the homogeneity (SD) was also less than 100 HU with corresponding high grades for subjective tagging scores. In a study of Taylor et al. the four used barium tagging preparations starting 1 or 2 days before scanning, and produced an average tagged fluid density of around 500 HU.
We also used the grading system for evaluation of the tagging quality by Zalis et al.\textsuperscript{10} This is however very subjective, and therefore a second observer also performed this analysis in order to measure observer agreement. We found high scores for tagging quality in almost all segments in both groups. Agreement was more than 90\% in five of six segments, and weighted kappa statistics were moderate to good, indicating there was a quite high agreement. We found that both observers yielded high scores for per polyp and per patient sensitivity (per patient sensitivity >90\% for polyps ≥10 mm in both groups). Specificity per patient was also >90\% in both groups, except for observer 1 in preparation group one (81\%), because of a higher number of false positives. Iannacone et al. also showed high sensitivity and specificity for polyp detection in a prospective CT colonography study with a minimal bowel preparation that started 2 days prior to the examination (200 ml of oral iodinated contrast medium).\textsuperscript{6} Per-patient sensitivity was even 100\% for polyps ≥10 mm.

Furthermore, reading times of CT colonography are correlated with the adequacy of tagging and the amount of residual faeces. A previous study showed that reading times were faster in unprepped patients who had more segments with fluid instead of dry residue faeces.\textsuperscript{22} In our study no difference was found in reading times between the two preparation groups, implying that readability of the examinations was equal.

Considering the patient acceptance, we found that patients of the 1-day preparation group found the diarrhoea less burdensome than the patients of the 2-day preparation group. This is probably caused by the duration of diarrhoea and the total amount of iodine contrast medium, which was 150 ml less in the 1-day preparation group. Also compliance was better in the second group; all patients took the 4 aliquots of contrast medium in group 2 compared with only 44 of the 50 patients who took all 7 aliquots of contrast medium in group 1. However, most patients (67\%) in both groups still found the cathartic colonoscopy preparation most burdensome, which was also found in previous studies that used iodine or barium tagging preparations.\textsuperscript{3,10,13}

In this study, a low-fibre diet was used with clear descriptions for the patients. It is assumed that this diet reduces bowel contents and results in better homogeneity of the tagged faeces. Fibres are water-holding and therefore will increase stool weight; however, colonic transit time is reduced because of stimulation of peristalsis.\textsuperscript{23,24} Most studies that use faecal tagging prescribe a low residue or low-fibre diet, but also studies exist that did not use a special diet.\textsuperscript{4,7}

There are some potential limitations in this study. A first limitation is that only supine positions are assessed for image quality and homogeneity measurements. The residual faeces will change position, but will not change in consistency and tagging quality; therefore, the results on these aspects will not be different in supine and prone positions.

Another disadvantage is that we used an ionic contrast medium that might cause anaphylactic reactions. However, serious adverse events with intravenous ionic contrast medium seldom appear, and no serious adverse reactions with oral iodine contrast medium are described.\textsuperscript{25} No adverse events occurred in this study. Barium can be used as an alternative, but it tags mainly the solid residual faeces and not fluid.\textsuperscript{26} Therefore, tagging is often inhomogeneous.\textsuperscript{10}
A third limitation is that no randomisation was used for the different bowel preparation schemes. This was due to the fact that patients were part of a larger FOBT screening trial in which we have changed the bowel preparation scheme after half of the patients were included.\textsuperscript{15} Patients were equally distributed with regard to sex, and also the indication (positive screening FOBT) was similar, but the age was significantly different in the two groups. Age could be of influence on consistency of stools, because in the elderly an increased prevalence of constipation is seen, especially after the age of 65 years.\textsuperscript{27} However, in this study we asked patients about their normal consistency of stools, and this was equal for both preparation groups. The consecutive inclusion of patients could also be detrimental because observers could have obtained increased reading skills in CT colonography. Indeed, we found an increased sensitivity per observer for lesions $\geq$6 mm in group 2. However, this increased sensitivity was in the patient group that received the smallest amount of tagging agent. Furthermore, a steep learning curve over the course of 100 examinations is not to be expected in readers with a previous experience of more than 250 CT colonographies.

**Conclusion**

A 1-day bowel scheme with meglumine-ioxithalamate and a low-fibre diet for CT colonography is better tolerated by patients than a 2-day bowel preparation scheme with the same tagging agent. Quality scores on tagging, consistency and amount of residual faeces and the homogeneity of the residual faeces were comparable in the two bowel preparation groups. Furthermore, the diagnostic accuracy of polyp detection remained high in the 1-day preparation group. Therefore, a 1-day preparation scheme with meglumine-ioxithalamate can be considered superior to a 2-day preparation scheme.

**Acknowledgements**

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References

Low-fibre diet in CT colonography limited bowel preparation: influence on image quality and patient acceptance

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ABSTRACT

**Purpose:** To determine if a low-fibre diet is necessary for an optimal tagging-only bowel preparation for CT colonography.

**Methods:** 50 consecutive patients received an iodine bowel preparation; 25 patients had a low-fibre diet (group 1) and 25 had no special diet (group 2). One observer determined the tagging quality per segment on a 5 point scale (1: inhomogeneous tagging, 5: excellent preparation) and the largest size of untagged faeces. Semi-automatic measurements of density and homogeneity of residual faeces were performed. Patient acceptance was assessed with questionnaires. Per polyp sensitivity for polyps ≥6mm was calculated for two experienced observers.

**Results:** Tagging quality was scored less than grade 5 in 15 segments (10%) in group 1 and in 25 segments (17%) in group 2 (p=0.098). In total one piece of untagged faeces ≥10mm was found in group 1 compared to twelve in group 2 (p<0.0001). Automatic measurement of density resulted in a mean of 594 HU in group 1 and 630 HU in group 2 (p=0.297). 22% of patients in group 1 indicated that the bowel preparation was extremely or severely burdensome compared to 8% of patients in group 2 (p=0.19). 32 polyps ≥6mm were found in group 1 and 30 in group 2. Sensitivities for polyps ≥6mm for observer 1 were respectively 84% and 77% (p=0.443) and 97% and 83% for observer 2 (p=0.099).

**Conclusion:** Use of a low-fibre diet in bowel preparation for CT colonography results in significantly less untagged faeces and shows a trend towards a better residue homogeneity.
INTRODUCTION

Computed tomography colonography (CT colonography) is an alternative method for colonoscopy to detect polyps and carcinomas in the colon and rectum. In recent studies high outcomes on sensitivity and specificity are reported for polyp detection.1-4 The advantage of CT colonography is that patients generally experience less burden from CT colonography than from colonoscopy.5,6 Most patients find the bowel preparation the most burdensome part of the examination and therefore it is important to minimize this aspect.6 A cathartic preparation with polyethylene glycol or sodium phosphate results in diarrhoea and a considerable patient burden, but a limited bowel preparation with an oral tagging agent only and no laxatives has proven to lead to a decreased patient burden of CT colonography with still sufficient image quality.7-11

In most studies with a tagging-only bowel preparation for CT colonography, a low-fibre diet or a clear liquid diet is prescribed.12-14 Dietary fibres are excreted almost intact from the colon because they are resistant to hydrolysis by endogenous enzymes of the human gastrointestinal tract and to bacterial breakdown.15-18 The assumption is that a low-fibre diet reduces residual bowel contents and that it results in a better homogeneity of the tagged faeces. Furthermore, left seeds and grains in a diet containing fibres may mimic polyps.

In a few previous studies however, good image quality was obtained by using CT colonography bowel preparation without any diet.8,9,11 The issue of bowel preparation has been addressed in studies that evaluated the use of a low-fibre or low-residue diet for barium enema.19-23 Some of these studies found no benefit from the use of a diet with respect to amount of faecal residue or diagnostic quality,19-21 but others did find that the amount of faecal residue diminishes and image quality improves after using a low-residue diet.22;23 To our knowledge, no study has been performed that evaluated the influence of a low-fibre diet on a CT colonography faecal tagging limited bowel preparation, with respect to sensitivity and specificity and tagging quality of the residual faeces.

This study aims to compare a limited bowel preparation with and without a low-fibre diet in order to determine if a low-fibre diet is necessary for a good image quality, high patient acceptance and accuracy for polyp detection in CT colonography.

MATERIALS AND METHODS

In total 50 consecutive patients who were Faecal Occult Blood Test (FOBT) positive in the frame work of the first or second round of a pilot study of FOBT-screening for bowel cancer were included.24,25 All were willing to undergo colonoscopy. Exclusion criteria were: patients who were unable to give informed consent, patients with terminal illness, severe psychiatric symptoms, colonoscopy or an FOBT in the previous two years, examinations with radiation exposure in the last 12 months, iodine contrast allergy, hyperthyroidism and pregnancy. The study was approved by the local Medical Ethics Committee. All patients
Chapter 3 | Low-fibre diet in CT colonography bowel preparation

gave written informed consent.

Bowel preparation
The first group of 25 consecutive patients received a bowel preparation of 4*50 ml meglumine-ioxithalamate (Telebrix Gastro 300 mg I/ml; Guerbet, Cedex, France). The day before examination 50 ml Telebrix was taken during each meal and a final 50 ml was taken 1.5h before CTC (total amount 200 ml of Telebrix). All patients had to use a low-fiber diet (see Table 1). At the day of the CT colonography examination, patients were only allowed to take a liquid food diet before the examination. This consisted of only clear and opaque liquid foods with a smooth consistency. Patients were allowed to take drinks or, when preferred, also liquid foods such as milkshakes, custard and yoghurt. The 25 patients of this first group participated in a previously published study, and the CT colonographies examined as part of this study were acquired as part of that previous study. The research presented herein (stool tagging measurements, subjective stool scores, patient acceptance and polyp detection) are wholly unique to this study. The second group of 25 patients were new inclusions and not part of the previous mentioned study. They also received 4*50 ml of meglumine-ioxithalamate like the first group, but did not need to follow a special diet on the day before CT colonography. On the day of the CT colonography examination these patients were only allowed to take a liquid food diet before examination just like the low-fiber diet group. Furthermore, all patients in this group were asked to describe precisely their food intake during their days of preparation.

Table 1 Low-fiber diet prescription for patients of preparation group 1

| Not allowed  | Fruits          | e.g. oranges, pineapple, mango, kiwi, dates, prunes, raisins, coconut |
|             | Vegetables      | e.g. green peas, tomatoes, onion, corn, French beans, mushrooms, asparagus |
|             | Grains          | e.g. wholemeal bread, muesli, unpolished rice, wholemeal pasta |
|             | Other           | Nuts, peanuts, popcorn, spiced herbs |

| Allowed      | Grains          | e.g. white bread or toast, white rice or pasta, pancakes |
|             | Fruits/vegetables | e.g. potatoes, cooked vegetables such as carrots, spinach and cauliflower, fresh fruits such as apple, pear or banana after removal of skin and pits |
|             | Sandwich fillings | e.g. cheese, meat, fish, eggs, sugar, all sweet sandwich spreads (no jam with fruit pieces) |
|             | Drinks          | e.g. lemonades, soda’s, coffee/tea, water, milk, alcohol |
|             | Other           | e.g. candy’s, ice-cream, cake, chocolate, salt, pepper |

CT colonography
CT scanning was performed on a 64 slice CT scanner (Brilliance, Philips Medical Systems, Best, the Netherlands). A low dose protocol with 40 ref mAs was used with z-axis tube modulation and automatic current selection. Slice collimation was 64 x 0.625 mm, pitch 1.2, slice thickness 0.9 mm, rotation time 0.4s and tube voltage 120 kV. Patients were scanned in first supine and then prone position. A muscle relaxant, 20 mg of
butylscopalamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) was injected before starting the insufflation of the colon. When contraindicated, 1 mg of glucagon hydrochloride (Glucagen; Novo-Nordisk, Bagsvaerd, Denmark), was injected instead. In patients with contraindications for both medicines, no muscle relaxant was administrated. A rectal balloon catheter (20 French Gauge) was inserted to insufflate approximately 3 liters of CO2 gas into the colon, using an automated insufflator with a manometer to measure the CO2 pressure and an automatic flow stop at 25 mmHg (Bracco, PROTOCO2L insufflator, New York, USA).

**CT colonography image analysis**
A primary 2D axial evaluation (window setting 1500, -250 HU) was done with 3D problem solving for the detection of polyps (View Forum, Philips Medical Systems, Best, the Netherlands). Two experienced observers (radiology research fellows; experience of 450 and 750 CT colonography examinations) reviewed all CT colonographies and identified lesions. Lesions were measured in multiplanar reformatted (MPR) images showing the maximal diameter of the lesion. Of each lesion the segment location, morphology (sessile, flat or pedunculated) and size were noted. The segmental location was recorded according the six colonic segments (coecum, ascending colon, transverse colon, descending colon, sigmoid and rectum) as defined in the article on CT colonography research reporting by Dachman et al.28 Additionally, the reading time per position was recorded for each observer.

**Colonoscopy**
In all patients the colonoscopy was performed within approximately 2 weeks after CT colonography. Bowel preparation for colonoscopy consisted of 4 liters polyethylene glycol electrolyte solution (KleanPrep; Helsinn Birex Pharmaceuticals, Dublin, Ireland) or 2 liters of another polyethylene glycol electrolyte solution (Moviprep; Norgine Limited, Mid Glamorgan, United Kingdom) and a clear liquid diet starting on the evening before colonoscopy. Experienced gastroenterologists and gastroenterology residents or nurse endoscopists with supervision, performed optical colonoscopy with a standard colonoscope (Olympus, Tokyo, Japan). Sedation (midazolam, Dormicum; Roche, Basel, Switzerland), analgetics (fentanyl, Fentanyl-Janssen; Janssen Pharmaceuticals, Beerse, Belgium) and a muscle-relaxant (butyl scopolamide bromide, Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) were standardly used. According to the technique of segmental unblinding, the findings of the CT colonography were revealed to the colonoscopist after completing the examination of one segment. Polyp size was estimated by comparison to an opened biopsy forceps. The colonoscopy was videotaped starting from the coecum. Lesion histology was classified according to the Vienna classification.29

**Image quality of CT colonography**

1. *Faecal residue*
For evaluation of the quality of the bowel preparations one experienced CT colonography reader (M.L.), who was blinded for the type of preparation, gave a score per segment (coecum, ascending, transverse, descending, sigmoid colon and rectum). Segments were
classified according to the segment description in Dachman et al. \(^{28}\) Scores were given on the supine scans only:

- The relative amount of faecal residue per segment compared to the luminal diameter was scored on a scale between 0 and 100%.
- The consistency of the faecal residues rated on a three point scale: 1. liquid, 2. partly solid/ partly liquid or 3. solid.
- The presence of adherent faeces was scored (yes/no).
- It was noted in which segments untagged solid faeces was present and per segment the size of the largest piece of untagged solid faeces was recorded (≤5mm, 6-10mm, and ≥10mm).
- The quality of tagging in the supine scans on a five point scale\(^{11}\): 1= uninterpretable images, untagged faeces, 2= poor interpretation, large amount of unopacified faeces, 3= moderate preparation, moderate amounts of unopacified faeces, 4= good preparation, small amounts of unopacified faeces, 5= excellent preparation no unopacified faeces.

At last the density (mean HU) and homogeneity (HU SD) of the faecal residue were measured on the supine scans by automatically extracting the residual faeces from the colon. Voxels containing residual faeces were identified in cross-sections at regular intervals of 10 mm perpendicular to the path by applying a threshold of 200 HU. Mean values of density and homogeneity were calculated per segment. Segments were defined by a radiology research fellow in one representative CT colonography dataset with a good distension. The distance of each segment border from the anus was compared to the total length of the colon and set as a reference distance-ratio for definition of segments in all CT colonographies. The radiology research fellow also verified all automatically measured faecal residues. For segments that contained faecal residues <200 HU (due to which automatic measurement failed), three manual ROI measurements were performed in this residual material by a research fellow (M.L.) (see fig. 1).

**Fig. 1** Example of a drawn region of interest (ROI) in faecal residue that could not be measured automatically due to a low density.
The slice numbers within a segment in which to perform these measurements were randomly generated (Excel for Windows, 2003). The mean attenuation of tagging can vary considerably between patients, and therefore we also calculated the relative standard deviation (SD / mean HU).

2. Colonic distension
The radiology research fellow (M.L.) gave a score for colonic distension per segment in the prone and supine position. A four point scale was used to score degree of distension: 1= bad distension (0-25% of estimated maximal diameter), 2= poorly distended (25-50% of maximal diameter), 3= sufficient distension (50-75% of estimated maximal diameter and no collapsed lumen at any point), 4= well distended (75%-100% of estimated maximal distension and no collapsed lumen at any point).

Patient acceptance
Six standardized questionnaires (used in previous studies)\(^6\)\(^-{13}\) were given to all patients: questionnaire (Q) 1 to fill in at home before both examinations, Q2 before the CT colonography and Q3 was sent five weeks after colonoscopy. In Q1 patients were asked about their normal defecation pattern and their education background. In Q2 questions about the amount and burden from diarrhoea were asked before CT colonography. Answers were filled in on a 5 point scale (1=no discomfort, 2=mild, 3=moderate, 4=severe or 5=extreme burdensome). In Q3 patients were asked which examination (including the bowel preparation) they found most burdensome, how burdensome they found the CT colonography examination (on the previously mentioned 5 point scale) and what examination they would prefer in the future (answered on a 7 point scale: 1=definitely CT colonography~ 7=definitely colonoscopy).

Polyp detection
The sensitivity and specificity were assessed as measures of the accuracy of polyp detection in both groups. Matching of polyps and tumours found on CT colonography was done by a research fellow (M.L.) by reviewing the colonoscopy video’s and reports. A true positive CT colonography polyp had a size within 50% margin of the corresponding colonoscopy polyp, was in the same or adjacent segment as at colonoscopy and resembled in morphology compared to the lesion seen on the videotaped colonoscopy. Furthermore the number of technical false negatives, polyps that were retrospectively not visible at CT colonography, and the number of false positives were counted per group.

Statistical analysis
Faecal tagging: Outcomes on faecal tagging quality were analyzed in different ways. The outcomes on the relative amount of residual faeces (percentage given by reviewer) were calculated using the Student-T-test. Consistency of residual faeces, the largest piece of untagged faeces, the quality of tagging and the colonic distension were compared performing an ordinal regression analysis; the first patient group (with low-fibre diet) was considered as the reference group. The presence of adherent faeces was compared with the Chi-square test. The density (mean HU), homogeneity (HU SD) and the relative
standard deviation (SD / mean HU) of the residual faeces were compared by using the Student-T-test (which assumes normally distributed data).

Patient acceptance: Characteristics of participants, including age, sex and socio-economical status were compared by means of proper statistics (e.g. Student-T-test, Chi-square test) depending on the type of data. The amount and burden of diarrhoea, the experience of burden of the preparation and the preference for preparations in both groups were compared by performing an ordinal regression analysis.

Polyp detection: The sensitivity and specificity of CT colonography for lesions larger or equal to 10 mm (including colorectal cancers, adenomas and hyperplastic polyps) and lesions larger or equal to 6 mm detected at colonoscopy were determined. Comparison between outcomes of the two patient groups was done with the Chi-square test. Reading times were compared by using the Student-T-test. Statistical analyses were performed using SPSS version 15.0.1 for Windows (SPSS). For all analysis, a p-value of <0.05 indicated a significant difference between the two preparation groups.

RESULTS

The first group (group 1; preparation with low-fibre diet) consisted of 14 men and 11 women and the second group (group 2; preparation without diet) of 15 men and 10 women (p=0.77). The mean age was 60.4 years (SD 5.4) in group 1 and 61.1 (SD 7.2) in group 2 (p=0.71). Educational level was high (university or higher vocational education) in 9 patients in both groups and moderate to low (only primary school, high school, or lower vocational education) in 16 patients in both groups (p=1.0). Regular daily stool consistency was soft in 21 patients in group 1 and 17 patients in group 2 (p=0.10).

Image quality

1. Faecal residue

The amount of faecal residue detected per segment is presented in Table 2. The largest amounts of faeces were present in the ascending and descending colon. Neither the per-segment nor the total amounts were significantly different between both groups. Consistency of the residual faeces was more often solid in patients of group 2 in the descending colon, sigmoid and rectum when compared to patients of group 1 (p=0.034; p=0.001 and p=0.020 respectively; see Table 2). Adherent faeces was present in nearly all segments, but in the rectum 10 patients of group 2 had adherent faeces versus one patient of group 1 (p=0.005). When considering the largest piece of untagged solid faeces in each segment, there were significantly more untagged faecal pieces in the segments in group 2 (p=<0.001). In group 2, in total twelve pieces of untagged faeces ≥10 mm were found compared to only one in group 1 (see Table 2 for overall results).

For the subjective scores of the quality of tagging no differences were found between the segments in both groups (p=0.098; see Table 2). But when the fibre-intake of patients in group 2 was analyzed we found that 10 patients from group 2 had not eaten
any fibres at the day before CT colonography (according to the list of fibre-rich food in Table 1). When groups were divided in patients that had eaten fibres (15 in total) and patients that had not eaten fibres (35), then a significantly lower tagging quality was found for the fibre-group (p=0.001). In figure 2, three examples are given of good and moderate bowel preparations.

The automated measurements resulted in a mean density of 594 HU for group 1 and 630 HU for group 2 (p=0.297 See Table 4). The measurements for the homogeneity resulted in a mean SD of 90 for group 1 and 77 for group 2 (p=0.005). The ratio’s (mean SD/mean HU) were 0.16 in group 1 and 0.13 in group 2 (p=0.081). But when groups were divided in patients that had eaten fibres (15) and patients that had not eaten fibres (35), then the ratio’s were 0.14 for the fibre-group and 0.15 for the non-fibre group (p=0.868) and only for the rectum a significant difference was found for the homogeneity.

2. Colonic distension

In total two segments in group 1 were graded as insufficiently or badly distended compared to six segments in group 2 (p=0.23).

Table 2 Amount and consistency of residual feces

<table>
<thead>
<tr>
<th></th>
<th>Amount fecal residue (% of lumen filled)</th>
<th>Consistency feces (fluid/ partly fluid and solid/ solid)</th>
<th>No. of segments containing adherent feces</th>
<th>Size of untagged feces (no/ &lt;6mm/ 6-9mm/ &gt;10mm)</th>
<th>Quality of fecal tagging; grade 1 (bad) to grade 5 (excellent)</th>
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<tr>
<td></td>
<td>Group 1 (SD 23)</td>
<td>25/21/0*</td>
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<td>0/1/1/0</td>
<td>0/0/1/0/20*</td>
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<td>Group 2 (SD 18)</td>
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<td>23/21/1</td>
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<td>0/0/1/0/20*</td>
</tr>
<tr>
<td>Coecum</td>
<td>25/21/0*</td>
<td>24/25/0*</td>
<td>23/21/1</td>
<td>0/1/1/0</td>
<td>0/0/1/0/20*</td>
</tr>
<tr>
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<td>0/0/1/1/5/19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 1 (SD 19)</td>
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<tr>
<td>Transverse colon</td>
<td>24/19/5/1</td>
<td>24/22/1/1</td>
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<tr>
<td></td>
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<td>Descending colon</td>
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<td>0/0/1/1/5/19</td>
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<td>24/22/1/1</td>
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<td>Sigmoid colon</td>
<td>24/19/5/1</td>
<td>24/22/1/1</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>Group 2 (SD 8)</td>
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<tr>
<td>Rectum</td>
<td>24/19/5/1</td>
<td>24/22/1/1</td>
<td>0/0/1/1/1</td>
<td>0/0/1/1/5/19</td>
<td></td>
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<tr>
<td></td>
<td>Group 1 (SD 10)</td>
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<td>24/22/1/1</td>
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<tr>
<td></td>
<td>Group 2 (SD 9)</td>
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<td>0/0/1/1/5/19</td>
<td></td>
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<tr>
<td>All colonic segments</td>
<td>24/19/5/1</td>
<td>24/22/1/1</td>
<td>0/0/1/1/1</td>
<td>0/0/1/1/5/19</td>
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</tbody>
</table>

*in some segments no feces was present; †p<0.05 when compared to group 1

47
Table 3  Tagging density and homogeneity measurements

<table>
<thead>
<tr>
<th></th>
<th>Density (HU)</th>
<th>p-value</th>
<th>Homogeneity (SD)</th>
<th>p-value</th>
<th>Ratio (SD/HU)</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
<td>Group 2</td>
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<tr>
<td>Coecum</td>
<td>584</td>
<td>608</td>
<td>0.516</td>
<td>85</td>
<td>81</td>
<td>0.535</td>
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<td>Ascending</td>
<td>585</td>
<td>616</td>
<td>0.409</td>
<td>88</td>
<td>76</td>
<td>0.047</td>
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<tr>
<td>Transverse</td>
<td>616</td>
<td>653</td>
<td>0.340</td>
<td>80</td>
<td>74</td>
<td>0.394</td>
</tr>
<tr>
<td>Descending</td>
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<td>665</td>
<td>0.712</td>
<td>89</td>
<td>77</td>
<td>0.020</td>
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<tr>
<td>Sigmoid</td>
<td>587</td>
<td>626</td>
<td>0.298</td>
<td>92</td>
<td>74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rectum</td>
<td>534</td>
<td>619</td>
<td>0.063</td>
<td>104</td>
<td>77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average*</td>
<td>594</td>
<td>630</td>
<td>0.297</td>
<td>90</td>
<td>77</td>
<td>0.005</td>
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</tbody>
</table>

*Average of each column

**Patient acceptance**

Almost all patients in both groups (24 in group 1 and 25 in group 2) experienced diarrhoea during the bowel preparation. Ten patients (42%) in group 1 experienced this as extremely to severely burdensome compared to 13 patients (52%) in group 2 (p=0.70). In the questionnaire six weeks after colonoscopy, five patients in group 1 (22%) indicated that the bowel preparation of CT colonography was extremely or severely burdensome compared to two patients (8%) in group 2 (p=0.19). When CT colonography and
colonoscopy including their respective preparation were compared, 71% of patients in group 1 found the colonoscopy most burdensome compared to 92% in group 2 (p=0.12). 65% of patients in group 1 would definitely or probably choose CT colonography for a future examination versus 64% in group 2 (p=0.75).

**Polyp detection**
In group 1, 14 polyps ≥10 mm were found at colonoscopy in 13 patients and 18 polyps of 6-9 mm in 12 patients. In group 2, 15 polyps of ≥10 mm were found in 10 patients and 15 polyps 6-9 mm in 9 patients. In Table 3 the per polyp sensitivity is presented. Sensitivities for both observers were not significantly different in both groups. The number of technical false negatives ≥6 mm was zero in group 1 and three in group 2. The number of false positives for observer 1 was five in group 1 and six in group 2. For observer 2 this was three and six respectively.

Observer 1 had a mean reading time of 15 minutes 16 seconds (SD 3 minutes 26 seconds) in group 1 and 16 minutes 41 seconds (SD 5 minutes 21 seconds) in group 2 (p=0.27). Reading times of observer 2 were 11 minutes and 32 seconds (SD 4 minutes and 7 seconds) in group 1 and 14 minutes and 47 seconds (SD 4 minutes) in group 2 (p=0.007).

<table>
<thead>
<tr>
<th>Table 4 Per polyp sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Polyps ≥6mm</td>
</tr>
<tr>
<td>Observer 1</td>
</tr>
<tr>
<td>Observer 2</td>
</tr>
<tr>
<td>Polyps ≥10mm</td>
</tr>
<tr>
<td>Observer 1</td>
</tr>
<tr>
<td>Observer 2</td>
</tr>
</tbody>
</table>

**DISCUSSION**
Our study found that an iodine tagging-only bowel preparation with a low-fibre diet for CT colonography results in less pieces of untagged faeces and less solid stool than an iodine preparation without specific diet prescription. A prescribed diet had no significant influence on the measured tagging density. When however the patients’ food intakes were analyzed we found that patients that had eaten a low-fibre diet (all patients from group 1 and 10 patients from group 2) were compared with patients that had eaten a diet containing fibres, we found a significantly better subjective tagging quality in patients that had eaten a low-fibre diet. There were no significant differences when comparing the polyp detection and the patient burden in both groups.

For the readability of CT colonography images it is important that a good homogeneity with a sufficiently high tagging density is obtained, certainly when a tagging
only preparation is used without laxatives that can remove residual faeces. When density decreases, detection of polyps becomes more difficult and more false positives are generated, thus as result the diagnostic accuracy can decrease. In phantom studies the optimum tagging density was probably around 700 HU or more. Currently we found tagging densities around 600 HU in each group which approaches this optimum tagging density. The homogeneity (mean SD) was significantly better for the group without diet, but when ratio’s (mean SD/ mean HU) were compared this did not result in a significant difference. This indicates that the density was high enough to compensate for differences in homogeneity (HU SD). For example, a measured homogeneity of 200 HU SD will have less influence in a preparation with a mean density of 700 HU compared to a preparation with a mean density of 300 HU. Furthermore the absolute differences in homogeneity were small (maximum difference was 27 HU in the rectum), and although significantly different, these relatively small differences probably do not greatly influence the CT colonography reading. This can be observed from the subjective scores of tagging quality that were even slightly more favourable for group 1 (with the low-fibre diet prescription). In a study of Zalis et al. it was also found that the measured homogeneity did not reflect the differences in qualitative assessment ratings of the readers. 

When the subjective reader scores were assessed, we found that in group 2 (without diet prescription) more pieces of untagged faeces and more adherent and solid stool was found compared to group 1. This could also result in a deterioration of polyp detection. We found that the sensitivity for detection of polyps ≥6mm was lower for both observers in the group 2, albeit not significantly. This may be due to the fact that patient groups were too small to draw conclusions on this.

Several previous studies in CT colonography have used a limited, tagging-only bowel preparation with barium or iodine tagging. In some studies a low-fibre diet or a low-residue diet kit was prescribed for CT colonography bowel preparation, while others did not use a specific diet description. In addition, there are a few studies on low-fibre or low-residue diets in double contrast barium enema bowel preparation. In half of these studies there was no effect found from the ingestion of a specific diet on the colon cleanness. However, in the study of Lee et al. there was a significant difference in the amount of retained faecal material and Virrki et al. found that a low residue diet with hydration resulted in significantly less residual faecal material and a significantly denser mucosal coating. For barium enema preparation the amount of residual faecal material is important because a clean colon is preferable. For CT colonography the amount may not influence the image readability. Instead the density and the homogeneity of the residual faeces are the most important aspects. This was not assessed in the barium enema studies.

Regarding the patient acceptance, we found no difference in degree of burden in patients that had to follow a restricted diet and in patients that did not. Therefore we think that a diet has a very minimal influence on patient burden and therefore it should be used to retain a good image quality.

Reading times might be an indicator for image quality. In this study the reading time of the second experienced observer increased significantly for group 2 and for observer 1 a trend towards an increase in reading time was seen. This could indicate that...
the images of the second group were more difficult to interpret because of a reduced quality of the images. The number of polyps ≥6mm in both groups was nearly equal thus this probably did not cause a difference in reading times.

There are a few potential limitations of this study. First and most important is probably that patient groups were relatively small; only 25 patients were included in each group. The sample size was calculated to be sufficiently large to meet the primary aim of comparing in the homogeneity and amount of untagged faeces, which were the main parameters of this study. Indeed, significant differences were found in these parameters. No differences were found in polyp detection, which might have been found when larger patient groups would have been compared. A second limitation is that patients were consecutively included and no randomization had taken place. This was due to the fact that the bowel preparation scheme was changed from low-fibre diet to a preparation without diet prescription during the study period. Both groups, however, consisted of a similar number of males and females and also regular stool consistency did not differ between groups. Third, the measurements of density and homogeneity were not completely automated because they had to be manually adjusted for regions with a tagging density beneath 200 HU. This is due to the fact that at a density beneath 200 HU also normal tissues, such as muscles and kidneys, are measured resulting in wrong outcomes for density and homogeneity of faecal material. Fourth, the subjective scores were performed by only one observer. Because the type of bowel preparation was blinded to the observer and the main aim was to compare outcomes between groups we think this is not a very important limitation. A last limitation is that we only tested if a diet influences an iodine tagging bowel preparation. A high-osmolar ionic preparation often results in diarrhoea while a barium preparation does not and tags mainly the solid faeces. From this study we cannot conclude if a specific diet is necessary with a barium tagging bowel preparation.

To conclude we have found in this study that a low-fibre diet used in a CT colonography iodine tagging bowel preparation results an improved subjective tagging quality of the residual faeces, while the measured tagging density remained equal. Adding a specific diet does not increase patient burden from the prescribed bowel preparation. No significant effects on polyp detection were found.

Acknowledgements
We thank all the staff of the Departments of Radiology and Gastroenterology of the Academic Medical Centre in Amsterdam who contributed to this study.
References

Reducing the oral contrast dose in CT colonography: Evaluation of faecal tagging quality and patient acceptance

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E. Dekker
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Submitted
ABSTRACT

Purpose: To evaluate what amount of iodine tagging oral contrast medium is necessary for an optimal computed tomography colonography limited bowel preparation without using laxatives.

Materials and Methods: Faecal occult blood test positive patients were randomly selected for one of three iodine bowel preparations: 1) 3*50 mL meglumine ioxithalamate (45 g I), 2) 4*25 mL meglumine ioxithalamate (30 g I) or 3) 3*25 mL (22.5 g I) meglumine ioxithalamate. Two experienced readers assessed the tagging quality per colonic segment on a 5-point scale and the presence of adherent stool. Also semi-automatic density and homogeneity measurements were performed. Patient acceptance was assessed with questionnaires.

Results: Per preparation group 15 patients were included. The quality of tagging was insufficient (score 1-2) in 0% of segments in group 1, 4% in group 2 and 5% in group 3 (p<0.001 compared to group 1). In group 1 in 11% of the segments adherent stool was present compared to 49% in group 2 and 41% in group 3 (p<0.001). Tagging density was 610, 514 and 533 HU in group 1, 2 and 3 respectively (p=0.065). Homogeneity was 85, 102 and 90 SD HU in group 1, 2 and 3 respectively (p=0.011). In group 1 two patients experienced no burden after contrast agent ingestion compared to one patient in group 2 and nine patients in group 3 (p=0.017).

Conclusion: A dose of 3*50 mL meglumine ioxithalamate is advisable for an optimal tagging quality despite beneficial effects on the patient acceptance in patients receiving a lower dose.
INTRODUCTION

High quality bowel preparation is essential in order to accurately detect colorectal polyps and carcinomas using computed tomography colonography (CT colonography). Several different CT colonography bowel preparation techniques have been evaluated in previous studies, including cathartic bowel preparation such as polyethylene glycol or sodium phosphate.\(^1\) However, oral contrast medium alone can also be used to ‘tag’ the residual faeces.\(^3\) Cathartic preparations often lead to excessive diarrhoea with concomitant patient discomfort, but preparation with an oral tagging agent has been proven to produce sufficient faecal tagging whilst minimising the unwanted side effect of diarrhoea.\(^4;6-10\) It is important to improve patient experience with the bowel preparation because this can increase compliance with CT colonography examinations, especially in the context of screening.\(^11\)

Tagging-only bowel preparations can consist of barium or iodine contrast tagging or a combination of both. The advantage of barium tagging is that it does not induce the diarrhoea which can result from the oral intake of high-osmolarity iodinated contrast media.\(^5;12\) However, barium tags mainly the solid stool and not the liquid components, which can lead to inhomogeneous tagging.\(^13\) On the contrary, a high-osmolarity iodine contrast medium softens the stool, causing a more homogeneous mixing with the iodine and thereby improving ease of CT colonography reading.\(^7\)

In a study of Iannacone et al. a two-day preparation with iodine tagging only (in total 74g iodine) was required for optimal polyp detection.\(^14\) Other studies have shown that a one-day preparation with iodine tagging is sufficient for optimal tagging and polyp detection.\(^15;16\) In the study by Campanella et al. iodine was administered only on the morning before the CT colonography (total iodine load 18.5 g) following a two-day preparation with a mild laxative. In order to minimize diarrhoea and keep the instructions to the patient as simple as possible, however, a minimal iodine dose without laxatives would be preferable. No previous study has used a minimal iodine dose lower than 30 mg without any laxatives.

The aim of this study was to assess the feasibility of a laxative free and low iodine load tagging bowel regimen for CT colonography. Patients received different bowel preparations and the tagging quality of the residual stool, patient acceptance and ease of interpretation of the CT colonography examination were then evaluated.

MATERIALS AND METHODS

Patients were offered colonoscopy at the gastroenterology department as the result of a positive faecal occult blood test (FOBT) in the second round of a large bowel cancer pilot screening study that invited 10,000 average risk persons between 50 and 75 years to participate.\(^17\) At the outpatient clinic all patients with a positive FOBT were informed about the CT colonography study and asked to participate. Exclusion criteria were: patients who were unable to give informed consent, patients with terminal illness, patients with
colorectal carcinoma symptoms within the last three months, colonoscopy in the previous two years, examinations with radiation exposure in the last 12 months, iodine contrast allergy, hyperthyroidism and pregnancy. After written informed consent for CT colonography had been obtained, patients were allocated to one of three preparation groups (see Table 1 for further details).

Table 1 Three different preparation regimes for CT colonography

<table>
<thead>
<tr>
<th>Preparations</th>
<th>Day -1</th>
<th>Day CTC</th>
<th>Total iodine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation 1</td>
<td>-2* 50 mL Telebrix: at lunch and dinner</td>
<td>-1*50 mL Telebrix 1.5h before CTC</td>
<td>150 ml 45 g I</td>
</tr>
<tr>
<td>Preparation 2</td>
<td>-3*25 mL Telebrix: at breakfast, lunch and dinner</td>
<td>-1*25 mL Telebrix 1.5h before CTC</td>
<td>100 ml 30 g I</td>
</tr>
<tr>
<td>Preparation 3</td>
<td>-2* 25 mL Telebrix at lunch and dinner</td>
<td>-1*25 ml Telebrix 1.5h before CTC</td>
<td>75 ml 22.5 g I</td>
</tr>
</tbody>
</table>

CTC: CT colonography

Allocation to a preparation group occurred sequentially: the first included patient enrolled in the study received preparation 1, second patient preparation 2, third preparation 3, fourth preparation 1 etc. The preparation schemes all consisted of the ingestion of meglumine-ioxithalamate (Telebrix Gastro 300 mg I/ml; Guerbet, Cedex, France) and a low-fibre diet on the day before CT colonography. On the day of CT colonography examination patients were only allowed to take drinks and liquid foods before the examination and they had to take their last bottle of Telebrix. Approval of the Medical Ethics Committee of our institution was obtained.

CT colonography examination

Before the examination a smooth muscle relaxant was injected intravenously (20 mg butylscopolamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany); or when contraindicated 1 mg Glucagon (Glucagen; Novo-Nordisk, Bagsvaerd, Denmark)). Approximately 3 litres of CO2 gas were insufflated via a rectal catheter into the colon, using an automated insufflator (Bracco, PROTOCO2L insufflator, New York, USA). All the examinations were performed using a 64-slice CT scanner (Brilliance, Philips Medical Systems, Best, the Netherlands). A low dose protocol with 25 ref mAs was used with z-axis tube modulation and automatic current selection. Slice collimation was 64*0.625 mm, pitch 1.2, slice thickness 0.9 mm, rotation time 0.4s and tube voltage 120 kV. Patients were scanned in supine and prone position.

Evaluation of tagging quality

Tagging quality was assessed on the supine scans alone by two experienced CT colonography readers (ML, experience of 500 CT colonography examinations with
colonoscopy verification; FZ, experience of 125 CT colonography examinations with colonoscopy verification) using several subjective scores. The subjective scores were used to determine the amount and consistency of the faecal residue, the tagging quality (5-point scale), the largest piece of untagged faecal material, the presence of adherent stool and the influence of the tagging quality on polyp detection (see Table 2). The evaluations were done per colonic segment: coecum, ascending, transverse, descending colon, sigmoid and rectum. Furthermore, the more experienced reader rated the distension per segment of the supine scans on a four point scale: 1) poor distension, 0-25% of maximal diameter distended; 2) moderate distension, 25-50% of maximal diameter; 3) sufficient distension, 50-75% of maximal diameter; 4) good distension, 75-100% of maximal diameter.

Table 2 Subjective scores of tagging quality

| Total amount of faecal residue per segment | 1. 0-25% of the lumen filled with faecal residue |
| Consistency of faecal residue | 2. >25-50% of the lumen filled with faecal residue |
| Quality of tagging | 3. >50-75% of the lumen filled with faecal residue |
| | 4. >75-100% of the lumen filled with faecal residue |
| 1. liquid | 2. partly solid/ partly liquid |
| 3. solid | 4. insufficient preparation; all residual faeces inhomogeneously tagged |
| 2. poor preparation; 1-<25% homogeneously tagged |
| 3. moderate preparation; 25-<50% homogeneously tagged |
| 4. sufficient preparation; 50 to <75% homogeneously tagged |
| 5. good preparation; 75-100% homogeneously tagged |
| Largest piece of untagged stool | 1. no untagged stool |
| | 2. <6 mm untagged stool piece |
| | 3. 6-<10 mm untagged stool piece |
| | 4. ≥10 mm untagged stool piece |
| Presence of adherent stool | 1. Yes, adherent (‘sticky’) stool present |
| | 2. No |
| Influence of quality of tagging on polyp detection | 1. diagnostic images for polyps of all sizes |
| | 2. diagnostic images only for polyps ≥6 mm |
| | 3. diagnostic images only for polyps ≥10 mm |
| | 4. non-diagnostic images, polyps ≥10 mm can be missed |

In addition, automatic density measurements were performed with specialized software (View Forum, Philips, Best, Netherlands). All voxels having a density >200 HU were considered to be faeces. Measurements were performed automatically in every 10mm perpendicular to the colon path and the mean values for density (HU) and homogeneity (SD of HU) were calculated per colonic segment. The colonic segments had been defined by a radiology research fellow (ML), by defining the borders of each segment in one sample colon. Ratios of the length per segment related to the total colonic length were calculated and applied to all CT colonographies in this study. All automatic measurements were checked by the research fellow. When measurements in a segment were inadequate
due to faecal remnants with a density below 200 HU, the radiology research fellow performed manual measurements of the faecal residue with three ROI’s placed in the segment. The slices in which the ROIs were placed were randomly selected by using a computer program (Windows Excel 2003, Microsoft). Only ROI’s with a surface larger than 30 mm² were measured. As the density and homogeneity can vary between patients and the combination of both measurements is important, we also calculated the relative homogeneity (=SD HU/mean HU).

**Polyp detection**

Two experienced CT colonography readers (ML, FZ; see previous paragraph) performed polyp detection at CT colonography before the colonoscopy. Images were read in primary 2D read (window setting 1500, -250 HU) with 3D problem solving on specialized software (View Forum, Philips, Best, Netherlands). A secondary 3D fly-through was also performed after the 2D read for additional evaluation. The lesions detected were classified as pedunculated, sessile or flat and were measured using electronic callipers in the largest diameter in multiplanar reformatted (MPR) images. No consensus read was performed and all lesions of ≥6 mm found by the CT colonography readers were unblinded during the colonoscopy. Reading times for the primary 2D and additional 3D read were registered.

**Colonoscopy**

Colonoscopies were performed by experienced gastroenterologists or gastroenterology-fellows under supervision. All patients received 2 L of polyethylene glycol electrolyte solution (Moviprep; Norgine Limited, Mid Glamorgan, United Kingdom) with a low-fibre diet for bowel preparation. Analgesics (fentanyl, Fentanyl-Janssen; Janssen Pharmaceuticals, Beerse, Belgium) and sedation (midazolam, Dormicu; Roche, Basel, Switzerland) were used as standard in all patients. The polyps detected at CT colonography were revealed per colonic segment to the colonoscopists according to the technique of segmental unblinding. Polyp size was estimated using opened biopsy forceps and the colonoscopy was videotaped from the caecum to enable matching of the colonoscopy and CT colonography polyps by a radiology research fellow (ML). Lesion histology was classified according to the Vienna classification.¹⁸

**Questionnaires**

All patients received four questionnaires with questions relating to patient experience of the preparation and the examination itself. In the first questionnaire, which was completed at home before the examinations, patients were asked about their normal daily stool consistency and frequency of defecation. The second questionnaire was completed directly after the CT colonography, and included questions about the experience of iodine contrast agent ingestion and the effect of the bowel preparation, as measured on a 5-point scale (1=not unpleasant, 2=minimally unpleasant, 3=moderately unpleasant, 4=severely unpleasant to 5=extremely unpleasant). Patients were also asked to indicate their preference for the CT colonography or the colonoscopy bowel preparation (as indicated on a 7 point scale: 1=definitely CTC – 7=definitely colonoscopy). The final questionnaire was sent to the patient’s home two weeks after the last examination. Patients were asked
which aspects of the examination were most difficult to tolerate and also whether activities of daily living were limited prior to the examination.

**Statistical analysis**

Participant characteristics, including age, sex, normal stool consistency and prior experience with colonoscopy were compared by means of proper statistics (e.g. Student-T-test, Chi-square test) depending on the type of data (e.g. continuous data, binomial data respectively).

Tagging quality outcomes were analysed in different ways. The subjective scores for the amount of residual faeces, consistency of residual faeces, colonic distension, presence of adherent stool, quality of tagging and influence on polyp detection by both reviewers were added and were compared performing the Chi-square trend test. The interobserver variability for the tagging quality was determined by giving percentages of total agreement in both observers. The calculation of kappa statistics was hampered by the low prevalence of certain scores resulting in unequal distributions in the crosstabs. The density and homogeneity of the residual stool and the SD/HU ratios were compared by using an ANOVA-test (normal distribution) and for the pairwise comparisons the Student T test was used.

The number of true positive lesions at CT colonography for lesions larger than or equal to 6 mm was determined. Lesions included adenomatous, hyperplastic and inflammatory polyps and colorectal carcinomas. Comparison of the CT colonography and colonoscopy findings was performed using segmental unblinding during colonoscopy by a research fellow (ML; previous experience of matching 325 cases). A true positive CT colonography polyp had a size within 50% margin of the corresponding colonoscopy polyp, was located in the same segment as at colonoscopy, or in an adjacent segment as at colonoscopy and resembled in morphology compared to the lesion seen on the videotaped colonoscopy in morphology. Furthermore the number of technical false negatives (lesions that were retrospectively not visible at CT colonography), perceptive false negatives (lesions that were retrospectively visible at CT colonography) and the number of false positives were retrospectively determined by this research fellow. Due to the relatively low patient numbers per group and the relatively low number of findings, no statistical analysis was performed. Reading times were compared using the Student-T-test.

From the questionnaires, patient experience of the preparation, especially regarding diarrhoea, and patient preference for a preparation regime were compared by using a Chi-square trend test.

Statistical analyses were performed using SPSS version 15.0.1 for Windows (SPSS) and Excel Windows version 2003. For analysis, a p-value of <0.05 was considered as statistical significant.
RESULTS

In total there were 80 eligible FOBT positive patients; one patient was excluded because of Graves disease and another 24 patients did not want to take part in this study, mainly because of the anticipated burden of the additional CT colonography examination. Finally 45 patients were included, 15 patients in each of the three preparation groups (see flowchart in fig. 1). In group 1, the number of males/females was 7/8, in group 2 7/8 and in group 3 11/4 (p>0.05 for all comparisons among the three groups). Mean ages in group 1, 2 and 3 were 62 years (SD 6.8), 62 years (SD 5.9) and 62 years (SD 7.4) respectively (p>0.05). Stool consistency prior to this study was hard in two patients in each group and soft in seven patients in each group. The other patients had a variable stool consistency (p>0.05). In group 1 four patients had had a previous colonoscopy. In group 2 this were two and in group 3 one patient. During the CT colonography examination Buscopan was used in 39 patients, Glucagon in four patients and in two patients no smooth muscle relaxant was used. The distension was rated insufficient (score 1 or 2) in one segment in group 1, four segments in group 2 and three segments in group 3. No complications occurred during the bowel preparation or the CT colonography examination.

Fig. 1 Flow-chart of the study

Quality of tagging
The total amount of faecal residue was highest in group 1; 23% of all segments were filled with >25% of faecal residue in group 1 versus 17% in group 2 and 11% in group 3 (for group 1 vs. 3: p=0.001). All subjective evaluation scores of the tagging quality with corresponding p-values are presented in Table 3. The consistency of the faeces was mainly
fluid in all segments, but in group 2 and 3 the faeces had a solid consistency in a significantly larger number of segments than in group 1. The quality of tagging was insufficient to moderate (score 1-3) in 1% of segments in group 1, in 14% of segments in group 2 and in 8% in group 3 (comparisons between groups yielded p-values <0.05; see Table 3 for exact values). When comparisons were made per colonic segment, all segments in group 1, except the sigmoid colon, had significantly higher scores than in group 2. No significant differences per colonic segment were found for group 1 compared to group 3. In fig. 2 examples of different quality scores are presented.

Table 3 Tagging quality scored by readers for all segments

<table>
<thead>
<tr>
<th></th>
<th>Preparation 1</th>
<th>Preparation 2</th>
<th>Preparation 3</th>
<th>p-values</th>
<th>Agreement observers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total amount of faecal residue per segment</strong></td>
<td>0-&lt;25%</td>
<td>77%</td>
<td>83%</td>
<td>89%</td>
<td>1 vs 2: 0.099</td>
</tr>
<tr>
<td></td>
<td>25-&lt;50%</td>
<td>18%</td>
<td>17%</td>
<td>10%</td>
<td>1 vs 3: <strong>0.001</strong></td>
</tr>
<tr>
<td></td>
<td>50-&lt;75%</td>
<td>5%</td>
<td>0%</td>
<td>1%</td>
<td>2 vs 3: 0.105</td>
</tr>
<tr>
<td></td>
<td>75-100%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Consistency of faecal residues</strong></td>
<td>Liquid</td>
<td>87%</td>
<td>53%</td>
<td>55%</td>
<td>1 vs 2: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>Liquid/solid</td>
<td>11%</td>
<td>27%</td>
<td>28%</td>
<td>1 vs 3: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>solid</td>
<td>2%</td>
<td>20%</td>
<td>17%</td>
<td>2 vs 3: 0.597</td>
</tr>
<tr>
<td><strong>Quality of tagging</strong></td>
<td>1 (insufficient)</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>1 vs 2: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0%</td>
<td>2%</td>
<td>4%</td>
<td>1 vs 3: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1%</td>
<td>10%</td>
<td>3%</td>
<td>2 vs 3: <strong>0.002</strong></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>9%</td>
<td>26%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (good)</td>
<td>90%</td>
<td>61%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td><strong>Largest piece of untagged stool</strong></td>
<td>No untagged</td>
<td>83%</td>
<td>62%</td>
<td>74%</td>
<td>1 vs 2: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>&lt;6mm</td>
<td>13%</td>
<td>22%</td>
<td>21%</td>
<td>1 vs 3: <strong>0.036</strong></td>
</tr>
<tr>
<td></td>
<td>6-9mm</td>
<td>4%</td>
<td>10%</td>
<td>4%</td>
<td>2 vs 3: <strong>0.004</strong></td>
</tr>
<tr>
<td></td>
<td>≥10mm</td>
<td>0%</td>
<td>6%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>Presence of adherent stool</strong></td>
<td>Yes</td>
<td>11%</td>
<td>49%</td>
<td>41%</td>
<td>1 vs 2: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>89%</td>
<td>51%</td>
<td>59%</td>
<td>1 vs 3: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 vs 3: 0.091</td>
</tr>
<tr>
<td><strong>Influence of quality of tagging on polyp detection</strong></td>
<td>1 (diagnostic)</td>
<td>89%</td>
<td>61%</td>
<td>67%</td>
<td>1 vs 2: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11%</td>
<td>29%</td>
<td>28%</td>
<td>1 vs 3: <strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0%</td>
<td>9%</td>
<td>5%</td>
<td>2 vs 3: 0.130</td>
</tr>
<tr>
<td></td>
<td>4 (not diagnostic)</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

The percentages of segments per tagging quality score are presented (results of both readers are added). Agreement between both observers is presented in the last column. P-values are given for all groups compared.

When considering the largest piece of untagged stool we found an untagged stool piece ≥6mm in 4% of the segments in group 1. For group 2 this was in 16% of all segments and for group 3 in 6% (comparisons between groups yielded p-values <0.05). In group 1 in only 11% of the segments adherent stool was present. This was significantly higher in group 2 (49% adherent stool) and group 3 (41%). Also the influence of the tagging quality on polyp detection was rated better in group 1 compared to group 2 and 3. The
interobserver variation for all qualitative imaging scores varied between 71% and 85% (see Table 3).

The average density of the tagged faeces in all colonic segments was 610 HU in preparation group 1, 514 HU in group 2 and 533 HU in group 3 (p=0.065, using the ANOVA test). In the descending colon the density was significantly higher in group 1 compared to the two other groups. The average homogeneity was 85 SD HU, 102 SD HU and 90 SD HU (p=0.011) in the three groups respectively. Ratios of the relative homogeneity (HU SD/mean HU) were 0.14, 0.21 and 0.18 (p=0.015) respectively. For the descending colon in both groups 2 and 3, the relative homogeneity ratio was higher compared to group 1. In Table 4 the values are presented per segment and significant differences between groups per segment are also indicated.
Table 4 Tagging density and homogeneity measurements

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Density (mean HU)</th>
<th>p-value</th>
<th>Homogeneity (SD HU)</th>
<th>p-value</th>
<th>Relative Homogeneity (SD HU/mean HU)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cecum</td>
<td>575</td>
<td>439</td>
<td>551</td>
<td>0.064</td>
<td>86</td>
<td>103</td>
</tr>
<tr>
<td>Ascending</td>
<td>602</td>
<td>478†</td>
<td>499</td>
<td>0.048</td>
<td>82</td>
<td>105†</td>
</tr>
<tr>
<td>Transverse</td>
<td>633</td>
<td>588</td>
<td>571</td>
<td>0.552</td>
<td>77</td>
<td>95†</td>
</tr>
<tr>
<td>Descending</td>
<td>666</td>
<td>555†</td>
<td>534†</td>
<td>0.035</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>609</td>
<td>541</td>
<td>519</td>
<td>0.262</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>Rectum</td>
<td>569</td>
<td>481</td>
<td>411</td>
<td>0.122</td>
<td>94</td>
<td>120</td>
</tr>
<tr>
<td>Total</td>
<td>610</td>
<td>514</td>
<td>533</td>
<td>0.065</td>
<td>85</td>
<td>102†</td>
</tr>
</tbody>
</table>

†indicates a significant difference when compared to values of group 1.

Polyp detection
In group 1, 17 lesions ≥6 mm were found at segmental unblinded colonoscopy in six patients. In group 2 there were 17 lesions in seven patients and, in group 3, 17 lesions in seven patients. Both observers detected 10 lesions in group 1, nine lesions in group 2 and 16 lesions in group 3 (see table 5 for all true positive and false negative lesions). In group 1, five lesions were missed due to a technical error by both observers (i.e. retrospectively not visible at the CT colonography); three sessile lesions and two flat lesions. Group 2 also contained five lesions missed due to a technical error; two sessile lesions and three flat lesions. In group 3, the one lesion missed was a pedunculated lesion. All perceptive errors made by both observers were lesions that were retrospectively hardly visible. See fig. 3 for two examples of lesions.

Observer 1 had a reading time of 10'58" (SD 2'52") in group 1, 12'10" (SD 3'00") in group 2 and 13'37" (SD 4'48") in group 3 (comparisons between groups yielded p-values >0.05). For observer 2 this was 18'17" (SD 6'35"), 19'03" (SD 7'46") and 18'37" (SD 5'22") for group 1, 2 and 3 respectively (p>0.05).

![False negative and true positive polyps](image)

Fig. 3 False negative and true positive polyps Fig. 3a: Pedunculated polyp 8 mm in the ascending colon retrospectively detected at CT colonography (perceptive false negative). Left is the supine axial image, right the prone axial image.
Fig. 3b: Carcinoma (neuro-endocrine tumour) of 12 mm in the rectum detected at CT colonography but only seen after segmental unblinding at colonoscopy. Left is the prone axial image, right is 3D image.

Table 5 Polyp detection

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Detection ≥6mm</th>
<th>Technical FN</th>
<th>Perceptive FN</th>
<th>FP ≥6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reader 1</td>
<td>Reader 2</td>
<td>Reader 1</td>
<td>Reader 2</td>
</tr>
<tr>
<td>1</td>
<td>9/17</td>
<td>10/17</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>53%</td>
<td>59%</td>
<td>(29-77)</td>
<td>(35-82)</td>
</tr>
<tr>
<td>2</td>
<td>9/17</td>
<td>8/17</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>53%</td>
<td>47%</td>
<td>(29-77)</td>
<td>(23-71)</td>
</tr>
<tr>
<td>3</td>
<td>16/17</td>
<td>16/17</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>94%</td>
<td>94%</td>
<td>(83-100)</td>
<td>(83-100)</td>
</tr>
</tbody>
</table>

Perceptive false negatives were visible in retrospect at CT colonography, whereas technique related errors were not. Between brackets 95% Confidence Intervals are given. FN: false negative; FP: false positive

Patient acceptance

Questionnaires 1 and 2 were filled in by all patients, questionnaire 3 was not filled in by two patients and questionnaire 4 was not returned by four patients. In groups 1 and 2, 14 patients experienced diarrhoea after ingestion of the contrast agent versus 10 patients in group 3 ($p=0.067$). In group 1 two patients experienced no arduous side-effects in regard to the effect of the oral contrast agent, with one patient in group 2 and nine patients in group 3 also reporting no arduous side-effects (see fig. 4; $p=0.017$). Patients in group 1 and 2 tolerated the preparation and examination significantly less well than group 3.
Chapter 4 | Reduction of the CT colonography oral contrast dose

Fig. 4 Symptoms experienced due to the effect of the contrast agent
In each group the patients were asked about their experience after contrast ingestion. No differences between groups existed (p-value: 0.017). On the y-axis the percentages of patients are presented.

Furthermore most patients in all groups preferred the CT colonography bowel preparation compared to the colonoscopy bowel preparation with no difference in preference for the three groups (fig. 5; p=0.222). When patients were asked which aspect of the whole examination was most difficult to tolerate, patients found the insufflation of CO2 for the CT colonography most arduous (67% in group 1, 62% in group 2 and 55% in group 3 (see fig. 6a). For colonoscopy the bowel preparation was the most poorly tolerated aspect, 57% in group 1, 46% in group 2 and 58% in group 3 (see fig. 6b).

Fig. 5 Preference of patients for CT colonography or colonoscopy bowel preparation
Patients were asked about their preference for bowel preparation; whether they would prefer to undergo the CT colonography or the colonoscopy bowel preparation. No differences between preparation groups existed (p-value: 0.222). On the y-axis the percentages of patients per group are presented. CTC: CT colonography; OC: optical colonoscopy
DISCUSSION

Our findings suggest that preparation 1, starting one day before the CT colonography and using three 50 ml doses of an iodine contrast agent (meglumine ioxithalamate; 45 g I), results in a good tagging quality. When only half of this dose is used, the patient tolerance increases significantly but the tagging quality declines with an increase in the amount of adherent and solid faeces. In addition, when the semi-automated measurements were considered, we found a significantly better homogeneity and relative homogeneity (SD HU/mean HU) in the first group that had taken the three 50 ml doses of the iodine contrast agent.

When a tagging only preparation is used for CT colonography, it is important that homogeneous mixing with the faeces is obtained without untagged faecal remnants. This increases ease of image interpretation, resulting in optimal polyp detection, increased specificity and improved reading efficiency. We found that the first preparation group that received in total 45 g I, had the best tagging quality rated by the observers. In the other groups with 30 g I or 22.5 g I, the tagging quality was rated significantly poorer, although, a large number of colonic segments still had an optimal score. In addition, more pieces of untagged stool were found in these groups. When considering the semi-automatic measurements, we found better homogeneity in the first preparation group compared to group 2. No large differences were observed in the density values but we combined these values with the homogeneity values (SD HU) to calculate the relative homogeneity (SD HU/mean HU). This value corrects for differences in mean density and represents the quality of tagging. For example, a low mean density of 200 HU with homogeneity of 80 SD HU, will result in a higher ratio of relative homogeneity (ratio=0.4) compared to a mean density of 600 HU with 80 SD HU (ratio=0.13). This relative homogeneity is an important tool for comparing the effects of differences in homogeneity and density. In group 2 and 3 we found significantly higher ratios compared to group 1.

No studies have previously been performed using these small amounts of iodine contrast agent and a short preparation time, without the addition of laxatives. Some earlier studies have shown, however, that excellent results can be obtained for polyp detection and tagging quality with a two- or one-day preparation. Furthermore the study of Campanella et al. showed that a dose of 18.5 g I just before CT colonography and two days of preparation with a laxative agent was also sufficient for adequate tagging. Due to the smaller amounts of contrast agent in the second and third group of patients in this study, the colon in those patients contained a lower concentration of the contrast agent which probably resulted in a lower amount of faecal residue but also led to less stool softening and thus more solid faecal remnants and more adherent (or ‘sticky’) faeces. Although overall quality in the second and third preparation groups was rated less, only a few segments were not considered to be diagnostic for finding polyps ≥6mm and only one segment was not diagnostic for finding polyps ≥10mm. Thus for a relatively large number of patients preparation with only 22.5 g of iodine contrast agent might be sufficient for an adequate polyp detection.
Fig. 6 Most unpleasant aspect of the examinations

Fig. 6a shows the aspect of the CT colonography examination that was tolerated least well by patients. On the y-axis the percentages of patients per group are presented. CTC: CT colonography

Fig. 6b shows the part of the colonoscopy examination that was tolerated least well by patients. OC: optical colonoscopy

Not many studies have calculated the effect of minimal bowel preparation on polyp detection although Iannacone et al. used a preparation of in total 200 ml iodine contrast (74 g I) and found a very high sensitivity of 86% for polyps ≥6mm.14 As patient numbers were too small in our study, we did not calculate sensitivity differences between preparation groups but the most important aspect of this study was to evaluate the tagging quality rather than evaluate polyp detection.

High amounts of iodine in tagging agents will induce diarrhoea and consequently will reduce patient tolerance of the examination.15 This can negatively influence patient compliance, especially in the context of population screening.11 In this study it was shown that a low amount of contrast agent started at lunch on the day before the CT colonography is tolerated better by patients than preparation with twice the amount of contrast agent or a preparation which starts at breakfast the day before. When patients were asked to indicate their preference for the CT colonography or the colonoscopy preparation, nearly all patients preferred the CT colonography preparation. This is consistent with results of earlier studies that showed that patients tolerate reduced
preparation better than cathartic preparation. Furthermore we used a low-fibre diet in our study because earlier research in our hospital has confirmed that a low-fibre diet can increase the tagging quality. Furthermore we used a low-fibre diet in our study because earlier research in our hospital has confirmed that a low-fibre diet can increase the tagging quality.23

Reading times increased somewhat for both readers over the three preparation groups, but differences were not significant. An increase in reading times could indicate that the images are more difficult to read because of the decreased tagging quality. This study has some weaknesses; primarily the low number of patients included in each preparation group. However, the numbers are sufficient to address the primary outcome measures, and therefore evaluation of the tagging quality in the CT colonography examinations could be performed as previous studies on bowel preparation have done. Due to the low number of polyps a meaningful comparison of performance in polyp detection between the groups was not possible. Another weakness of this study is that only an iodine preparation was tested and no barium contrast agent was assessed. As it has already been shown that iodine in small amounts results in homogeneous mixing in contrast to barium contrast agents, we focussed only on reducing the amount of iodine tagging to produce a shorter preparation time. Small amounts of iodine are absorbed in the colon so the use of oral iodine contrast agents can result in mild allergic or rarely in severe anaphylactic reactions. As our patients took their iodine contrast agent at home, we wanted to avoid the risk on anaphylactic reactions so all patients with a previous iodine contrast allergy were excluded from the study. No complications due to the bowel preparation occurred in this study.

To conclude, we found that the iodine preparation with the largest amount of iodine contrast agent (45 g I) had the best results on tagging quality with the lowest number of untagged stool particles. The results for measured density and homogeneity were also most favourable in the group with the largest amount of tagging agent. Further decrease of the iodine dose does not seem advisable, despite the beneficial effects on the patient acceptance.

Acknowledgements
We thank Catherine Grierson from the John Radcliffe Hospital, Oxford, United Kingdom, for her critical review of this manuscript.
References

Using CT colonography as a triage technique after a positive faecal occult blood test in colorectal cancer screening

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ABSTRACT

Purpose: The purpose of this study was to evaluate the effectiveness of CT colonography (CTC) as a triage technique in faecal occult blood test (FOBT)-positive screening participants.

Methods: Consecutive guaiac (G-FOBT) and immunochemical (I-FOBT) FOBT-positive patients scheduled for colonoscopy underwent CTC with iodine tagging bowel preparation. Each CTC was read independently by two experienced observers. Per patient sensitivity, specificity and positive and negative predictive values (PPV and NPV) were calculated based on double reading with different CTC cut-off lesion sizes using segmental unblinded colonoscopy as the reference standard. The acceptability of the technique to patients was evaluated with questionnaires.

Results: 302 FOBT-positive patients were included (54 GFOBT and 248 I-FOBT). 22 FOBT-positive patients (7%) had a colorectal carcinoma and 211 (70%) had a lesion ≥6 mm. Participants considered colonoscopy more burdensome than CTC (p<0.05). Using a 6 mm CTC size cut-off, per patient sensitivity for CTC was 91% (95% CI: 85% to 91%) and specificity was 69% (95% CI: 60% to 89%) for the detection of colonoscopy lesions ≥6 mm. The PPV of CTC was 87% (95% CI: 80% to 93%) and NPV 77% (95% CI 69% to 85%). Using CTC as a triage technique in 100 FOBT-positive patients would mean that colonoscopy could be prevented in 28 patients while missing ≥10 mm lesions in 2 patients.

Conclusion: CTC with limited bowel preparation has reasonable predictive values in an FOBT-positive population and a higher acceptability to patients than colonoscopy. However, due to the high prevalence of clinically relevant lesions in FOBT-positive patients, CTC is unlikely to be an efficient triage technique in a first round FOBT population screening programme.
INTRODUCTION

Colorectal carcinoma (CRC) is the second leading cause of cancer deaths in the USA and many other countries, with an approximate lifetime risk of 6%. Most CRCs are assumed to develop from benign, neoplastic adenomatous polyps. Early detection and treatment of CRCs and colorectal adenomas could reduce mortality. Therefore, several countries are currently investigating or have already started a CRC screening programme using a faecal occult blood test (FOBT).

The FOBT is a cost-effective, safe test that is acceptable to patients and that detects more cancers at a less advanced stage than would have presented symptomatically. Screening with FOBT has been demonstrated to reduce CRC-related mortality by 14–16% over 10–18 years. Similar to other screening tests, such as mammography or PAP smear, the FOBT generates a considerable number of false positives. In CRC screening trials, between 0.8% and 15% of participants tested had a positive FOBT result, while 55–65% of participants with a positive FOBT result had no CRC or adenoma. As a result these participants undergo an unnecessary colonoscopy, which is considered by many individuals as an investigation with significant burden and risk of complications.

A potential solution to reduce this number of unnecessary colonoscopies would be the introduction of a triage instrument. A prerequisite for using a triage instrument is that it has the ability to identify correctly participants without CRC or large polyps in those with an FOBT-positive result. With a very high negative predictive value (NPV), the number of FOBT-positive patients receiving a colonoscopy could be reduced while no cases with CRC or large polyps would be missed. CT colonography (CTC) has been shown to have good per patient test characteristics in detecting CRC and large polyps. Its per patient sensitivity was 96% in the detection of colorectal cancer, with a sensitivity of 93% in identifying polyps ≥10 mm and 86% for polyps ≥6 mm. The specificity for polyps ≥10 mm was 97% and for polyps ≥6 mm 86%.

Good adherence to a population screening examination can be obtained if the offered screening method is highly acceptable to patients. Previous studies have shown that CTC examinations are experienced as less burdensome than colonoscopy. The burden of the CTC may be reduced even further if the examination is performed without an extensive bowel preparation as is required for colonoscopy. So far, the accuracy and acceptability to patients of CTC have only been evaluated in a screening setting and in a high-risk population, not in FOBT screening-positive patients as a triage technique.

In this study we evaluated the use of CTC in an FOBT-positive screening population in terms of its diagnostic accuracy, positive predictive value (PPV) and NPV, and its burden, relative to colonoscopy.
METHODS

Study population
In two FOBT screening pilot studies in The Netherlands a cohort of approximately 30,000 individuals between 50 and 75 years of age received an FOBT test at home, of which half received a non-rehydrated guaiac test (G-FOBT; Haemoccult II, Beckman Coulter, Fullerton, California, USA) and the other half received a semi-quantitative immunochemical test with a cut-off level of 50 ng/ml for positive testing (I-FOBT, OC-sensor, Eiken Chemical, Tokyo, Japan). This was the first pilot study of CRC screening in The Netherlands, thus invitees had not received any other CRC screening test previously. The results of this FOBT pilot study have been reported in detail elsewhere.18,19 The FOBT-positive patients scheduled to undergo colonoscopy were invited to undergo a CTC before the colonoscopy at the Academic Medical Centre of Amsterdam, Radboud University Nijmegen Medical Centre or the Erasmus Medical Centre of Rotterdam, The Netherlands. Exclusion criteria were: terminal illness, severe psychiatric symptoms, colonoscopy or another FOBT in the previous 2 years, examinations for research purposes with radiation exposure in the last 12 months, iodine contrast allergy, hyperthyroidism and pregnancy. The CTC study had been approved by the institutional review boards of the three institutions and written informed consent was obtained from all participants.

CT colonography
Bowel preparation
A non-cathartic bowel preparation was used to reduce patient discomfort. Two different bowel regimes were used. The first 153 participants received preparation 1 and the following 149 participants received preparation 2. Preparation 1 started 2 days before CTC and consisted of ingestion of 50 ml of high-osmolar ionic monomer meglumine ioxithalamate (Telebrix Gastro 300 mg I/ml; Guerbet, Cedex, France) with each meal ending with 50 ml 1.5 h before CTC (total 350 ml). In addition, patients followed a low-fibre diet for 2 days and took only liquids on the evening and morning before CTC. Preparation 2 started 1 day before CTC with the low-fibre diet and 50 ml of Telebrix four times (total 200 ml). The amount of ingested contrast agent was reduced during the second half of this study because new publications on CTC bowel preparation showed that only 1 day of bowel preparation results in good image quality and polyp detection.15,16,20

CTC technique
Examinations were performed using a low dose protocol with 40 or 32 reference mAs on two 64-slice CT scanners (Table 1). Participants were scanned in the supine and prone position. A muscle relaxant, 20 mg of butylscopolamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) or, when contraindicated, 1 mg of glucagon hydrochloride (Glucagen; Novo-Nordisk, Bagsvaerd, Denmark), was injected immediately prior to insufflation of the colon. A flexible balloon-tipped rectal catheter (20 French gauge) was inserted to insufflate approximately 3 litres of CO2 gas into the colon, using an automated
insufflator (ProtoCO2l, Bracco Diagnostics, Princeton, New York, USA). No intravenous contrast medium was administered.

**Table 1 CT parameters**

<table>
<thead>
<tr>
<th></th>
<th>Philips Brilliance¹</th>
<th>Siemens SOMATOM Sensation²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collimation</td>
<td>64 x 0.625 mm</td>
<td>64 x 0.6 mm</td>
</tr>
<tr>
<td>Tube voltage</td>
<td>120 kV</td>
<td>120 kV</td>
</tr>
<tr>
<td>Pitch</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Reference mAs</td>
<td>40 mAs</td>
<td>32 mAs</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>0.9 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Rotation time</td>
<td>0.4 s</td>
<td>0.5 s</td>
</tr>
<tr>
<td>Dose modulation</td>
<td>z-axis</td>
<td>CARE Dose 4D³</td>
</tr>
</tbody>
</table>

¹Brilliance, Philips Medical Systems, Best, the Netherlands; ²SOMATOM Sensation, Siemens Medical Solutions, Munich, Germany; ³CARE dose 4D incorporates x-y and z-axis modulation

**CTC image analysis**

Because of the restricted bowel regime and the presence of tagged stool, a primary 2D axial evaluation (primary window setting 1500, 2250 HU) was carried out with 3D problem solving for the detection of polyps. This was performed on a workstation with specialised software (View Forum, Philips Medical Systems, The Netherlands; Aquarius Workstation, TeraRecon, San Matteo, California, USA). Two of seven experienced observers (radiologists and research fellows) who had each evaluated at least 100 CTCs verified by colonoscopy (range 100–700 CTCs) identified lesions in the FOBT-positive participants. The results of two observers were combined: CTC was considered positive if at least one observer had detected a lesion (“double reading”). This approach was used to enhance detection as CTC is used as a triage technique for which sensitivity and NPV are critical. The chance of missing a relevant lesion in an FOBT positive should be minimised. Lesions were measured at the multiplanar reformatted (MPR) setting that showed the maximal diameter of the detected lesion. For each lesion, the location, morphology, size and probability (on a 5-point scale: 0, 25, 50, 75 or 100%) were annotated. Flat polyps were defined as lesions that protrude <2.5 mm from the adjacent mucosa. Only lesions ≥6 mm that the observer reported with a ≥50% probability were considered positive and unblinded at colonoscopy.

Quality of bowel preparation was rated on a scale from 1 (uninterpretable images due to untagged faeces) to 5 (excellent preparation with almost no untagged faeces) by each observer. When the CTC was judged insufficient for evaluation by two observers, the patient was excluded for analysis. All CTCs were also interpreted on extracolonic findings by one of five gastrointestinal radiologists. Findings were classified according to the CTC Reporting and Data System (C-RADS; for classification of categories see Table 5).

**Colonoscopy**

Within approximately 2 weeks (mean 11 days; SD 10 days) after CTC, a colonoscopy was performed. Bowel preparation consisted of 4 litres of polyethylene glycol electrolyte solution (KleanPrep; Helsinn Birex Pharmaceuticals, Dublin, Ireland) or 4 litres of macrogol
solution (Colofort; Laboratoires Macors, Auxerre, France) and a clear liquid diet starting the evening before colonoscopy. Experienced gastroenterologists, gastroenterology fellows and colonoscopy nurses with supervision performed optical colonoscopy with a standard colonoscope (Olympus, Tokyo, Japan). Sedation (midazolam, Dormicum; Roche, Basel, Switzerland), analgesics (fentanyl, Fentanyl-Janssen; Janssen Pharmaceuticals, Beerse, Belgium) and a muscle relaxant (butylscopolamine bromide, Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) were commonly used in all patients (only 2% refused sedation). During the withdrawal of the colonoscope starting from the caecum, the colonoscopy was videotaped and the findings of the CTC were revealed to the colonoscopist after completing the examination of one colonic segment. This technique is called “segmental unblinding” and leads to an enhanced reference standard due to combination of CTC and colonoscopy results.

Polyp size was estimated by an opened biopsy forceps or by a linear measure probe (Olympus, Tokyo, Japan). In participants with an incomplete colonoscopy, the colonoscopy was repeated at a later time point. The histology of the lesion biopsies was classified as normal, hyperplastic, adenoma (serrated, tubular, tubulovillous or villous) or carcinoma according to the Vienna classification. Advanced adenomas were defined as adenomas ≥10 mm, with high-grade dysplasia or with a villous component >20%.

Questionnaires and participation
Six standardised questionnaires, also used in previous CTC studies, were given to all participants. Questionnaire 1 was to be completed at home before both examinations, questionnaires 2–5 before and just after CTC and colonoscopy, and questionnaire 6 was sent 5 weeks after colonoscopy. In questionnaire 1, participants were asked about their demographic characteristics. In questionnaire 2 (before the CTC) and questionnaire 4 (before colonoscopy) questions about discomfort of bowel preparation were asked on a 5-point scale (1=no burden, 2=mild, 3=moderate, 4=severe or 5=extreme burden). Questions about discomfort of the examination were also asked after the examinations on a 5-point scale (questionnaire 3 and 5, respectively). In questionnaires 5 and 6, participants were asked which examination or bowel preparation they found most burdensome and what examination they would prefer in the future (answered on a 7-point scale: 1=definitely CTC to 7=definitely colonoscopy). The participation rate was calculated for all FOBT-positive patients who attended the outpatient clinic. Reasons for not participating in the CTC study were noted for all FOBT positive subjects who attended the outpatient clinic.

Statistical analysis
The sensitivity, specificity, PPV and NPV of CTC using a CTC lesion size cut-off of ≥10 mm and ≥6 mm were calculated on a per patient basis for two size categories: lesions ≥10 mm and lesions ≥6 mm found at colonoscopy. This was done for both G-FOBT and I-FOBT at a 50 and 100 ng/ml cut-off. For our calculations the largest polyp size measured by CTC by the two observers was used when calculating the accuracy of CTC as a triage technique. A patient with a matched polyp that measured 4 mm at CTC, for example, but was measured as 6 mm at colonoscopy was considered as a false negative (using a >6 mm cut-off at CTC). Furthermore, we calculated the PPV and NPV for different CTC cut-off
values and plotted them on a graph. Per polyp sensitivity for colonoscopy was calculated using the false-negative lesions at colonoscopy (known after unblinding of the CTC results). Answers on acceptability of the technique to patients and degree of burden between CTC and colonoscopy were compared using ordinal regression analysis. Differences in quality of bowel preparation were tested with the Chi-square test.

**RESULTS**

Between June 2006 and May 2008, 356 participants were included in the CTC triage study in the participating centres. In Fig. 1 a flowchart is given, presenting the numbers of participants that gave informed consent and the numbers of excluded participants. The data of 302 participants were complete for analysis. The mean age of the participants was 61 years (SD 6). Further demographic characteristics of the participants are given in Table 2. A total of 248 participants had a positive I-FOBT and 54 participants had a positive G-FOBT. This difference was due to the differences in FOBT participation rate (I-FOBT had a 12.7% higher participation rate) and FOBT positivity rate; 2.4% of returned tests was positive for the G-FOBT and 8.5% for the I-FOBT with 50 ng/ml cut-off.18,19,26

**Table 2 Demographic Characteristics and FOBT type**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>61 (± 6)</td>
</tr>
<tr>
<td>Male/ female (ratio)</td>
<td>187 /115 (1.6:1)</td>
</tr>
<tr>
<td>Ethnicity: total number of whites</td>
<td>291 (97%)</td>
</tr>
<tr>
<td>Highest education level:</td>
<td></td>
</tr>
<tr>
<td>-primary school</td>
<td>20 (7%)</td>
</tr>
<tr>
<td>-high school</td>
<td>27 (9%)</td>
</tr>
<tr>
<td>-vocational education</td>
<td>173 (57%)</td>
</tr>
<tr>
<td>-university</td>
<td>77 (25%)</td>
</tr>
<tr>
<td>-not provided</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Netto Income per month</td>
<td></td>
</tr>
<tr>
<td>&lt;2059$/ &gt;2059$ / not provided</td>
<td>88/ 131/ 83</td>
</tr>
</tbody>
</table>

FOBT: G-FOBT 54 (18%)  I-FOBT 248 (82%)

FOBT, faecal occult blood test; G-FOBT, guaiac FOBT; I-FOBT, immunochemical FOBT

**FOBT and colonoscopy results**

CRC was found in 22 participants (7%); these were 14 participants in the I-FOBT group (PPV CRC 6%) and 8 participants in the G-FOBT group (PPV CRC 15%). A total of 208 lesions ≥10 mm were found in 142 participants (47%) and 398 lesions ≥6 mm in 211 participants (70%). The PPV for lesions ≥10 mm in the G-FOBT-positive group was 59% vs 44% in the I-FOBT-positive group. For lesions ≥6 mm the PPVs were 67 and 70% respectively. In table 3 the distribution of lesions per histology type is given (see van Rossum et al18 for more details on the FOBT results). In total, 14 lesions ≥6 mm were found at colonoscopy after unblinding of the CTC results, and thus were false negative for colonoscopy. This results in a per polyp sensitivity for colonoscopy of 96% for lesions ≥6
mm. In 11 participants (3.6%) bleeding followed after polypectomy during colonoscopy for which one participant needed a hospital stay of one night. In none of the participants did a perforation occur.

Table 3 Information on histology types of all removed lesions at colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>All FOBT positives</th>
<th>I-FOBT 50 ng/ml (248 participants)</th>
<th>G-FOBT (54 participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>22</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Adenoma</td>
<td>574</td>
<td>473</td>
<td>101</td>
</tr>
<tr>
<td>Hyperplastic polyp</td>
<td>207</td>
<td>182</td>
<td>25</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory polyp</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Lipoma</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

FOBT, faecal occult blood test; G-FOBT, guaiac FOBT; I-FOBT, immunochemical FOBT

CT colonography

There were no complications at CTC. The CTCs of 10 participants were rated of insufficient quality for evaluation. The quality of bowel preparation in both preparation groups was not rated significantly different.

Sensitivity and specificity

When using a CTC cut-off ≥10 mm, the per patient sensitivity of CTC was 82% (95% CI 74% to 89%) and the specificity was 86% (95% CI 80% to 93%) for finding lesions at colonoscopy ≥10 mm. One participant with a carcinoma was missed at CTC (sensitivity 95%) and 24 participants (17%) with an adenoma of ≥10 mm were missed. Twenty-three of these adenomas measured between 10 and 16 mm at colonoscopy and one measured 30 mm. The missed carcinoma was a flat rectal carcinoma that was even retrospectively not visible at CTC. In the 24 participants with a missed adenoma, 20 of these had a lesion that was detected at CTC but measured between 6 and 9 mm, thus being smaller than the 10 mm cut-off. In table 4 results for sensitivity and specificity are shown for I-FOBT with 50 and 100 ng/ml cut-off and for G-FOBT separately.

When using a CTC cut-off ≥6 mm the per patient sensitivity of CTC was 91% (95% CI: 85% to 97%) and the specificity was 69% (95% CI: 60% to 78%) for finding lesions at colonoscopy ≥6 mm. Again the participant with the flat rectal carcinoma was missed using this cut-off; 15 participants (8%) with an adenoma of ≥6 mm and 6 (5%) with an adenoma of ≥10 mm were missed.
Positive and negative predictive values

The PPV of CTC was 84% (95% CI: 77% to 91%) for the detection of lesions ≥10 mm found at colonoscopy, when using a cut-off ≥10 mm at CTC. The NPV using this cut-off was 84% (95% CI: 77% to 91%). Using a cut-off of ≥6 mm (for CTC and colonoscopy lesions) the PPV of CTC was 87% (95% CI: 80% to 93%). An NPV of 77% (95% CI 69% to 85%) corresponded to this cut-off. Using CTC triage with a 10 mm cut-off in 100 FOBT positive patients would mean that colonoscopy could be prevented in 54 patients, while missing ≥10 mm lesions in 9 patients. For a 6 mm cut-off this would mean prevention of colonoscopy in 28 patients, while missing ≥10 mm lesions in 2 patients. Figure 2 shows a
comparison of PPV and NPV for different CTC cut-off values. A cut-off value of 9.5 mm for CTC had a PPV of 81% and an NPV of 86% for the detection of colonoscopy lesions ≥10 mm; for 10.5 mm this was 89% and 83%. For a 5.5 mm cut-off this was 85% and 81% and for 6.5 mm this was 90% and 71%, respectively, for detection of colonoscopy lesions ≥6 mm.

Table 4 Per patient sensitivity, specificity, positive and negative predictive values for CTC per lesion size category

<table>
<thead>
<tr>
<th>Both FOBT</th>
<th>I-FOBT 50 ng/ml</th>
<th>I-FOBT 100 ng/ml</th>
<th>G-FOBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions ≥10 mm¹</td>
<td>% ratio 95% CI</td>
<td>% ratio 95% CI</td>
<td>% ratio 95% CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>82 116/142 74-89</td>
<td>80 88/110 72-88</td>
<td>81 69/85 74-89</td>
</tr>
<tr>
<td>Specificity</td>
<td>86 138/160 80-93</td>
<td>86 119/138 79-93</td>
<td>88 58/66 81-94</td>
</tr>
<tr>
<td>PPV</td>
<td>84 116/138 77-91</td>
<td>82 88/107 75-90</td>
<td>90 69/77 84-96</td>
</tr>
<tr>
<td>NPV</td>
<td>84 138/164 77-91</td>
<td>84 119/141 77-92</td>
<td>78 58/74 70-86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Both FOBT</th>
<th>I-FOBT 50 ng/ml</th>
<th>I-FOBT 100 ng/ml</th>
<th>G-FOBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions ≥6 mm²</td>
<td>% ratio 95% CI</td>
<td>% ratio 95% CI</td>
<td>% ratio 95% CI</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91 192/211 85-91</td>
<td>90 157/174 84-96</td>
<td>90 100/111 84-96</td>
</tr>
<tr>
<td>Specificity</td>
<td>69 63/91 60-89</td>
<td>72 53/74 63-80</td>
<td>68 27/40 57-77</td>
</tr>
<tr>
<td>PPV</td>
<td>87 119/220 80-93</td>
<td>88 157/178 82-95</td>
<td>88 100/113 82-95</td>
</tr>
<tr>
<td>NPV</td>
<td>77 63/82 69-85</td>
<td>76 53/70 67-84</td>
<td>71 27/38 62-80</td>
</tr>
</tbody>
</table>

95% CI: 95% Confidence Interval; PPV: Positive Predictive value, NPV: Negative Predictive Value; ¹detection of lesions ≥10mm at colonoscopy using a CTC size cut-off of ≥10mm; ²detection of lesions ≥6mm at colonoscopy using a CTC size cut-off of ≥6mm

Extracolonic findings
In total 12 E4 extracolonic findings were reported in 9 participants (2.7%). These findings had not previously been diagnosed in these patients. See table 5 for the detected extracolonic findings classified according to the C-RADS classification and the additional procedures that have been performed.
**Chapter 5 | CT colonography triage in FOBT positives**

**Fig. 2** Plot of the PPV versus the NPV when using different cut-off size values for CTC for detection of true colonoscopy lesions of ≥10mm and ≥6mm. The curve shows a plot of PPV versus 1-NPV. Results for detection of patients with lesions on colonoscopy of ≥10mm, for cut-off sizes for CTC lesions of equal or larger than 8, 9, 9.5, 10, 10.5, 11 and 12 mm are shown. And results for detection of lesions of ≥6mm are shown for CTC cut-off sizes of 4, 5, 5.5, 6, 6.5, 7, 8mm.

**Table 5** Extracolonic findings in FOBT positive participants

<table>
<thead>
<tr>
<th>C-RADS classification¹</th>
<th>Number of participants²</th>
<th>Type of E4 findings³</th>
<th>Additional procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>138 (42.6%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td>164 (50.6%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td>13 (4.0%)</td>
<td>-</td>
<td>Imaging: 3</td>
</tr>
<tr>
<td>E4</td>
<td>10 (3.1%)</td>
<td>Aortic aneurysm: 2</td>
<td>Imaging: 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iliac aneurysm: 1</td>
<td>Operation: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extracolonic mass: 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung nodules: 2</td>
<td></td>
</tr>
</tbody>
</table>

¹C-RADS classification: E1 normal exam or anatomic variant; E2 clinically unimportant finding (e.g. liver or kidney cysts); E3 likely unimportant finding (e.g. indeterminate renal lesions); E4 potentially important finding (e.g. aortic aneurysm, solid mass in liver or kidney); ²Numbers represent all participants that received a CTC scan (thus also participants that refused a colonoscopy after CTC and participants with a CTC that was of insufficient quality for polyp detection); ³All extracolonic findings found in 9 participants

**Questionnaires and participation**

When comparing the two examinations, 16% of all participants experienced the CTC examination as extremely or severely burdensome versus 41% for the colonoscopy examination (p<0.05; see fig 3A). For the bowel preparations, 23% of all participants experienced the CTC bowel preparation as extremely or severely burdensome, compared
with 34% for colonoscopy (p>0.05; see fig 3B). After 5 weeks, 85% of the participants rated the colonoscopy as the most burdensome examination of the two. A majority of 67% of all participants would choose CTC as first examination after FOBT in future screening. Of all participants that were scheduled to undergo colonoscopy, 356 (54%) were also willing to undergo CTC (see fig 1). The main reason for not participating in CTC triage was that participants did not want to undergo an unnecessary additional examination (67%).

Fig. 3 (A; left) Degree of burden for both examinations overall. Participants found the colonoscopy examination significantly more burdensome than the colonoscopy preparation. (B; right) Degree of burden from CT colonography and colonoscopy bowel preparations. No significant difference was found between the degree of burden from the colonoscopy bowel preparation and the CT colonography bowel preparation.

DISCUSSION

CTC has proven to be an accurate technique for detection of colorectal polyps and carcinomas.10,12 This study investigated the role of CTC with a limited bowel preparation as a triage technique after positive FOBT in order to reduce the number of unnecessary colonoscopies. We found a high per patient sensitivity of CTC in the FOBT-positive subjects, especially for finding lesions ≥6 mm at colonoscopy. The sensitivity for finding lesions ≥10 mm was somewhat lower, which may have resulted from the fact that most patients had only one lesion of ≥10 mm but multiple lesions of ≥6 mm, resulting in a higher probability
of detecting at least one lesion ≥6 mm in a patient. It is important to realise, however, that most polyps of 6–9 mm are serendipitous findings because they usually do not bleed and therefore are not the main target of an FOBT screening programme.

When considering the usefulness of CTC as a triage technique, one should aim for a high NPV. NPVs in this study were fair but did not approach 100%, which would be ideal in a triage setting. When the CTC cut-off level was decreased, the NPV increased as result, but the number of false positives also increased, which is not preferable. The PPVs differed somewhat for CTC performance in the FOBT groups; the lowest PPV was found for I-FOBT with 50 ng/ml cut-off. This difference most probably occurred because of a difference in lesion prevalence in the FOBT groups, which can result in a different proportion of false positives.

One of the main reasons for performing CTC triage in FOBT positive subjects instead of a direct colonoscopy is that the acceptability has been reported to be better for CTC than for colonoscopy. In this study too the majority of participants reported a lower burden of the total examination including bowel preparation for CTC than for colonoscopy. Furthermore, 67% of the participants would prefer CTC instead of colonoscopy as first choice for future examination.

A triage technique is only useful when the number of patients that receive the colonoscopy will be substantially reduced. In this study we found that if 100 FOBT-positive subjects undergo a CTC, 46% will have to undergo a colonoscopy when using a CTC cut-off size of 10 mm. When considering costs of the initial management only, two different strategies are possible: CTC as triage and subsequent colonoscopy in CTC-positive patients or a direct colonoscopy in all FOBT-positive patients. Using a 10 mm cut-off, CTC examination costs must not exceed 54% of colonoscopy costs. However, this cost ratio does not seem applicable when the current costs for these examinations are considered. In a recent cost-effectiveness study by Regge et al, CTC examination costs are calculated as US$665 and colonoscopy costs as US$877. Thus here the CTC costs are 76% of the colonoscopy costs. Even when using a cut-off size of 6 mm, 73% will have to undergo colonoscopy after CTC and costs of CTC must not exceed 27% of colonoscopy costs. Hence, from an economic perspective, the use of CTC as a triage technique is most probably not efficient. Its apparent inefficiency resulted primarily from the high PPV of both FOBTs; 44% in those who were I-FOBT positive and 59% in those who were G-FOBT positive. This PPV of both FOBT-positive groups was much higher than expected considering the PPV for adenomas and cancer in earlier studies. However, a lower lesion prevalence is found when using lower cut-off levels for the I-FOBT. Furthermore, a few studies have reported a decrease in lesion prevalence in successive FOBT screening rounds. The use of CTC might then become more cost-efficient. Additionally, when calculating cost-efficiency, the false-negative lesions at colonoscopy should also be considered. In our study the per polyp sensitivity of colonoscopy was high (96%) for lesions >6 mm.

When considering the positivity rate of the FOBT itself, this was similar to that found in previous studies. In a review by Hewitson et al, the positivity rate of the G-FOBT varied from 0.8% to 5.3%, and other studies showed I-FOBT positivity rates of 4.7% and 6.9%. In this study, 2.4% of returned G-FOBTs and 8.5% of returned I-FOBTs with 50 ng/ml cut-off were positive. A higher positivity rate of the FOBT consequently results in a higher number of false positives, which would make CTC as triage more efficient. The PPV
of the I-FOBT was indeed lower than that of the G-FOBT; however, still 46% of patients in the I-FOBT group had an adenoma or cancer \( \geq 10 \text{ mm} \). Therefore, CTC triage seems not to be an efficient strategy in this first round FOBT.

In contrast to previous CTC studies, we calculated the diagnostic accuracy by using the CTC lesion size as the cut-off: participants will be referred for colonoscopy based on the size of lesions measured at CTC. This method of analysing CTC as a triage technique may give a more realistic view than the method of matching CTC and colonoscopy polyps, and then using the colonoscopy lesion size as the reference size for data reporting. In this study reporting of sensitivity or specificity per lesion histology was considered irrelevant for the evaluation of triage with CTC, because the histology cannot be defined at CTC and only polyp size can be used as an indicator for referral to colonoscopy. Polyp size is an important parameter because larger polyps \( \geq 10 \text{ mm} \) have a higher chance of malignant development.\(^{2,31}\) A disadvantage of this method is that differences in measurement of lesions at CTC and colonoscopy are not corrected by matching. Previous studies have shown that quite large differences in measurement of CTC and colonoscopy lesions can exist.\(^{32,33}\) These differences can cause an increase in the number of false positives and false negatives of CTC in the setting of triage.

The graph of the predictive values for different CTC polyp size cut-offs shows an optimal cut-off for CTC (highest PPV and NPV) at 10 or 10.5 mm and 6 or 6.5 mm, respectively (see fig. 2). These cut-offs might be different in other settings with another method of measurement (2D vs 3D) and different observers.\(^{34,35}\) In this study, a 2D measurement was performed because a primary 2D read was carried out in the tagging-only prepared CTCs. Currently, there is lack of consensus on the optimal method of measurement; some studies showed that 2D measurement was most accurate,\(^{34,36,37}\) while others recommended 3D measurement.\(^{35,38}\)

A known advantage of CTC compared with colonoscopy is the lower complication rate. Previous studies reported perforation rates of 0.009% for CTC in screening participants\(^{39}\) and of 0.3% for screening colonoscopy.\(^{40,41}\) In this study no complications occurred during CTC, whereas 11 of those screened reported rectal blood loss after colonoscopy. No perforations occurred during colonoscopy. However, we must realise that colonoscopy is not only diagnostic but also incorporates treatment. Subjects with lesions at CTC will also have to undergo colonoscopy and have similar risks of complications.

At CTC, extracolonic findings should be reported for ethical reasons.\(^{42}\) In this study group the number of highly relevant findings (E4) was low (3.1%), especially when compared with other studies with high or average risk patients, where incidences of highly relevant findings have been reported ranging between 9% and 23%.\(^{43-45}\) The results of our study are comparable with what was found in a large CTC screening trial with asymptomatic patients.\(^{11}\) This could be due to the low radiation dose protocols in these studies, which might result in a reduced visibility and detection of E4 findings.\(^{46}\) The significant extracolonic findings will inevitably lead to increased costs due to additional examinations and treatment when CTC is used as triage technique. Pickhardt et al showed that costs per screened person increased by US$98.56 due to extracolonic findings in CTC screening.\(^{47}\)

A potential limitation of this study is that bowel preparation with meglumine ioxithalamate was reduced from 2 days to just 1 day after inclusion of 153 participants.
This was done to diminish the burden of the bowel preparation even more and because newly published literature pointed out that 1 day preparation was sufficient.\textsuperscript{15,16,20} No differences in image quality were seen by the CTC observers, so this change of bowel preparation regime probably did not influence outcomes.

Another potential limitation is that all CTCs were scored by two observers who varied during the research period. To facilitate a quick review process, the results of both observers were combined (double reading) and no consensus reading was performed. Due to the double reading the number of false negatives decreases and the sensitivity and NPV increase, at the expense of the specificity and PPV.\textsuperscript{48} A double read is more costly and might not be time-efficient for screening or triage purposes in large populations. A computer-aided detection (CAD) system could be a solution to this problem, but on the other hand the additional value of CAD for experienced readers has not been proven.\textsuperscript{49}

A third potential limitation is that selection might have occurred between participants and nonparticipants in this CTC study. However, when aspects of age, gender and lesion prevalence between the FOBT-positive subjects in this study and the first original FOBT pilot study are compared, no differences are observed when considering those characteristics.\textsuperscript{18}

Conclusion

In conclusion, this study shows that CTC with limited bowel preparation is unlikely to be an efficient triage technique in a first round FOBT population screening programme. The patient burden of the CTC was lower than that of colonoscopy and most participants preferred CTC to colonoscopy for future examination. However, due to the high lesion prevalence in the FOBT-positive group and the relatively high miss rate of relevant lesions at CTC, CTC should not be considered as a triage technique in this specific first round FOBT population. In further FOBT screening rounds, lesion prevalence is possibly lower and in this situation CTC could be more effective.

Acknowledgements

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Colorectal
CT colonography with limited bowel preparation for the detection of colorectal neoplasia in an FOBT positive screening population

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ABSTRACT

**Purpose:** Aim was to evaluate the accuracy of computed tomography colonography (CTC) for detection of colorectal neoplasia in a Faecal Occult Blood Test (FOBT) positive screening population.

**Methods:** In three different institutions, consecutive FOBT positives underwent CTC after laxative free iodine tagging bowel preparation followed by colonoscopy with segmental unblinding. Each CTC was read by two experienced observers. For CTC and for colonoscopy the per-polyp sensitivity and per-patient sensitivity and specificity were calculated for detection of carcinomas, advanced adenomas, and adenomas.

**Results:** In total 22 of 302 included FOBT positive participants had a carcinoma (7%) and 137 had an adenoma or carcinoma ≥10 mm (45%). CTC sensitivity for carcinoma was 95% with one rectal carcinoma as false negative finding. CTC sensitivity for advanced adenomas was 92% (95% CI: 88–96) vs. 96% (95% CI: 93–99) for colonoscopy (p = 0.26). For adenomas and carcinomas ≥10 mm the CTC per-polyp sensitivity was 93% (95% CI: 89–97) vs. 97% (95% CI: 94–99) for colonoscopy (p = 0.17). The per-patient sensitivity for the detection of adenomas and carcinomas ≥10 mm was 95% (95% CI: 91–99) for CTC vs. 99% (95% CI: 98–100) for colonoscopy (p = 0.07), while the per-patient specificity was 90% (95% CI: 86–95) and 96% (95% CI: 94–99), respectively (p <0.001).

**Conclusion:** CTC with limited bowel preparation performed in an FOBT positive screening population has high diagnostic accuracy for the detection of adenomas and carcinomas and a sensitivity similar to that of colonoscopy for relevant lesions.
INTRODUCTION

Colorectal cancer screening is aimed mainly at detecting advanced adenomas and early stage colorectal cancer. Although a large part of adenomas will not develop into a carcinoma, a specific subgroup of advanced adenomas is believed to have an increased risk of developing into carcinoma. Such advanced adenomas are now understood to include adenomas of 10 mm or larger and adenomas with advanced histological features: villous histology or high-grade dysplasia. The removal of these adenomas leads to a reduction in the expected incidence of CRC. Screening for colorectal neoplasia and subsequent removal of adenomas identified through screening can therefore reduce cancer mortality.

In screening for colorectal cancer, the Faecal Occult Blood Test (FOBT) is the only screening test with a documented reduction in CRC-related mortality. Unfortunately, the FOBT has a limited positive predictive value. Large randomized trials have shown that the prevalence of carcinomas in an FOBT positive screening population is between 5.6% and 17.7%, while the prevalence of adenomas ranges between 15% and 55%. These numbers indicate that a large number of positive FOBTs are false positives: these screening participants have a positive FOBT test but no colorectal neoplasia.

In principle, CT colonography can image both adenomas and carcinomas. In an FOBT positive screening population, CT colonography might therefore be able to detect all relevant lesions that should be removed or that need follow-up. As a consequence, CT colonography might be used as a triage instrument in FOBT positives, but in our previous study this did not seem efficient. Another possibility is to use CT colonography only in patients that are unfit for or are unwilling to undergo colonoscopy. All screening participants with a positive FOBT without relevant lesions at CT colonography could then be safely withheld colonoscopy.

Recent studies have reported a high sensitivity for the detection of colorectal neoplasia on CT colonography in average risk screening participants. One recent study investigated the accuracy of CT colonography in FOBT positives (no screening) and found a sensitivity of 87% for advanced neoplasia. Another study found lesions 6 mm and larger in 40% of patients at CT colonography in an FOBT screening population. Colonoscopy was not performed in all patients, so no accuracy could be calculated. Up to our knowledge no previous study has assessed the accuracy of CT colonography for detection of advanced neoplasia in population-based FOBT screening.

The main aim of the present study was to assess the sensitivity and specificity of CT colonography with a limited bowel preparation for detecting colorectal neoplasia in an FOBT positive screening population.
METHODS

Study population
Data were collected in an invitational FOBT pilot screening trial in the Netherlands. A cohort of approximately 30,000 individuals between 50 and 75 years was randomly allocated to receive either an immunochemical test with a 50 ng/mL cut-off (I-FOBT, OC-sensor, Eiken Chemical Co, Tokyo, Japan) or a non-rehydrated guaiac test (G-FOBT; Haemoccult II, Beckman Coulter, Fullerton, CA). Details about the invitation, participant recruitment, and evaluation of eligibility have been described in detail elsewhere. All FOBT positives invited to undergo colonoscopy at the gastroenterology department were asked to undergo additionally CT colonography before colonoscopy. Excluded were participants with a terminal illness, those who had had a colonoscopy or an FOBT in the previous 2 years, inflammatory bowel disease or an examination with radiation exposure in the last 12 months, participants with hyperthyroidism, with an iodine contrast allergy or a pregnancy, as well those persons unable to give informed consent. Institutional review board approval was obtained before study initiation. Eligible participants were informed about the study purpose and asked for written consent.

CT colonography
Bowel preparation
The first 153 participants received a 2-day preparation with ingestion of 7 times 50 mL highosmolal ionic monomer meglumine-ioxithalamate during meals (Telebrix Gastro 300 mg I/mL; Guerbet, Cedex, France) and a low-fibre diet. The other 149 participants received a 1-day preparation with 4 times 50 mL of meglumine-ioxithalamate and a low-fibre diet. No laxatives were used and patients were encouraged to drink additional glasses of water. The reason to reduce the amount of ingested contrast agent during this study was that new studies on CT colonography bowel preparation showed that image quality and polyp detection remained sufficient with only 1 day of bowel preparation. After evaluation we found that both preparations had a high acceptance and good image quality.

CT colonography examination
Scans were made on two 64-slice CT scanners in supine and prone position. The scan protocol for the first scanner (Brilliance, Philips Medical Systems, Best, the Netherlands) was: 120 kV, pitch 1.2, rotation time 0.4 s and a 40 reference mAs with dose-modulation. For the other scanner (SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany) this was: 120 kV, 1.4, 0.5 s, and 32 reference mAs with dose-modulation. Before starting the insufflation, a smooth muscle-relaxant (20 mg of butylscopolamine bromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany)) was injected intravenously. When contraindicated 1 mg of glucagon hydrochloride was injected intravenously (Glucagen; Novo-Nordisk, Bagsvaerd, Denmark). In participants with contraindications for both smooth muscle-relaxants, no bowel relaxant was administrated.
CO2 gas was insufflated into the colon using a flexible balloon-tipped rectal catheter (20 French Gauge) using an automated insufflator (ProtoCO2l, Bracco Diagnostics, Princeton, NY). The total amount of CO2 insufflated and the in-room time were noted per participant.

**CT colonography analysis**
Evaluations were performed on a workstation with specialized software (View Forum, Philips Medical Systems, Best, the Netherlands; Aquarius Workstation, TeraRecon, STAD, USA). A primary 2D axial evaluation (window setting 1500, -250 HU) was done with 3D problem solving. Additionally a quick uni-directional 3D fly through was performed after the primary 2D evaluation. Electronic cleansing software was not available. Lesions were identified at each CT colonography by two out of seven experienced observers (radiologists and research fellows) who had evaluated at least 100 CT colonographies with colonoscopic verification (range 100–700 CT colonographies). All observers had passed a CT colonography exam with 25 cases by scoring above a predefined sensitivity threshold of 90% for lesions ≥10 mm. The observers reported observing time per viewing method (2D or 3D). The maximal diameter of each lesion was measured by using electronic callipers applied to a multiplanar reformatted (MPR) setting. The location, morphology, size, and probability were noted for each lesion. According to the Paris criteria, flat polyps were defined as lesions that protrude less than 2.5 mm from the mucosa. Both observers scored distension (four-point scale: 1 poorly distended to 4 good distension) and quality of bowel preparation (five-point scale: 1 very inhomogeneous tagging to 5 excellent preparation). When one of these was judged insufficient (score 1 or 2) by both readers in both scans, the participant was excluded for analysis.

**Colonoscopy**
Colonoscopy was planned within 3 weeks after CT colonography. Four litres of polyethylene glycol electrolyte solution (KleanPrep; Helsinn Birex Pharmaceuticals, Dublin, Ireland) or 4 L of macrogol solution (Colofort; Laboratoires Macors, Auxerre, France) and a clear liquid diet the preceding evening were used for colonoscopy. The examination was performed by experienced gastroenterologists, gastroenterology fellows and colonoscopy nurses with supervision, using a standard colonoscope (Olympus Medical Systems Europe, Hamburg Germany). With the segmental unblinding technique, lesions 6 mm or larger found at CT colonography were revealed to the colonoscopist by a research fellow [ML] after completing the examination of one segment. Colonoscopies were videotaped starting from the caecum. The colonoscopist estimated lesion size by an opened biopsy forceps or by a linear measure probe (Olympus Medical Systems Europe, Hamburg Germany). Histology of lesions was classified as normal, inflammatory, hyperplastic, adenoma (serrated, tubular, tubulovillous, or villous), or carcinoma. Advanced neoplasias were defined as adenomas 10 mm or larger in diameter, with a villous architecture or high-grade dysplasia on histology, or an invasive carcinoma.

**Polyp matching**
Matching of all lesions and tumours of 6 mm and larger found on CT colonography was done by a research fellow [ML] by reviewing the colonoscopy video’s and reports.
Colonoscopy with segmental unblinding served as an enhanced reference standard. A lesion on CT colonography was classified as a true positive when colonography and colonoscopy lesion size were within 50% margin, lesions were in the same or adjacent segment and the morphology at CT colonography resembled morphology of the lesion seen on the videotaped colonoscopy. Lipoma and normal mucosa were considered false positives for CT colonography when scored as a lesion by the CT colonography observer. False negative lesions at CT colonography could be due to a perceptive error or a technical error. Perceptive errors were visible on retrospect at CT colonography, whereas technique related errors were not.

Statistical analysis
The results of the two observers were combined in a double reading procedure. If at least one observer had detected a lesion this was considered a positive finding. We also calculated the mean result for both observers.

The CT colonography per-polyp sensitivity was calculated by using all true positive lesions at CT colonography and the false negative lesions found at colonoscopy. This was done separately for adenomatous polyps and for carcinomas ≥10 mm, for adenomas and carcinomas between 6 and 9 mm, as well as for all lesions in these size categories, also including hyperplastic and inflammatory polyps. In addition, we evaluated the per-polyp sensitivity for advanced neoplasia and per lesion morphology, classified as flat, sessile, or pedunculated. Differences were tested with the Chi-square test statistic. The per-polyp sensitivity of colonoscopy was calculated by using the true positive and false negative lesions, found after unblinding of the CT colonography results. Comparisons between CT colonography and colonoscopy sensitivity and influence of additional 3D reading were evaluated using the McNemar test statistic.

The per-patient sensitivity was defined as the number of participants with at least one true positive adenoma or a carcinoma ≥10 and ≥6 mm at CT colonography relative to all participants with an adenoma or carcinoma in that size category identified after colonoscopy with segmental unblinding. The per-patient specificity was defined as the number of participants negative on CT colonography relative to all participants with a negative colonoscopy result. A participant with both one true positive and one false negative finding at CT colonography was defined as a true positive. All non-adenomatous lesions were counted as false positives, also for the calculation of the colonoscopy specificity.

We estimated interobserver agreement by calculating kappa statistics with corresponding 95% confidence intervals for the two readers and by calculating the total number of concordant cases. The two reviewers were considered to agree if they both recorded at least one true lesion in the same participant or if both recorded no findings. The kappa values were interpreted as follows: <0.20 poor agreement; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 good; 0.81–1.00 excellent. All calculations were performed using a statistical software package (SPSS for Windows version 15.0.1, Chicago, IL).
RESULTS

A total of 314 FOBT positive participants underwent CT colonography before colonoscopy between June 2006 and May 2008. Twelve participants had an incomplete CT colonography or colonoscopy. In two colonoscopies the caecum was not reached because of extreme pain and a colonic stricture. In four CT colonographies the bowel preparation was insufficient and in six the distension was insufficient. Finally 302 participants could be included in the analysis (54 guaiac FOBT, 248 immunochemical FOBT). Totally 187 males and 115 females were included (see article13, for additional demographic characteristics and a flow-diagram of the study).

Colonoscopy

Colonoscopy was successful in 312 participants. One participant (0.3%) had a bleeding after polypectomy for which hospitalization was required. With colonoscopy 22 carcinomas were detected in 22 participants (7%), two carcinomas were smaller than 10 mm; 184 adenomas and carcinomas 10 mm or larger were detected in 137 participants (45%). Another 138 adenomas and carcinomas between 6 and 9 mm were detected in 60 participants (20%). In total 180 advanced adenomas were found, of which 164 were 10 mm or larger. Furthermore, three lipomas and one hamartoma were found. Table 1 summarizes the distribution of lesions according to size and morphology. Lesions with no histology available were not considered as an adenoma or carcinoma. Six adenomas ≥10 mm were found with colonoscopy only after unblinding of the CT colonography results. The latter also resulted in 8 lesions between 6 and 9 mm that were additionally found, of which 4 were adenomas. In Table 2 the per-polyp sensitivity for colonoscopy is presented.

Table 1 Distribution of adenomatous or non-adenomatous lesions per size category and per type of morphology

<table>
<thead>
<tr>
<th>Size Category</th>
<th>&lt;6 mm</th>
<th>6-9 mm</th>
<th>≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedunculated</td>
<td>Adenoma or carcinoma</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>All lesion types¹</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>Sessile</td>
<td>Adenoma or carcinoma</td>
<td>228</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>All lesion types¹</td>
<td>418</td>
<td>126</td>
</tr>
<tr>
<td>Flat</td>
<td>Adenoma or carcinoma</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>All lesion types¹</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>All polyps and carcinomas</td>
<td>488</td>
<td>190</td>
</tr>
</tbody>
</table>

¹All lesion types: adenomas, carcinomas, hyperplastic, hamartomous or infectious lesions. These also include polyps that were lost after polypectomy and polyps with unclear histology

CT colonography

The mean in-room time for CT colonography was 21’58” (SD 7’20”) per participant. In total, 260 participants (86%) received an intravenous injection of Buscopan while 29 (9.7%) received Glucagen. The average amount of CO2 insufflated was 4.1L (SD 2.1L). No
complications were associated with the CT colonography examination. The mean reading time for the 2D read was 10´43˝ (SD 5´21˝) and the additional 3D accounted for 4´16˝ (SD 1´30˝).

### Table 2 Per-polyp sensitivity for CT colonography compared to colonoscopy

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>CT colonography</th>
<th>Colonoscopy</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced adenomas</td>
<td>92% (88-96)</td>
<td>96% (93-99)</td>
<td>p=0.26</td>
</tr>
<tr>
<td></td>
<td>165/178</td>
<td>173/180</td>
<td></td>
</tr>
<tr>
<td>Adenomas and carcinomas 6-9 mm</td>
<td>78% (71-85)</td>
<td>97% (94-100)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>108/138</td>
<td>134/138</td>
<td></td>
</tr>
<tr>
<td>Adenomas and carcinomas ≥10 mm</td>
<td>93% (89-97)</td>
<td>97% (94-99)</td>
<td>p=0.17</td>
</tr>
<tr>
<td></td>
<td>171/184</td>
<td>178/184</td>
<td></td>
</tr>
<tr>
<td>All lesions¹ 6-9 mm</td>
<td>75% (69-81)</td>
<td>96% (93-99)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>142/190</td>
<td>190/198</td>
<td></td>
</tr>
<tr>
<td>All lesions¹ ≥10 mm</td>
<td>92% (88-96)</td>
<td>97% (95-99)</td>
<td>p=0.035</td>
</tr>
<tr>
<td></td>
<td>191/208</td>
<td>208/214</td>
<td></td>
</tr>
</tbody>
</table>

¹All lesion types: adenoma, carcinoma, hyperplasia, hamartomous or infectious. Also includes not-removed polyps and polyps with unclear histology. Between brackets is the 95% confidence interval

**Per-polyp analysis**

Of the 22 detected cancers at colonoscopy, 21 were also found at CT colonography with double reading, resulting in a sensitivity of 97% (95% CI: 87–100). The one missed colorectal cancer was a flat rectal carcinoma of 20 mm, hardly visible in retrospect (see Fig. 1). CT colonography detected 171 of 184 adenomas and carcinomas ≥10 mm (sensitivity 93%; 95% CI: 89–97). This was not significantly different from the colonoscopy sensitivity (p = 0.17). See Table 2 for results on per-polyp sensitivity of CT colonography compared to colonoscopy. For lesions ≥10 mm CT colonography sensitivity was 92% (95% CI: 88–96), which was lower than the colonoscopy sensitivity (p = 0.035). In this study, 165 of the 180 advanced adenomas were detected at CT colonography, resulting in an estimated sensitivity of 92% (95% CI: 88–96). The colonoscopy sensitivity for advanced adenomas was 96% (95% CI: 93–99) (p = 0.26). In Table 3 the sensitivity of CT colonography per morphology and size category is given separately.

CT colonography sensitivity in detecting flat lesions was lower than that of pedunculated lesions in both size categories (p < 0.001). The sensitivity of sessile lesions 6–9 mm was lower than that for pedunculated lesions (p < 0.01). Figures 2 and 3 show examples of a pedunculated and flat lesion found at CT colonography and colonoscopy. In Table 4, the false negatives are categorized in false negatives due to perspective error and false negatives due to technical error. The largest percentage of technical false negatives consisted of flat lesions (5 out of 14 flat lesions; 36% for ≥10 mm and 8 out of 19; 42% for 6–9 mm). One lesion ≥10 mm and 15 lesions of 6–9 mm were seen at secondary 3D reading only. Of these lesions, four had a flat histology, eleven were sessile, and one pedunculated. The additional 3D read detected lesions increased the sensitivity from 67% (95% CI: 60–74) to 75% (95% CI: 69–81) for lesions between 6 and 9 mm (p < 0.000), without a similar increase for lesions ≥10 mm: 91% (95% CI: 88–95) vs. 92% (95% CI: 88–96) (p = 1).
Table 3 Per-polyp sensitivity of CT colonography per size category and per lesion type for adenomatous polyps and for all histology types (double read)

<table>
<thead>
<tr>
<th></th>
<th>6-9 mm</th>
<th>≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenomas and carcinomas</td>
<td>Adenomas and carcinomas</td>
</tr>
<tr>
<td></td>
<td>95% (88-100)</td>
<td>95% (91-99)</td>
</tr>
<tr>
<td></td>
<td>38/40</td>
<td>104/109</td>
</tr>
<tr>
<td>Pedunculated All lesions¹</td>
<td>96% (90-100)</td>
<td>95% (91-99)</td>
</tr>
<tr>
<td></td>
<td>43/45</td>
<td>112/118</td>
</tr>
<tr>
<td>Sessile Adenomas and carcinomas</td>
<td>76% (67-85)*</td>
<td>95% (90-100)</td>
</tr>
<tr>
<td></td>
<td>65/86</td>
<td>95% (91-99)</td>
</tr>
<tr>
<td></td>
<td>60/63</td>
<td>71/76</td>
</tr>
<tr>
<td></td>
<td>90/126</td>
<td>6/12</td>
</tr>
<tr>
<td></td>
<td>93% (88-99)*</td>
<td>71/76</td>
</tr>
<tr>
<td></td>
<td>43/65</td>
<td>12/16</td>
</tr>
<tr>
<td></td>
<td>All lesions¹</td>
<td>93% (88-99)*</td>
</tr>
<tr>
<td></td>
<td>112/128</td>
<td>71/76</td>
</tr>
<tr>
<td></td>
<td>Flat Adenomas and carcinomas</td>
<td>42% (14-70)*</td>
</tr>
<tr>
<td></td>
<td>5/12</td>
<td>7/12</td>
</tr>
<tr>
<td></td>
<td>9/19</td>
<td>57% (31-83)*</td>
</tr>
<tr>
<td></td>
<td>Adenomas and carcinomas</td>
<td>47% (25-70)*</td>
</tr>
<tr>
<td></td>
<td>All lesions¹</td>
<td>47% (25-70)*</td>
</tr>
<tr>
<td></td>
<td>9/19</td>
<td>8/14</td>
</tr>
</tbody>
</table>

¹All lesion types: adenoma, carcinoma, hyperplasia, hamartomous or infectious. Also includes not-removed polyps and polyps with unclear histology. Between brackets is the 95% confidence interval. * Significantly different sensitivity compared to the pedunculated lesions p < 0.05

Per-patient sensitivity and specificity
In Table 5 the CT colonography and colonoscopy sensitivity and CT colonography specificity per patient for adenomas and carcinomas of both size categories are given. The per-patient sensitivity of CT colonography was 95% (95% CI: 91–99) for adenomas and carcinomas ≥10 mm and 93% (95% CI: 89–96) for adenomas ≥6 mm. The specificity for the identification of participants without any adenoma or carcinoma of ≥10 mm was 90% (95% CI: 86–95), for ≥6 mm this was 70% (95% CI: 62–79). Comparing CT colonography and colonoscopy no significant difference was found in the sensitivity for adenomas and carcinomas ≥10 mm.

Table 4 Number of false negatives per size category and per lesion type

<table>
<thead>
<tr>
<th></th>
<th>6-9 mm</th>
<th>≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perceptive false negative Pedunculated</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Sessile</td>
<td>7 (5.6%)</td>
</tr>
<tr>
<td></td>
<td>Flat</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td></td>
<td>Technical false negative Pedunculated</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td></td>
<td>Sessile</td>
<td>28 (22.4%)</td>
</tr>
<tr>
<td></td>
<td>Flat</td>
<td>8 (42.1%)</td>
</tr>
</tbody>
</table>

Percentages are the number of false negatives related to the total number of lesions of this type

Interobserver agreement
For per-patient analysis for lesions ≥10 mm, a kappa value of 0.90 (95% CI, 0.85–0.94) was calculated for the interobserver agreement. For lesions ≥6 mm this was 0.82 (95% CI, 0.76–0.88).
Table 5 Per-patient sensitivity and specificity for adenoma detection

<table>
<thead>
<tr>
<th></th>
<th>Adenomas and carcinomas ≥6 mm</th>
<th>Adenomas and carcinomas ≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity (per patient)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC double read</td>
<td>93% (89-96)†</td>
<td>95% (91-99)</td>
</tr>
<tr>
<td>CTC mean 2 readers</td>
<td>89% (85-94)†</td>
<td>92% (88-97)†</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>98% (96-100)</td>
<td>99% (98-100)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC double read</td>
<td>70% (62-79)†</td>
<td>90% (86-95)†</td>
</tr>
<tr>
<td>CTC mean 2 readers</td>
<td>77% (69-85)†</td>
<td>93% (90-97)†</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>93% (89-98)</td>
<td>96% (94-99)</td>
</tr>
</tbody>
</table>

Lesions that were not adenomatous or carcinoma were counted as false positive. Between brackets is the 95% confidence interval. †Indicates significant difference compared to colonoscopy. CTC, CT colonography.

Fig. 1. False negative rectal carcinoma images of the supine (a) and prone scans (b) of a patient with a rectal carcinoma. This lesion was not detected at CT colonography by both observers and retrospectively hardly visible. Arrows indicate the tumour seen at CT colonography and colonoscopy (c).

Fig. 2. Pedunculated tubulovillous adenoma 15 mm, submerged in tagged faeces: (a) is an MPR view of the supine position, (b) the axial supine view, (c) the lesion is removed at colonoscopy.
Fig. 3. Flat serrated adenoma 12 mm. This flat adenoma was detected by both CT colonography observers: (a) is the 2D axial image of the prone scan and (b) is the 3D view. Arrows indicate the flat lesion, (c) is the lesion seen at colonoscopy.

**DISCUSSION**

In the Joint Guideline for screening on colorectal cancer from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology a number of alternative colorectal screening tests are recommended, including the FOBT. The FOBT is a cheap and simple screening test for colorectal cancer with a high negative predictive value, but it has the disadvantage that it generates a large number of false positives, resulting in lower positive predictive value which will result in a higher number of unnecessary invasive colonoscopic examinations. Ours is the first study to investigate the diagnostic accuracy of CT colonography for detection of colorectal neoplasia in an FOBT positive screening population. In the present study there was a high prevalence of colorectal neoplasia in the FOBT positive participants: almost two-thirds of all participants had one or more adenomas or a carcinoma. The vast majority of these lesions were detected by the CT colonography readers resulting in a high sensitivity for detection of adenomas and carcinomas.

In a recent study of Regge et al., the per-patient sensitivity for detection of advanced neoplasia of 6 mm and larger in FOBT positive individuals was 87%, which is comparable to the sensitivity we found in our study. Also the specificity was similar; in both studies this was 77% (mean percentage of all readers). The FOBT positives in the previous study were no screening participants, but increased risk patients that could already have had symptoms. This is different than in our study that included FOBT positives from a population screening program. Furthermore, when compared to earlier studies that evaluated CT colonography for adenoma detection in screening participants, we found a similar sensitivity and specificity. In these studies, sensitivities for detection of adenomas and carcinomas ≥10 mm were 90% or more. Different than in our study, these studies contained average risk screening participants with a low lesion prevalence and all patients received an extensive cathartic bowel preparation. When using a limited bowel preparation, we found a sensitivity of 93% for detection of colorectal neoplasia ≥10 mm in FOBT positive screened participants, not significantly different than
the sensitivity of colonoscopy (97%). For the detection of advanced adenomas, CT colonography had a sensitivity similar to that of colonoscopy.

The prevalence of lesions is an important issue when evaluating the use of a diagnostic test in screening participants. In the present study there was a high lesion prevalence in the FOBT positive group, almost 65% of all positives had an adenoma or carcinoma of 6 mm and larger. Therefore, the CT colonography does not seem an effective triage instrument in FOBT positives (see 13), but because of the high sensitivity it might have a role in patients with severe comorbidities that are unfit to undergo colonoscopy or patients unwilling to undergo colonoscopy.

The per-patient specificity for the detection of large lesions was lower than that of colonoscopy, 90% vs. 96%. For the medium size category (6–9 mm) we found a sensitivity of 78% which was significantly lower than that of colonoscopy. One flat rectal carcinoma was missed at CT colonography and was even retrospectively hardly visible. It is already known from earlier studies that lesions with a flat morphology are easily missed at CT colonography.27,28 Furthermore, the rectum is a difficult colonic segment to examine because the distension is not always optimal, especially not in supine position, and an inflated rectal balloon can mask rectal lesions.29,30 One previous paper described a malignant rectal lesion missed due to the presence of the inflated balloon.31 A digital rectal examination could be performed to reduce the number of false negative rectal lesions in this segment. Its feasibility in clinical practice is questionable because a digital rectal examination has to be performed by an experienced person. In many centres CT colonography is performed independently by radiographers.

We found in the present study that sensitivity for detection of pedunculated lesions was high at CT colonography. For lesions ≥10 mm the sensitivity in detecting flat lesions was significantly lower than the sensitivity in detecting pedunculated and sessile lesions. Most of the false negative lesions were not visible retrospectively and have to be considered as technically false negatives. In this population the number of flat lesions was low, so this did not greatly affect CT colonography polyp sensitivity.

Each CT colonography was examined by two observers and their results were combined. This double reading procedure is time consuming but it resulted in a higher per-patient sensitivity. This was also found in a previous study by Johnson et al.32 A disadvantage of this double reading is that the number of false positives increases as well, consequently, the per-patient specificity decreases. The mean specificity of both readers for adenomas and carcinomas ≥6 mm is 77% compared to a 70% specificity for the double read. In this high lesion prevalence FOBT positive population it is important to obtain a high sensitivity so participants are not wrongly withheld colonoscopy.

Another method to improve the sensitivity of CT colonography is the use of an additional 3D reading after the primary 2D reading. We found that for detection of lesions between 6 and 9 mm, the sensitivity increased when using 3D reading after the 2D reading. In particular additional sessile and flat lesions were found after 3D viewing. Flat lesions are easily missed and probably best detected at a 3D viewing method.28 A previous study showed that an additional 3D read resulted in a higher sensitivity for detection of polyps.33 The main reason for not performing a primary 3D and evaluating a primary 2D review method only in the present study was the use of a limited bowel preparation without having the availability of a cleansing algorithm.
A potential limitation of the present study is that we changed the bowel preparation after half of the participants had received a CT colonography. This was done because articles had been published during the study period indicating that a 1-day bowel preparation was sufficient for qualitative faecal tagging, simultaneously reducing patient burden.\textsuperscript{20–22} We retrospectively compared the quality of the bowel preparation in the 2- and 1-day preparation groups and found no differences in homogeneity of stool and detection of polyps while participant acceptance increased.\textsuperscript{23} Another potential limitation is that due to a limited bowel preparation an immediate colonoscopy after a positive CT colonography is not possible. In our opinion, however, the advantage of an improved patient acceptance is more important than this disadvantage. Furthermore, we did not use a consensus read between the two observers. The main reasons for this were that we wanted to reduce time spent on examining the CT colonographies and we aimed to obtain a high sensitivity by combining the scores of both observers.

**Conclusion**

In conclusion we found that CT colonography has a high diagnostic accuracy for detection of colorectal neoplasia in an FOBT positive screening population. Even with the use of a limited bowel preparation, the sensitivity of CT colonography for detection of large adenomas and carcinomas in our study was similar to that of colonoscopy and therefore CT colonography can be used in FOBT positives that are unfit for or unwilling to undergo colonoscopy. Double reading and additional 3D reading increased the sensitivity of CT colonography.

**Acknowledgments**

We thank all other persons of the departments of Radiology and Gastroenterology and Hepatology of the Academic Medical Center in Amsterdam, the University Medical Center Nijmegen and the Erasmus MC University Medical Center Rotterdam who contributed to this study. Furthermore, we would like to thank Philips Medical Systems for providing all necessary workstations. Supported by the Netherlands Organization for Health Research and Development (ZonMW: project number 62300036).
References

Radiation dose in CT colonography—trends in time and differences between daily practice and screening protocols

M. H. Liedenbaum
H. W. Venema
J. Stoker

**ABSTRACT**

**Purpose:** The purpose of this study was to evaluate the currently used effective doses in CT colonography (CTC) and to search for trends in time.

**Methods:** A PubMed search for articles and a search for congress abstracts concerning CTC was performed. Research institutions were sent a CTC dose questionnaire concerning the type of CT system employed and the CT parameters used. With the ImPACT CT Dosimetry Spreadsheet effective doses were calculated. Of 83 institutions, 34 returned a complete questionnaire; 21 (62%) used 64-detector row CT and 17 (50%) used dose modulation.

**Results:** The median effective dose per institution was 5.7 mSv (2.8 mSv supine; 2.5 mSv prone) for screening protocols and 9.1 mSv (5.2 and 3.0 mSv, respectively) for daily practice protocols (p<0.05). Doses did not differ significantly between CT machines with different numbers of detector rows. In 17 institutions incorporated in a study in 2004 as well, the median dose for daily practice protocols changed from 11 mSv in 2004 to 9.7 mSv now (n.s.).

**Conclusions:** The median effective dose for CTC is significantly lower for screening than for daily practice protocols. Although the number of CTC protocols with dose modulation increased substantially since 2004, no significant decrease in effective dose was found.
INTRODUCTION

Currently, multi-detector computed tomography (CT) systems with a large number of detector rows (e.g., 40 or 64), dose modulation or automated current selection (ACS) is widely used for all applications including CT colonography (CTC). These technical improvements will have an effect on image quality, but also on radiation exposure. Dose efficiency is improved with an increasing number of detector rows due to the decrease of the effect of overbeaming, which is the additional radiation due to the penumbra effect. On the other hand, dose efficiency is lost with machines with a larger number of detector rows, because of increased amount of overranging, which is the difference between the exposed length and the planned length of the CT examination. ACS automatically adjusts the tube current to the size of the patient to reduce the differences in noise level between thin and thicker patients. Differences in image quality will therefore be reduced for patients of different sizes. Dose modulation adjusts the tube current according to the changing patient anatomy. This can give an overall reduction in dose level per patient, while the image quality is preserved.

For CTC it is important to reduce radiation dose for optimization of the benefit-risk ratio of the examination, especially when used in low-risk screening patients. The lifetime cancer risk associated with the radiation exposure using a typical current CT technique for paired (supine and prone) CTC was estimated to be 0.14% for a 50 year old, which might be reduced by factors of 5 or even 10 with optimized CTC protocols. Important is however to identify acceptable thresholds of image quality so that radiation dose optimization can take place. In earlier research it was found that with low doses still good image quality and high diagnostic accuracy were obtained at CTC. In a previous study the effective radiation dose in CTC protocols of 28 research institutions was surveyed. Most institutions at that time used CT systems with 4, 8 or 16 detector arrays. The median effective dose per institution was 5.1 mSv per position and 10.2 mSv in total. No CT systems with more than 16 detector rows, no dose modulation or automated current selection were used at that time.

The aim of the present study was to investigate the current effective dose for CTC in daily practice and screening protocols and to compare doses for the protocols used with machines using different numbers of detector rows. Furthermore, current effective doses were compared with the results of the former dose evaluation study.

METHODS

Dose questionnaire
A PubMed search was performed with MESH heading ‘CT colonography,’ and all articles published from January 2004 until January 2007 describing a study on CTC accuracy were selected. Articles in a language other than English or case reports were excluded. Furthermore, all abstracts of the Congress of the Radiological Society of North America (RSNA) 2006, European Congress of Radiology (ECR) 2006 and the Symposium on Virtual
Colonoscopy in Boston 2006 were searched for studies with CTC. In addition all institutions that were invited for a questionnaire in the study by Jensch et al.\textsuperscript{12} were included, if this was not yet the case. All selected institutions received a mail in which they were invited to fill in a questionnaire. Reminder e-mails were sent after 4 and 7 weeks. In Table 1 the questions of the dose evaluation questionnaire are listed. The data for the present study were collected between April and September 2007.

**Estimation of effective doses**

The effective dose for each protocol was estimated using the ImPACT CT Dosimetry Spreadsheet (www.impactscan.org/ctdosimetry.htm).\textsuperscript{13,14} With this spreadsheet effective doses can be calculated for a hermaphrodite with a length of 170 cm and a weight of 70 kg.\textsuperscript{15} In the calculation of effective dose, a nominal scan trajectory of 43 cm was assumed (from the diaphragm to the groin). Data for the additional anatomical length exposed due to overranging were obtained from the CT-Expo spreadsheet, and the effective length of the volume examined was used in the calculation of the effective dose.\textsuperscript{16} Calculation of effective dose is straightforward for the situation without ACS or dose modulation. With ACS the tube current is constant, but depends on the size of the patient, and with dose modulation the tube current also varies per slice and per tube angle (in case X/Y modulation is used), which complicates the calculations of effective dose. In this situation we used the average effective mAs value that was used for a CTC of an average-sized patient of 170 cm and 70 kg.

In case not the effective mAs, but the CTDI\textsubscript{vol} was provided, the average effective mAs was obtained from the ImPACT spreadsheet; when the doselength product (DLP) was provided the CTDI\textsubscript{vol} was obtained by dividing by the length of the volume examined. In case data for patients of deviant weight were provided, the effective mAs value for a patient of 70 kg was estimated with an empirical relationship, using data of Kalra et al.\textsuperscript{17} (see Fig. 1). Data of the CTC protocols for daily practice and screening were evaluated separately, and classified according to the number of detector rows of the CT machine in question. When an institution used protocols with and without dose modulation, the protocols with dose modulation were used. However, when an institution used more than one protocol for daily practice or screening that differed otherwise, both protocols were used, and the average effective dose for the institution was calculated.

Results of dose calculations were sent to all institutions to check for possible errors. Of the institutions that returned a questionnaire in a former CTC dose evaluation study as well,\textsuperscript{12} comparisons were made between the effective dose at that time (2004) and now. At that time overranging was not taken into account and therefore we recalculated the effective doses for this study including the effect of overranging. The number and percentages of multi-detector row CT systems with a different number of detector rows were calculated for 2004 and 2007, as were the number of institutions that used dose modulation in 2007.
Table 1 Questions in the dose evaluation questionnaire

<table>
<thead>
<tr>
<th>Questions in the dose evaluation questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Practice Protocol? y/n</td>
</tr>
<tr>
<td>Type of patients for DP protocol:</td>
</tr>
<tr>
<td>-Symptomatic</td>
</tr>
<tr>
<td>-Surveillance</td>
</tr>
<tr>
<td>-Other:</td>
</tr>
<tr>
<td>Screening Protocol? y/n</td>
</tr>
<tr>
<td>Type of CT scanner: (manufacturer and type)</td>
</tr>
<tr>
<td>Number of slices: 1,2,4,8,16,40 or 64</td>
</tr>
<tr>
<td>Collimation per slice: mm</td>
</tr>
<tr>
<td>Tube voltage: ... kV</td>
</tr>
<tr>
<td>Rotation time: ... sec</td>
</tr>
<tr>
<td>Pitch (table feed per rotation/ total collimation): ...</td>
</tr>
</tbody>
</table>

For scans without automatic current selection or dose modulation:

- Tube current: ... mA
- Tube current x Rotation time: ... mAs
- Tube current x Rotation time/ Pitch: ... effective mAs or mAs per slice

For scans with automatic current selection and/or dose modulation (for an average male patient, i.e. approximately 170 cm and 70 kg):

- Length patient: ... cm
- Weight patient: ... kg
- Preset or reference mAs (if available): ... mAs
- Realized DLP: ... mGy*cm
- Realized average mAs: ... mAs
- Realized CTDIvol: ... mGy
- Length of scan or scans: ... cm
- Use of X/Y modulation: y/n
- Use of Z modulation: y/n

Institutions were asked to complete the form for both supine and prone protocols and for the daily practice and screening protocols (or only one protocol if not both in use). Indications for daily practice patients were: 1. symptomatic patients with symptoms of colorectal cancer or other colorectal disease, 2. surveillance patients for repeat examination on colorectal cancer or other colorectal disease or 3. DLP: Dose Length Product. CTDIvol: Computed Tomography Dose Index.

**Sensitivity analysis parameters dose modulation**

We performed a sensitivity analysis to determine the influence of deviations in our data or assumptions in case of dose modulation on the outcomes of the study. The above-mentioned correction of mAs values for patients of deviant weight are only approximate; it is known that this correction is different for different CT manufacturers, and even within one CT model the mA weight curve can to a certain extent be adjusted.\textsuperscript{18,19} We checked the influence of the choice of the correction by recalculating some of the data using 50% less or 50% more mAs correction for deviant weight than the correction shown in Fig. 1. We also checked the sensitivity of the outcomes on our assumption of a patient weight of 70 kg in case no unambiguous information was provided. If errors had been made, we assumed that the weight should have been somewhat larger, and therefore recalculations were made for weights of 75 and 80 kg.
**Fig. 1** Example of relation of tube current and weight in CT systems when dose modulation is applied

**Table 2** Corrections of mAs values according to weight in 6 institutions

<table>
<thead>
<tr>
<th>Position¹</th>
<th>Weight (kg)</th>
<th>mAs</th>
<th>mAs²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin</td>
<td>supine/prone</td>
<td>75</td>
<td>56</td>
</tr>
<tr>
<td>Leuven</td>
<td>prone</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>London</td>
<td>supine/prone</td>
<td>67</td>
<td>113/110</td>
</tr>
<tr>
<td>Perth</td>
<td>supine</td>
<td>75</td>
<td>200</td>
</tr>
<tr>
<td>Ulm</td>
<td>supine/prone</td>
<td>84</td>
<td>162</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buenos Aires</td>
<td>supine/prone</td>
<td>80</td>
<td>49</td>
</tr>
<tr>
<td>Leuven</td>
<td>supine</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>prone</td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>Ulm</td>
<td>supine/prone</td>
<td>76</td>
<td>49</td>
</tr>
</tbody>
</table>

¹Position: patient position where dose modulation is applied. ²mAs: corrected mAs value for weight
Statistical analysis

For the effective dose and the various CT parameters, medians, minimum and maximum values were determined. The effective doses in the scanners with a different number of detector rows were compared by using the Kruskal-Wallis test. Differences between daily practice and screening protocols and between protocols of 16-, 40- and 64-detector row scanners with and without dose modulation were analyzed with the Wilcoxon-Mann-Whitney test. For comparison of results of the former study and the present study, we used the Wilcoxon signed ranks test. A p-value of less than 0.05 was considered to be significant.

Table 3 Daily practice protocols in different institutions with median values of scan parameters and effective dose per protocol

<table>
<thead>
<tr>
<th>Number of simultaneously acquired slices</th>
<th>64</th>
<th>40</th>
<th>16</th>
<th>4</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of protocols</td>
<td>21</td>
<td>1</td>
<td>11</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Tube voltage (kV)</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Rotation time (s)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.75</td>
</tr>
<tr>
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<td>0.625</td>
<td>1.25</td>
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</tr>
<tr>
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<td>113</td>
<td>62/56</td>
<td>83.5/30.5</td>
<td>55</td>
</tr>
<tr>
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<td>12</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
<td>9.1</td>
<td>13.7</td>
<td>11.5</td>
<td>9.1</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*Results for median values of collimation and effective mAs for supine and prone positions (supine/prone)*

RESULTS

Response

With the search, 83 institutions were identified. After two reminder e-mails to non-responding institutions, we obtained a response from 50 institutions (60%), and from these institutions we received 37 (45%) questionnaires. Five authors answered that CT colonography was no longer performed, and eight authors responded positively, but finally did not return the questionnaire notwithstanding reminder e-mails. Three authors filled in the questionnaire with insufficient information for calculation of the effective dose, thus 34 institutions remained with complete questionnaires. Of these 34 institutions, 22 performed CTC for both daily practice and screening purposes, 11 only for daily practice and 1 institution only for screening. Indications for patients receiving CTC examinations in daily practice are indicated in Fig. 2.

Data on dose modulation

Seventeen institutions indicated that they used dose modulation for protocols for supine or prone scans, or both. Six of these institutions provided data for patients of 70 kg, and six institutions provided data for patients of another weight. Table 2 shows these weights, the uncorrected mAs values and the estimated mAs values for a patient of 70 kg using the...
relationship of Fig. 1. Five institutions did not provide unambiguous information on weight, and it was assumed that the weight of the patient was 70 kg.

**CT parameters: daily practice and screening protocols**

Overall, 37 CT machines were used by 34 institutions; 3 institutions use CT machines from 2 different manufacturers. In Table 3 a summary is given of the protocols for the daily practice patients. No significant differences in effective dose were found between scanners with different detector rows and between protocols with and without dose modulation. The median effective dose in 39 daily practice protocols was 9.1 mSv (range 2.8–22), 5.2 mSv (1.0–14.1) for supine and 3.0 mSv (0.6–9.8) for prone CT acquisition. The median effective dose per institution was also 9.1 mSv (2.8–22). The median values for the 25 protocols for screening CT colonography in 22 institutions are given in Table 4. No significant difference in effective dose was found between scanners with different detector rows. The median effective dose for the screening protocols was 5.6 mSv (range 2.6–14.7), 2.8 mSv (1.0–6.1) for supine and 2.5 mSv (0.6–9.8) for prone CT acquisition. The median effective dose per institution was 5.7 mSv (2.6–12.2). See Fig. 3 for a histogram of the effective doses of daily practice and screening protocols. Overviews of CT parameters and effective dose for daily practice protocols and screening protocols per institution are given in Tables 5 and 6. The effective doses for the screening protocols were significantly lower than for the daily practice protocols (p=0.007).

**Table 4** Screening protocols in different institutions with median values of scan parameters and effective dose calculations per protocol

<table>
<thead>
<tr>
<th>Number of simultaneously acquired slices</th>
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<th>16</th>
<th>4</th>
<th>1</th>
</tr>
</thead>
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<tr>
<td>Number of protocols</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tube Voltage (kV)</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Rotation time (s)</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Collimation (mm)</td>
<td>0.6</td>
<td>1.125</td>
<td>1.125</td>
<td>5</td>
</tr>
<tr>
<td>Effective mAs</td>
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<td>40/32¹</td>
<td>44</td>
<td>57</td>
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<tr>
<td>Dose modulation</td>
<td>7</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Effective dose (mSv)</strong></td>
<td><strong>5.8</strong></td>
<td><strong>5.6</strong></td>
<td><strong>7.8</strong></td>
<td><strong>4.3</strong></td>
</tr>
</tbody>
</table>

¹Results for median value of effective mAs for supine and prone (supine/prone).

**Sensitivity analysis parameters dose modulation**

Recalculations using 50% less or 50% more mAs correction than the nominal correction for the six institutions that provided data for deviant weight (Table 2) produced the following results: Effective doses per institution remained the same except for screening protocols in which the median dose for 50% less correction increased from 5.7 to 5.9 mSv. Recalculations for the five institutions that did not provide unambiguous information on weight resulted in a reduction of the median effective dose for daily practice from 9.1 to 8.9 mSv (for 75 kg) and to 8.2 mSv (80 kg) and for screening from 5.7 to 5.6 mSv and to 5.4 mSv for 75 and 80 kg, respectively.
Overranging planned trajectory of the volume examined
The increase in dose due to overranging of the planned trajectory of the volume examined was calculated for each CT protocol. For 64- and 40-detector-row CT systems the increase in dose was on the average 14%, for 16-detectorrow CT systems 10% and for 4-detector-row and singledetector-row CT systems 4%.

Comparison with CTC performed in 2004
We compared effective doses of the 17 institutions that also responded to our questionnaire in the first study. In this study only the effective doses for daily practice were determined. In these institutions the median effective dose for daily practice was at that time 11.0 mSv (range 4.2–21.0). In these figures the effect of overranging has been taken into account. The current median dose in these institutions is 9.7 mSv. This difference is not significant. In the present study, 17 institutions used dose modulation (50%) together with automatic current selection, while in 2004 no institution used this for CTC. Finally we compared the number of detector rows of the CT systems used in the earlier study and now. In 2004, 82% (23/28) of the institutions used a CT system with fewer than 16 detector rows and 18% (5/28) used a 16-detector-row CT system. In 2007 only 18% (6/34) used a CT system with fewer than 16 detector rows and 62% (21/34) used a 64-detector-row CT system.
### Table 5 Daily practice protocols

<table>
<thead>
<tr>
<th>City</th>
<th>Scanner Type</th>
<th>Slice number x Collimation</th>
<th>Voltage (kV)</th>
<th>Rotation time (s)</th>
<th>Pitch</th>
<th>Effective mAs</th>
<th>Effective dose supine (mSv)</th>
<th>Effective dose prone (mSv)</th>
<th>Total effective dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam</td>
<td>Philips Brilliance 64</td>
<td>64x0.625</td>
<td>120</td>
<td>0.75</td>
<td>0.984</td>
<td>58</td>
<td>3.2</td>
<td>3.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Bari</td>
<td>Toshiba Aquilion 16</td>
<td>16x1</td>
<td>120</td>
<td>0.5</td>
<td>0.875</td>
<td>29</td>
<td>3.0</td>
<td>3.0</td>
<td>6.1</td>
</tr>
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<td>Toshiba Aquilion 64</td>
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<td>48</td>
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<td>5.1</td>
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<td>Siemens Sensation 64</td>
<td>32 x 0.6</td>
<td>120</td>
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<td>1</td>
<td>205/82²</td>
<td>12.5</td>
<td>5.0</td>
<td>17.4</td>
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<tr>
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<td>Philips Brilliance 64</td>
<td>64 x 0.625</td>
<td>120</td>
<td>0.5</td>
<td>0.64</td>
<td>50</td>
<td>2.8</td>
<td>2.8</td>
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<td>Candiolo¹</td>
<td>GE Lightspeed 16</td>
<td>16 x 1.25</td>
<td>120</td>
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<td>25</td>
<td>2.0</td>
<td>2.0</td>
<td>4.0</td>
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<td>120</td>
<td>0.7</td>
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<td>178/25²</td>
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<td>2.0</td>
<td>16.1</td>
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<td>0.6</td>
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<td>100/28²</td>
<td>8.0</td>
<td>2.2</td>
<td>10.2</td>
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<td>Siemens Sensation 16</td>
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<td>1</td>
<td>200/60²</td>
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<td>GE Lightspeed plus</td>
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<td>2.8</td>
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<td>10.4</td>
</tr>
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<td>54</td>
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</tbody>
</table>

**Median per protocol**

---

¹ Institutions that use 2 scan protocols
² Protocol with different settings for supine and prone (supine/prone). The total effective dose is the sum of the supine and prone dose; for these calculations the not rounded off numbers are used.
<table>
<thead>
<tr>
<th>City</th>
<th>Scanner Type</th>
<th>Slice number x Collimation</th>
<th>Voltage (kV)</th>
<th>Rotation time (s)</th>
<th>Pitch</th>
<th>Effective mAs</th>
<th>Effective dose supine (mSv)</th>
<th>Effective dose prone (mSv)</th>
<th>Total effective dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bari</td>
<td>Toshiba Aquilion 16</td>
<td>16x1</td>
<td>120</td>
<td>0.5</td>
<td>0.875</td>
<td>29</td>
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<td>6.1</td>
</tr>
<tr>
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<td>Siemens</td>
<td>32 x 0.6</td>
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<td>0.5</td>
<td>0.75</td>
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<td>4.8</td>
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<td>1.375</td>
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</tr>
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<td>50</td>
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<td>50/30(^2)</td>
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<td>1</td>
<td>50/100(^2)</td>
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<td>Latina</td>
<td>GE VCT</td>
<td>64x0.625</td>
<td>120</td>
<td>0.5</td>
<td>1</td>
<td>100/50(^2)</td>
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<td>0.9</td>
<td>40/12</td>
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<td>16x1.25</td>
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<td>0.5</td>
<td>1.375</td>
<td>32</td>
<td>2.5</td>
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<td>Siemens Definition</td>
<td>32x0.6</td>
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<td>0.5</td>
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<td>90/100(^2)</td>
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<td>0.6</td>
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<td>4x1</td>
<td>120</td>
<td>0.5</td>
<td>1.25/1.40(^1)</td>
<td>80/30(^1)</td>
<td>4.9</td>
<td>1.8</td>
<td>6.7</td>
</tr>
<tr>
<td>New York (1)</td>
<td>GE Lightspeed 16</td>
<td>16x1.25</td>
<td>120</td>
<td>0.5</td>
<td>1.375</td>
<td>51</td>
<td>6.1</td>
<td>6.1</td>
<td>12.2</td>
</tr>
<tr>
<td>New York (2)</td>
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<td>1x5</td>
<td>120</td>
<td>0.5</td>
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<td>57</td>
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<td>2.1</td>
<td>4.3</td>
</tr>
<tr>
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<td>32x0.6/24x1.2</td>
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<td>34</td>
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<td>2.0</td>
<td>4.0</td>
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<tr>
<td>Pisa</td>
<td>GE Light Speed Plus</td>
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<td>0.5</td>
<td>1.5</td>
<td>37</td>
<td>1.7</td>
<td>1.7</td>
<td>3.3</td>
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</table>

Table 6 Screening protocols
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<th>Institution</th>
<th>Scanner Model</th>
<th>Tube Config. 1</th>
<th>Tube Config. 2</th>
<th>Tube Config. 3</th>
<th>Tube Config. 4</th>
<th>Tube Config. 5</th>
<th>Tube Config. 6</th>
<th>Tube Config. 7</th>
<th>Median per Protocol</th>
</tr>
</thead>
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<tr>
<td>Rochester¹</td>
<td>GE LightSpeed 16</td>
<td>16x0.625</td>
<td>120</td>
<td>0.5</td>
<td>1.375</td>
<td>62</td>
<td>5.7</td>
<td>5.7</td>
<td>11.5</td>
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<tr>
<td></td>
<td>Siemens Sensation 64</td>
<td>32x0.6</td>
<td>120</td>
<td>0.5</td>
<td>1.4</td>
<td>43</td>
<td>2.6</td>
<td>2.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Roeselare</td>
<td>Siemens Sensation 64</td>
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<td>120</td>
<td>0.5</td>
<td>1.4</td>
<td>10/30²</td>
<td>1.0</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Rome</td>
<td>Siemens Sensation 64</td>
<td>32x0.6</td>
<td>120</td>
<td>0.5</td>
<td>1</td>
<td>100/10²</td>
<td>6.1</td>
<td>0.6</td>
<td>6.7</td>
</tr>
<tr>
<td>San Francisco</td>
<td>GE VCT</td>
<td>64x0.625</td>
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<td>0.5</td>
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<td>7.5</td>
</tr>
<tr>
<td>Ulm</td>
<td>Philips Mx 8000</td>
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<td>0.75</td>
<td>1</td>
<td>42</td>
<td>2.8</td>
<td>2.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>

¹Institutions that use 2 scan protocols ²Protocol with different settings for supine and prone (supine/prone). The total effective dose is the sum of the supine and prone dose; for these calculations the not rounded off numbers are used.
DISCUSSION

In this dose evaluation study, we give an overview of the current protocols and estimates of the effective dose for CTC. A questionnaire was used to obtain information on the scanner types and CT parameters that are used at present for CTC. The effective doses were lower for the screening protocols than for the daily practice protocols, with median values of respectively 5.7 and 9.1 mSv (p<0.05). No differences in effective doses were found for the different detector row CT systems. The median effective dose of CTC for the institutions that also were included in the dose evaluation study of 2004 was slightly lower than in 2007 (9.7 and 11.0 mSv, respectively), but this difference was not significant.

It is not unexpected that the effective doses for screening protocols are lower than for daily practice protocols. When CTC is used as a screening procedure for patients at average risk for colorectal cancer, the radiation dose must be minimized to maintain the appropriate benefit-risk ratio.\(^{20,21}\) An earlier study has shown good diagnostic accuracy with low tube current protocols. Even for effective doses considerably less than 1 mSv per CTC examination (supine and prone), only a minimal, not significant decrease in sensitivity for polyps of ≥6 mm compared to a dose level of 10 mSv was found.\(^{10}\) Other studies have also shown that CT studies with a lower dose can give sufficient image quality for polyp detection.\(^{8,22,23}\) In this study a median dose for screening protocols of 5.6 mSv was found, with a range of 2.6 to 14.7 mSv. Obviously there is still ample opportunity for dose reduction in screening CTC. The number of CT systems with 16 or more detector rows now used for CT colonography has increased considerably in comparison with the previous questionnaire (2004).

In this study the effective dose for the 64-detector-row CT systems did not significantly differ from that found for 16- and 4-detector-row CT systems: for the daily practice protocols the dose was 9.1 mSv for 64-detector-row CT systems and 11.7 and 9.1 mSv for 16- and 4-detector row machines, respectively. All new CT systems can be operated with dose modulation with the possibility of dose reduction without loss of image quality.\(^{24}\) Half of the institutes now use dose modulation in their CTC protocols. Until now this appears not to have resulted in a reduction in effective dose. In comparison with the effective doses in 2004 of the former study, the effective doses for daily practice protocols showed a small, not significant reduction from 11.0 mSv in 2004 to 9.7 mSv at present. The effective doses for these protocols have thus remained virtually the same during the last few years. This may have different reasons. A number of institutions may value a higher image quality more than a lower dose. This hypothesis is supported by the large range of effective doses found in the present study: from less than 3 mSv to more than 20 mSv. Some of these differences may be explained by differences in the CT examination, for example, the use of intravenous contrast medium (which is mostly used for high-risk patients that require higher image quality) necessitates a higher dose.\(^{25}\)

This study has some limitations. Only 50 (60%) of the 83 institutions that were found with our search responded. Of the responding institutions 37 returned the questionnaire and 5 answered they had stopped performing CTC (in total 51% of all sent e-mails). A reason for not returning the questionnaire might be difficulties with obtaining
the CT parameters, especially for the institutions that use a CT protocol with dose modulation. The accuracy of data obtained with any questionnaire is never completely reliable, and that is especially the case in the present situation for the protocols with dose modulation. Of course more accurate results would have been obtained if we had examined a humanoid phantom in all institutions with their CTC protocol(s), but this was practically not feasible. A first uncertainty is that we made the approximation to use the average mAs value (instead of the actual, varying mA value) in the estimation of the effective dose. This appears to be a reasonable approximation, however.\textsuperscript{16}

Secondly, some institutions provided both effective mAs values and CTDI values and/or DLP values. In case discrepancies were present between these values, the effective mAs values were used in the dose calculations. Only for two institutions larger (>25%) discrepancies were present, however. We also performed an analysis to determine how sensitive the outcomes of the study are for any deviations in the data or assumptions in case of dose modulation. It appeared that the influence of the exact relation between weight and mAs value (Fig. 1) was limited. Also the exact choice of the weight for 5 of the 17 institutions that used dose modulation and did not provide unambiguous information on the weight of the patient influenced the results only to a limited degree.

Conclusion
The median effective dose for CTC colonography at present is significantly lower for screening protocols (5.6 mSv) than for daily practice protocols (9.1 mSv), which is important because of differences in benefit-risk ratios for patients in screening and in daily practice. We found that the use of CT systems with a different number of detector rows does not influence the effective dose. Furthermore, the current effective dose has not significantly changed compared to the dose in 2004, but the number of CTC protocols with dose modulation increased substantially.

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References

2007
Evaluation of a standardized CT colonography training program in novice readers

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Submitted
Abstract

**Purpose:** To evaluate a standardized CT colonography (CTC) training program in novice readers.

**Methods:** Six physicians (one radiologist, three residents and two radiology research-fellows) and three technicians started a CTC training program. A series of 200 CTC's with colonoscopic verification was selected from an existing research database, with 100 normal cases and 100 cases with at least one polyp $\geq 6$ mm. CTC reading was done individually with immediate feedback of the colonoscopy outcome after each CTC. The increase in per-polyp sensitivity was calculated per 50 CTC's, for lesions $\geq 6$mm. Using logistic regression analyses, the number of CTCs to reach 90% sensitivity for lesions $\geq 6$mm was estimated. Reading times were registered.

**Results:** The average per-polyp sensitivity for lesions $\geq 6$mm was 77% in the first set of 50 CTCs, 77% in the second set ($p=0.99$ vs. first set), 80% in the third set ($p=0.26$ vs. second set) and 91% in the fourth set ($p<0.001$ vs. the third set). The estimated number of CTCs to be evaluated to reach a 90% per polyp sensitivity for lesions $\geq 6$mm was 164. Six of the nine readers reached this level of competence within 175 CTCs. Reading times decreased significantly from the first 50 CTC's to the second 50 CTCs in 6 readers.

**Conclusions:** Novice CT colonography readers can obtain a sensitivity equal to that of experienced readers after practicing on average 164 CTCs. For most readers 175 CTCs are sufficient for adequate training, while some readers will need additional training after this.
INTRODUCTION

The evaluation of computed tomography colonography (CT colonography) examinations is preferably performed by experienced readers. It has been shown that carcinoma and polyp detection improve with practice. So far, no consensus exists about the level of experience and how the desired level can be acquired best. Several training programs have been developed, relying on different methods for training. These include reading of CT colonographies with colonoscopy feedback, peer reviewed reading of CT colonography, and a course with presentations of cases and instructions on the use of CT colonography software. The number of CT colonography examinations that has been recommended for adequate training varies from 50 to more than 100.

Training in interpreting radiological images is necessary to reduce errors in detection of abnormalities. Three types of errors are recognized: errors of search (the radiologists’ gaze completely misses the abnormality), errors of detection (the eyes of the radiologist pass over the abnormality but not long enough to be recognized) and errors of decision (the abnormality is not correctly identified). The first two types can be avoided when a reader gains experience in examining the specific exam. Errors of decision can be decreased when a set of examples of true and false positives is provided to a radiologist for training.

One study was using a teaching file of 40 CT colonographies in training radiologists and technologists. The investigators found that the trainees performed worse than experienced radiologists. Another study assessed the training effect in medical students and technologists using a teaching file of 50 cases. After this training the participants in the training program interpreted 50 cases, which resulted in a sensitivity and specificity similar to that of experienced radiologists. In yet another study novice readers were presented 100 CT colonography learning cases. The authors of this study concluded that computer aided detection can improve sensitivity in the first 20 cases.

So far, no study has tried to estimate the number of CT colonography examinations to be evaluated by physicians and technicians to reach a sufficient level of competence. There are some colonoscopy studies that have evaluated a learning curve in gastroenterology residents. One study found that for a sufficient competence in screening and diagnostic colonoscopy, an experience of more than 150 procedures is required. During the training period the cecal intubation time decreased and the success rate for completion of the procedure improved significantly, but the polyp detection rate remained equal. The aim of our study presented was primarily to determine how many CT colonography training examinations have to be evaluated by novice readers to obtain an adequate level of competence in polyp detection.
METHODS

Philips Medical Systems (Best, the Netherlands) provided CT colonography software and four workstations for this study. The authors had full control of all data and information submitted for publication.

Patient selection
Cases were selected from an existing database of 302 fecal occult blood test (FOBT) positive individuals between 50 and 75 years old, who had participated in a study reported in detail elsewhere. The study had been approved by the local Medical Ethics Committee. Informed consent was obtained from all participants, including informed consent for additional studies with the CT colonography examinations. All FOBT positive participants had received a bowel preparation of meglumine-ioxithalamate (Telebrix Gastro 300 mg I/ml; Guerbet, Cedex, France) starting two days (in total 7*50 ml of Telebrix Gastro) or one day (in total 4*50 mL of Telebrix Gastro) before CT colonography examination.

CT colonography had been performed with automatic insufflation of CO₂ (Bracco, PROTOCO2L insufflator, New York, USA) and scans were made in prone and supine positions. A low dose scan protocol was used on a 64-slice CT scanner (Brilliance, Philips Medical Systems, Best, the Netherlands) with 120 kV, pitch 1.2, slice thickness 0.9 mm, rotation time 0.4s, 40 ref mAs and dose modulation or on another 64-slice scanner (SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany) with 120 kV, 1.4, 0.5s and 32 reference mAs with dose-modulation. All CT colonography examinations had been read prospectively by two of seven experienced observers, who had read between 125 and 700 CT colonography interpretations with colonoscopic verification. Observers had marked all polyps and indicated the morphology, size and location. All CT colonographies of insufficient quality due to insufficient distension or inhomogeneous tagging of the feces judged by the experienced readers were excluded.

All participants had undergone a subsequent colonoscopy with segmental unblinding within 2 weeks after CT colonography. A radiology researcher [ML] had matched all CT colonography polyps with the found colonoscopy polyps based on criteria for size, location and morphology matching.

Case selection
A radiology CT colonography research fellow [ML] selected 200 CT colonography training cases from the series of 302. Cases were arranged in groups of 50 cases with equal lesion prevalence. In each group of 50 cases there were 25 normal examinations, i.e. without lesions ≥6 mm (i.e. polyps and carcinomas) at colonoscopy, and 25 examinations with lesions ≥6 mm. The 25 examinations with lesions ≥6 mm included approximately 15 examinations with one or more polyps of ≥10 mm and 10 examinations with one or more lesions between 6 and 9 mm. Table 1 summarizes the actual number of lesions per group of 50 cases, as well as the sensitivity of the double read of the two experienced readers in the previous study.
**Table 1** Distribution of lesions among the 200 cases

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Without lesions ≥6mm</th>
<th>1st 50 cases</th>
<th>2nd 50 cases</th>
<th>3rd 50 cases</th>
<th>4th 50 cases</th>
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<td>15</td>
<td>16</td>
<td>15</td>
<td>16</td>
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<tr>
<td>Lesions only between 6-9mm</td>
<td>10</td>
<td>8</td>
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<table>
<thead>
<tr>
<th>Number of lesions*</th>
<th>Number of polyps ≥10mm</th>
<th>9 pedunculated</th>
<th>7 sessile</th>
<th>2 flat</th>
<th>14 pedunculated</th>
<th>6 sessile</th>
<th>12 pedunculated</th>
<th>5 sessile</th>
<th>3 flat</th>
<th>11 pedunculated</th>
<th>4 sessile</th>
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<tr>
<td>Lesions 6-9mm</td>
<td>3 pedunculated</td>
<td>10 sessile</td>
<td>2 flat</td>
<td></td>
<td>6 pedunculated</td>
<td>10 sessile</td>
<td>5 flat</td>
<td></td>
<td>3 pedunculated</td>
<td>19 sessile</td>
<td>2 flat</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4 pedunculated</td>
<td>13 sessile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Sensitivity experienced readers (double read) | *Lesions ≥10mm | 95% | 95% | 86% | 94% |
|                                               | *Lesions ≥6mm  | 83% | 88% | 93% | 89% |

*Lesions include polyps (adenomatous and hyperplastic) and carcinomas.

**CT colonography training program**

Nine novice readers started and completed the CT colonography training program (see Table 2 for levels of radiological experience). They were one radiologist, three radiology residents, two radiology research-fellows and three technicians. None of the readers had any previous experience with CT colonography reading.

**Table 2** Experience of participating readers

<table>
<thead>
<tr>
<th>Reader</th>
<th>Experience in Radiology Department</th>
<th>FP training?</th>
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<tr>
<td>R1</td>
<td>12 years</td>
<td>No</td>
</tr>
<tr>
<td>R2</td>
<td>3 years</td>
<td>Yes</td>
</tr>
<tr>
<td>R3</td>
<td>4 years</td>
<td>Yes</td>
</tr>
<tr>
<td>R4</td>
<td>1 year</td>
<td>No</td>
</tr>
<tr>
<td>R5</td>
<td>½ year</td>
<td>No</td>
</tr>
<tr>
<td>R6</td>
<td>0 years</td>
<td>Yes</td>
</tr>
<tr>
<td>T1</td>
<td>3 years</td>
<td>Yes</td>
</tr>
<tr>
<td>T2</td>
<td>8 years</td>
<td>No</td>
</tr>
<tr>
<td>T3</td>
<td>33 years</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Radiologist, radiology residents and research fellows; *FP training in polyps and pitfalls

The training program started with reading two articles on pitfalls in CT colonography. Then a basic course was given, with presentations on anatomy and pathology of the colon, CT colonography bowel preparation, performance of the examination, CT colonography viewing methods and instructions on how to use the viewing software (see description of the course in Fig. 1). After this, all participants received an individual training of four CT
colonography cases by an experienced radiology CT colonography research fellow [M.L.],
mainly for instructions in using the software. Half of the readers - 2 technicians and 3 physicians - received an additional hour of training in pitfalls and polyps. The other group - 1 technician and 3 physicians - did not receive the additional training. The reader groups were matched on age and gender. The additional training consisted of 40 images of polyps, stool, lipomas, carcinomas, folds, diverticulas and veins. The correct lesion type had to be selected, using multiple choice questions. After each question, the correct answer was given immediately. Then 200 CT colonography cases were read individually on a workstation with specialized software (Philips View Forum, Version 6.2.2, Best, the Netherlands). A primary 3D read with 2D problem solving was done by all readers using an enhanced 3D viewing method (unfolded cube) after electronic cleansing. At the time of study the cleansing algorithm was not yet commercially available (View Forum, Philips Medical Systems, Best, the Netherlands).17 All readers performed a secondary 2D reading for evaluation of collapsed segments and uncleansed areas (if present). Readers recorded the level of certainty (0, 25, 50, 75 or 100%), diameter and location (cecum, ascending, transverse, descending, sigmoid colon or rectum) of all lesions found. The polyp diameter was measured in the 2D MPR setting using electronic calipers. All readers recorded the time used for examining the primary 3D and 2D read per position (supine and prone). After each case the reader was invited to verify the reading results by checking the colonoscopy matched lesions, which were also available on the workstation after finalizing the reading of that case. A radiology CT colonography research fellow [ML] was available for answering questions on false negative or false positive polyps. The last 25 cases were presented as an exam, so no feedback was available for the readers for these cases.

**Analysis of lesion detection**

Only lesions registered with a certainty level greater than or equal to 50% were taken into account for analysis. All lesions found by the novice readers that matched the previously found CT colonography lesions verified at colonoscopy were considered as true positives. Lesions reported by the novice readers that did not match the lesions verified at colonoscopy were considered as false positives. When a novice reader did not report a lesion in a case, and no lesion was found at colonoscopy, that was defined as a true negative. When the readers did not report a lesion, and lesions had been found at colonoscopy which had not been seen by any of the expert readers on CT colonography, these were also considered true negatives, since we wanted to compare novice readers to experienced readers. Most of these lesions were technical false negatives, i.e. retrospectively not visible (see reference 18). Lesions that were perceptive errors, i.e. retrospectively visible, in the original study were considered as true positive when found by the novice readers. A per-polyp analysis was performed to calculate sensitivity for lesions ≥10 mm and ≥6 mm. A per-patient analysis was performed for calculation of the specificity for lesions ≥6 mm.
Chapter 8 | CT colonography training of novice readers

**Fig. 1** Training program

We a priori determined a required level of sufficient polyp detection. This level was set at a sensitivity of 95% for lesions $\geq 10$ mm, 90% for lesions $\geq 6$ mm and a per-patient specificity of 80% for lesions $\geq 6$ mm. We chose these levels because they corresponded to the results of the individual experienced observers from our former study, when excluding the technical false negatives (i.e. retrospectively not visible) for calculation of the sensitivity.\(^{1}\)

**Statistical analysis**

Previous studies showed that a learning curve of 50 CT colonographies is not sufficient and that there can be an improvement in performance even after 100 CT colonographies. We estimated that 200 CT colonography examinations were necessary to evaluate whether novice readers could achieve the desired sensitivity level after the learning series.

We calculated the sensitivity and specificity for each set of 50 cases, for each reader separately, and for all readers combined. Changes in average sensitivity and specificity between consecutive sets of 50 cases were evaluated for statistical significance.
using the Chi-square test statistic. We also compared the average sensitivity and specificity per set of 50 cases of the group of readers who received the additional training to the group of readers who did not receive this training using the Chi-square test.

For each reader a learning curve was estimated using the outcomes of per-polyp sensitivity for lesions $\geq 10$ mm and lesions $\geq 6$ mm (including colorectal cancers, adenomas and hyperplastic polyps) and per-patient specificity for lesions $\geq 6$ mm. This curve was calculated using logistic regression analysis. We used restricted cubic splines to select the most appropriate functional relation between number of cases evaluated and sensitivity and specificity. We tested for a learning effect by comparing a null model (intercept only) with a model that included one or more coefficients for the number of cases evaluated, using the generalized likelihood ratio test statistic. For each reader separately and for the average of all readers the number of cases necessary to reach the desired level of competence for sensitivity and specificity was estimated based on the fitted logistic regression model.

Differences in reading time were calculated by comparing mean reading times in consecutive sets of 50 cases and comparison of outcomes were done using the student-T-test. Statistical analyses were performed using SPSS version 15.0.1 for Windows (SPSS). For all analysis, a p-value of $<0.05$ indicated a significant difference between groups.

RESULTS

Learning curve CT colonography

Per polyp sensitivity

The average sensitivity for lesions $\geq 6$ mm in the first set of 50 cases was 77% (95% CI: 72 to 82). In the second, third and fourth set of 50 cases the average sensitivity was 77% (95% CI: 72 to 81), 80% (95% CI: 76 to 84) and 91% (95% CI: 87 to 94) respectively. A significant difference in sensitivity was only found between the third and fourth set of 50 cases ($p<0.001$) but not between the first and the second ($p=0.99$), and between the second and the third set ($p=0.26$). In Table 3 the sensitivity for all readers is presented.

When we calculated the average sensitivity for lesions $\geq 6$ mm per 50 cases for the group of readers who had received the additional pitfalls training we found sensitivities of 77% (95% CI: 71 to 84), 75% (95% CI: 69 to 81), 79% (95% CI: 73 to 84) and 90% (95% CI: 85 to 95) respectively. For the readers who did not receive the additional training, sensitivities were 76% (95% CI: 68 to 83), 78% (95% CI: 72 to 85), 82% (95% CI: 76 to 88) and 91% (95% CI: 87 to 96) for the four sets of 50 cases respectively.

When comparing the sensitivities per sets of 50 cases of the readers who had received the additional training to the readers who did not receive training we found p-values of $p=0.77$, $p=0.51$, $p=0.41$ and $p=0.33$ respectively.
The sensitivity for lesions ≥10 mm was 83% (95% CI: 78 to 89), 96% (95% CI: 91 to 99), 96% (95% CI: 94 to 99) and 96% (95% CI: 93 to 99) for the four sets of 50 cases (Table 3). A significant difference was found between the first and second set of 50 cases (p<0.001), but not between later sets (p=0.72 and p=0.76, respectively).

Estimated individual sensitivity learning curves for polyps ≥6 mm are presented in Figure 2. When observing these curves it is visible that almost all readers first had an increase in sensitivity, then a slight decrease or plateau-phase after 80-100 cases whereafter sensitivity increased again.

Per patient specificity

The average per patient specificity for lesions ≥6 mm was 85% (95% CI: 81 to 89) for the first set of 50 cases, 88% (95% CI: 84 to 92), 87% (95% CI: 82 to 91) and 86% (95% CI: 81 to 90) for the second, third and fourth set of 50 cases, respectively. See table 3 for individual results of the learning curve specificity for lesions ≥6 mm. No significant differences between subsequent case groups were found. For lesions ≥10mm the average per patient specificity was 94% (95% CI: 91 to 97), 95% (95% CI: 92 to 97), 96% (95% CI: 94 to 98) and 97% (95% CI: 94 to 99) for the four respective sets of 50 cases. No significant differences between subsequent case groups were found.

---

**Table 3** Per polyp sensitivity

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesions ≥6mm</td>
<td>Lesions ≥10mm</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Cases</td>
</tr>
<tr>
<td>R1</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>R2</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>R3</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>R4</td>
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<td>89</td>
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<td>R5</td>
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<td>R6</td>
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<td>79</td>
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<tr>
<td>T1</td>
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<td>T2</td>
<td>73</td>
<td>66</td>
</tr>
<tr>
<td>T3</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Average</td>
<td>77</td>
<td>77</td>
</tr>
</tbody>
</table>

Percentages indicate sensitivity. Numbers between brackets are 95% Confidence Intervals.
Fig. 2 Per polyp analysis, lesions ≥6mm
When we calculated the specificity for lesions $\geq 6$ mm per 50 cases for readers who had received the additional pitfalls training we found specificities of 90% (95% CI: 85 to 95), 93% (95% CI: 89 to 97), 86% (95% CI: 80 to 92) and 85% (95% CI: 79 to 91) respectively. For the readers who did not receive the additional training, specificities were 79% (95% CI: 71 to 86), 81% (95% CI: 74 to 88), 87% (95% CI: 80 to 94) and 87% (95% CI: 80 to 94) for the four sets of 50 cases respectively. When comparing the specificities per sets of 50 cases of the readers who had received the additional training to the readers who did not receive training we found p-values of $p=0.01$, $p=0.05$, $p=0.89$ and $p=0.64$ respectively.

**Number of cases to reach the desired level of competence**

We estimated that, on average, readers would have to read 164 CT-colonography cases to reach a per-polyp sensitivity of 90% for polyps $\geq 6$ mm. In Table 4 the estimates for all individual readers are presented. Three readers (R6, T1 and T2) did not reach the desired level of per-polyp sensitivity within 200 cases. The other 6 readers had reached this level after 131 to 168 cases. When analyzing the per-polyp sensitivity for lesions $\geq 10$ mm we
found that on average 67 cases had to be examined to reach the desired level. Two readers (R1 and T2) did not reach this level. For the per-patient specificity of lesions ≥6mm we found that all readers, except reader R1, did not improve in specificity during the training program. The likelihood ratio test statistic did not reach significance. All readers had a specificity of 80% or more, except reader R1 (see Table 3).

Table 4 Number of cases per reader in order to reach the desired level of competence

<table>
<thead>
<tr>
<th>Reader</th>
<th>Sensitivity lesions ≥6mm¹</th>
<th>Sensitivity lesions ≥10mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>168</td>
<td>57</td>
</tr>
<tr>
<td>R2</td>
<td>146</td>
<td>53</td>
</tr>
<tr>
<td>R3</td>
<td>156</td>
<td>76</td>
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<tr>
<td>R4</td>
<td>131</td>
<td>57</td>
</tr>
<tr>
<td>R5</td>
<td>131</td>
<td>74</td>
</tr>
<tr>
<td>R6</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>T1</td>
<td>&gt;200</td>
<td>195</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>T3</td>
<td>163</td>
<td>61</td>
</tr>
<tr>
<td>Average</td>
<td>164</td>
<td>67</td>
</tr>
</tbody>
</table>

¹Desired level of competence for the sensitivity for lesions ≥6mm is 90%. ²Desired level of competence for sensitivity for lesions ≥10mm is 95%. ³Desired level of competence for specificity for lesions ≥6mm is 80%.

Reading times

Reader R1 did not register all reading times, therefore only the reading times from the other eight observers were analyzed. In fig. 3 all reading times per observer per 50 cases are given. The mean reading time for all observers was 12'58" (SD 4'52"). For the first 50 cases mean reading times for all observers were 16'26" (SD 5'55"), 12'09" (SD 4'04") for the second 50 cases (p<0.001 when compared to the first 50 cases), 11'30" (SD 4'06") for the third 50 cases (p=0.43 when compared to the second 50) and 11'48" (SD 3'24") for the last 50 cases (p=0.70 when compared to the third 50). Reading times decreased significantly from the first 50 CTC’s to the second 50 CTC’s in 6 readers.

DISCUSSION

The results of this study show that novice readers can reach a sensitivity equal to that of an experienced reader after practicing 175 CT colonography training cases with colonoscopy feedback. We estimated that an average number of 164 cases would be needed to reach a desired level of sensitivity in detecting lesions ≥6 mm. A few readers did not reach the desired level of sensitivity and specificity after 200 cases and probably would need more training.
It has been generally accepted that for adequate reading of CT colonography a dedicated training program with a sufficient number of training cases has to be followed.\textsuperscript{6} CT colonography is nowadays recognized as a possible screening technique and it can replace the barium enema examination for detection of both polyps and cancer.\textsuperscript{19-21} Consequently, this relatively new examination has become widespread in use and many new novice readers have to start reading CT colonography examinations. From earlier studies it became clear that more than 50 to 100 CT colonography cases were necessary to obtain a sufficient accuracy for lesion detection.\textsuperscript{5,7,9} In our study on average 164 CT colonography training cases were needed to gain a sufficient sensitivity. From a practical point of view, one could round up this number and use a CT colonography training program with 175 colonoscopy verified cases which most likely will suffice in the majority of observers. Three readers, of which two technologists and one radiology research fellow, did not reach this level, and probably need additional training. Because our study was limited to 200 cases we do not know the number of cases they should have to read additionally. It might also be possible that one or more of these readers will never reach an adequate level of competence.

Fig. 3 Reading times

Although we analyzed only a small number of readers, it became clear that different readers in a radiology practice are able to learn CT colonography: radiologists, radiology residents, radiology research fellows and technologists. Earlier studies have also shown that radiology residents and technicians can reach sensitivities similar to that of as radiologists.\textsuperscript{1,22} From our study it became clear that smaller lesions (6 to 9 mm) are more difficult to detect. A significant increase in sensitivity in detecting lesions \( \geq 6 \) mm was only
seen between 150 to 200 cases. For larger lesions, i.e. lesions ≥10 mm, we found an earlier increase, namely between 50 and 100 cases. This illustrates that smaller lesions are less conspicuous and readers need more perceptual learning to reduce the errors of search and detection.\textsuperscript{3,23} Other than errors of search and detection, errors of decision exist. These can be avoided when more knowledge on e.g. anatomy and pathology is obtained. For this reason we started our training program with a series of lectures. About half of the readers also received an additional training program on pitfalls in CT colonography. Some studies that evaluated CT colonography learning used a training program to teach CT colonography pitfalls and true positive lesions.\textsuperscript{2,4,24} In our study we did not find an effect on sensitivity of readers who received this additional training, but we did find an effect on specificity for lesions ≥6mm. The group of readers who did not receive the additional training had a significantly lower specificity in the first and second set of 50 cases than the group that received the additional training. This was however mainly due to one reader (R1) in the first group that had a very low specificity. It is however difficult to draw solid conclusions on this, because we only analyzed a small number of readers in our study.

When using CT colonography it is important to limit the number of false positive cases, because this will induce many unnecessary colonoscopies. We found that only one reader (R1) did not reach the desired level of specificity. All other readers stayed on a nearly constant level of specificity larger than 80% and no increase in learning was observed. This indicates that most readers will not report many false positives when they start reading CT colonography. Reader R1 however might have needed more training after 200 CT colonographies to reach a desired specificity level. A few other studies evaluated specificity in CT colonography training programs. In two studies the specificity increased, but this was observed in a training set of only 50 or 60 CT colonographies in total.\textsuperscript{2,3} In our study a training set of only 50 CT colonographies was not sufficient to gain an optimal sensitivity, thus an increase of specificity within the first series of 50 cases will not be relevant for the desired number of training cases.

Reading times decreased with learning, especially after the first 50 cases. These results are consisted with results of earlier studies. In the study of Hock et al. with 100 CT colonography cases reading times decreased from 15.67 minutes in the first training session (without CAD) to 13.42 minutes in the last session.\textsuperscript{4} In the study of Burling et al. experienced radiologists also reported significantly faster than novice radiologists and technicians.\textsuperscript{25}

Although we performed an extensive study on learning curves in CT colonography using a large training subset of 175 training cases and 25 exam cases, some aspects of training in CT colonography still remain unclear. We used a set of cases with a 50% disease prevalence, optimal for calculating both sensitivity and specificity. An enriched training set with a higher number of lesions might result in a steeper learning curve for sensitivity. The training set in the study of Dachman et al., for example, consisted of 83% abnormal CT colonography cases.\textsuperscript{2} A disadvantage of this method is that specificity is possibly less well trained, which could result in a higher number of false positives and consequently a lower positive predictive value in a daily practice, where lesion prevalence is much lower. Furthermore the use of CAD could influence the learning curve in novice
The most optimal training program is not clear yet and should be evaluated in further research.

This study has some limitations. A first limitation is that only one of the physicians was an abdominal radiologist, the others were residents and research fellows in training. One previous study showed that non radiologists can perform CT colonography equally good as radiologists. In our study one technologist and also most of the radiology fellows and residents performed equally or even slightly better than the radiologist. Because we only had a limited number of readers, differences between different reader groups could not be meaningfully calculated and tested for significance. A second limitation is that no feedback was provided in the last 25 cases, because these cases were considered as an exam in our department. Some of the readers (R1, R6 and T2) performed differently in those last cases, with a slight decrease in sensitivity and/or specificity (not significant). For example more fecal remnants and other polyp-like structures were marked as true lesion than in the previous cases. Thirdly we calculated the sensitivity considering only the true positive lesions of the experienced observers from our earlier study. Therefore the sensitivity percentages reported here cannot be compared to sensitivities reported in other studies. Fourthly, we only evaluated the learning curve using a primary 3D reading paradigm and not a 2D paradigm. Because previous research had shown that novice readers perform better when using primary 3D reading we have chosen to use only this reading paradigm. Fifthly, we did not analyze detection of carcinomas separately, because the number of carcinomas in our dataset was only small (see Table 1). We found it most important that true lesions were detected (either adenomas, carcinomas or hyperplastic polyps). Another limitation is that we evaluated a learning curve on patients that had received an iodine tagging bowel preparation, while using a cleansing algorithm. Therefore results might not be generalized to preparations with cathartic or barium preparations.

Conclusions
To conclude we found that CT colonography reading can be adequately performed after dedicated training by inexperienced radiologists, radiology fellows and radiology technicians. An average number of 164 CT colonographies with colonoscopic verification was needed to reach a sensitivity that equals that of an experienced reader. Six of nine readers reached the level of sufficient competence within 175 training cases. A few readers do not reach this level after 200 cases and might need more training or might even not be able to reach this level at all.

Acknowledgements
We thank Wouter van Elzelingen of the University of Amsterdam for his contribution to this study. We thank Philips Medical Systems for providing us their workstations for this project.
References

Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology.


Primary uncensored 2D versus primary electronically cleansed 3D in limited bowel preparation CT colonography. Is there a difference for novices and experienced readers?

Ayso H. de Vries
Marjolein H. Liedenbaum
Shandra Bipat
Roel Truyen
Iwo W. O. Serlie
Rutger H. Cohen
Saskia G. C. van Elderen
Anneke Heutinck
Oskar Kesselring
Wouter de Monyé
Lambertus te Strake
Tjeerd Wiersma
Jaap Stoker

ABSTRACT

*Purpose:* The purpose of this study was to compare a primary uncleansed 2D and a primary electronically cleansed 3D reading strategy in CTC in limited prepped patients.

*Materials and methods:* Seventy-two patients received a low-fibre diet with oral iodine before CT colonography. Six novices and two experienced observers reviewed both cleansed and uncleansed examinations in randomized order. Mean per-polyp sensitivity was compared between the methods by using generalized estimating equations. Mean per-patient sensitivity, and specificity were compared using the McNemar test. Results were stratified for experience (experienced observers versus novice observers).

*Results:* Mean per-polyp sensitivity for polyps 6 mm or larger was significantly higher for novices using cleansed 3D (65%; 95% CI 57–73%) compared with uncleansed 2D (51%; 95%CI 44–59%). For experienced observers there was no significant difference. Mean per-patient sensitivity for polyps 6 mm or larger was significantly higher for novices as well: respectively 75% (95%CI 70–80%) versus 64% (95%CI 59–70%). For experienced observers there was no statistically significant difference. Specificity for both novices and experienced observers was not significantly different.

*Conclusion:* For novices primary electronically cleansed 3D is better for polyp detection than primary uncleansed 2D.
INTRODUCTION

CT colonography (CTC) has consistently been shown to have a high accuracy for the detection of colorectal neoplasia, and has recently been included in the official guidelines for colorectal cancer screening. An important disadvantage of the technique is that many patients find the bowel preparation burdensome. Therefore efforts have been made to prepare patients for CTC with a less extensive bowel preparation. Minimizing bowel preparation may increase patient compliance, but will result in larger amounts of residual faeces in the colon. A prerequisite is that faecal material is labelled with oral contrast (i.e. faecal tagging) in order to differentiate faecal material from colonic structures.

To our knowledge, all limited prepared CTC studies have been performed using primary two-dimensional (2D) display methods. The rationale for this approach is that submerged segments can be better assessed in 2D. Previous studies in patients with extensive bowel preparation have indicated that primary three-dimensional (3D) reading may result in less false negative findings compared with primary 2D reading. If a similar empty endoluminal view could be achieved by electronic removal of tagged material (“electronic cleansing”) in patients who have undergone limited bowel preparation, primary 3D could be a method of choice.

However, specific artefacts of electronic cleansing were described that potentially reduced the accuracy of CTC. This may be the reason for the paucity of papers on the use of electronic cleansing. A specifically noticeable problem is posed by the distracting ‘ridges’ or ‘pseudopolyps’ emanating from locations where air, soft tissue and tagged material meet.

We hypothesized that especially for inexperienced observers a primary electronically cleansed 3D (PEC3D) method may have advantages for evaluation of the colon: polyps are visible for longer than in a 2D method and PEC3D provides a more intuitive reproduction of reality. In this study we used a cleansing algorithm that was devised to improve 3D image quality at the junctions of air, soft tissue and tagged material.

Therefore the purpose of this study was to assess whether there was any difference in accuracy between two different reading strategies for the detection of colorectal polyps in a patient population that had undergone a reduced bowel preparation. The results of primary uncleansed 2D (PU2D) and primary electronically cleansed 3D (PEC3D) were stratified for reader experience.

MATERIALS AND METHODS

Study population
The institutional review board of our hospital approved the study. All patients gave written informed consent. The CT datasets used in this study were a consecutive series of FOBT (faecal occult blood test) positive patients that were included in the framework of a previous comparative study of two different faecal occult blood tests.
Bowel preparation
Bowel preparation started 2 days before CTC and consisted of seven 50-ml aliquots of meglumine ioxithalamate (Telebrix Gastro 300 mg I/ml; Guerbet, Cedex, France) administered orally (undiluted) with each meal (breakfast, lunch and dinner). The use of oral contrast was combined with a low-fibre diet. The evening and morning before the CTC examination no solid foods were allowed. Explicit instructions about fluid intake were not given. No laxatives were used in order to minimize patient discomfort.

Scan parameters
CTC was executed according to state-of-the-art techniques. Patients were examined in prone and supine position after the intravenous administration of bowel relaxants (Buscopan; Boehringer Ingelheim, Germany or, if contraindicated, Glucagon; Novo-Nordisk, Bagsvaerd, Denmark). CO2 was automatically insufflated (PROTOCO2L, EZ-E-M). Patients were not given intravenous contrast medium. Examinations were performed on a 64-slice multidetector CT system (Brilliance, Philips Medical Systems, Best, the Netherlands) with a reference mA s value of 40 mA s (z-axis tube modulation and automatic current selection was used). Collimation was 64×0.625 mm, pitch 1.2, slice thickness 0.9 mm, rotation time 0.4 s and tube voltage 120 kV.

Reading methods
The examinations were read in random order i.e. the PU2D and PEC3D datasets were interspersed. The observers were blinded to the results of the reference standard. To avoid recall bias, we aimed to maximize the interval between the PU2D and PEC3D reading of the same patient. This period varied per observer (mean 33 days, range 7–66) (Table 1). All detected lesions were recorded in a digital database. The method of detection (PU2D or PEC3D), colon segment and size of the lesion (as measured in the primary review method) of all findings were documented.

Primary uncleansed 2D (PU2D)
The PU2D interface is illustrated in Fig. 1 (ViewForum 6.1, Philips Medical Systems), using axial CT images (W 1,250, L 50). Observers were free to adjust the window setting when appropriate. To further elucidate suspected findings on 2D, an uncleansed 3D display and a 3D colon overview could be viewed for problem solving. The dual-screen interface simultaneously displayed both supine and prone scan positions.

Primary electronically cleansed 3D (PEC3D)
The PEC3D interface is illustrated in Fig. 2. The unfolded cube review method (ViewForum 6.1, Philips Medical Systems) was developed to maximize the area of visible colon surface and was previously validated. The unfolded cube display method was simultaneously displayed with corresponding original—uncleansed—2D multiplanar reformatted images and a 3D colon overview for problem solving. The dual-screen interface simultaneously displayed both supine and prone examinations. At the time of study the cleansing algorithm (View-Forum, Philips Medical Systems, Best, the Netherlands) was not yet commercially available. In short, the
algorithm assumes that the measured density in a voxel arises due to a combination of three materials: soft tissue, air and tagged material. Initially, the percentage of materials in each voxel is determined. Subsequently, the partial volume of tagged material is replaced by air and the new density is calculated. Finally, a 3D method visualizes the colon from an endoluminal perspective as if there were no faecal remains. During the study the algorithm was not yet integrated into the system and was therefore processed on a separate computer (Precision 690, Dell, Round Rock, USA). Afterwards, the cleansed data were reloaded on the workstation.

Table 1 Individual observer performance in PU2D and PEC3D

<table>
<thead>
<tr>
<th>Observer</th>
<th>Experience</th>
<th>Number of primary 2D CTC’s verified by colonoscopy</th>
<th>Number of primary 3D CTC’s verified by colonoscopy</th>
<th>Review times (s)</th>
<th>Mean interval (days) between both review methods (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2D</td>
<td>3D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Novice</td>
<td>40</td>
<td>50</td>
<td>765</td>
<td>870 (0)</td>
</tr>
<tr>
<td>2</td>
<td>Experienced</td>
<td>500</td>
<td>100</td>
<td>574</td>
<td>593 (15)</td>
</tr>
<tr>
<td>3</td>
<td>Novice</td>
<td>40</td>
<td>10</td>
<td>756</td>
<td>964 (36)</td>
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<td>4</td>
<td>Novice</td>
<td>40</td>
<td>10</td>
<td>404</td>
<td>376 (7)</td>
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<tr>
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<td>Novice</td>
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<td>10</td>
<td>259</td>
<td>419 (60)</td>
</tr>
<tr>
<td>6</td>
<td>Experienced</td>
<td>300</td>
<td>50</td>
<td>432</td>
<td>579 (66)</td>
</tr>
<tr>
<td>7</td>
<td>Novice</td>
<td>40</td>
<td>10</td>
<td>634</td>
<td>795 (30)</td>
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<tr>
<td>8</td>
<td>Novice</td>
<td>40</td>
<td>10</td>
<td>403</td>
<td>447 (20)</td>
</tr>
</tbody>
</table>

Mean experienced observer

Mean novice observers

Mean interval (days) between both review methods (SD)

SD standard deviation *Denotes statistically significant difference between the review methods of both groups

Fig. 1 Interface of the PU2D method

Uncleansed 3D images were used for problem solving. In the corresponding scan positions a large stalked polyp can be seen in the descending colon
Observers
Eight physicians participated in this study: two experienced observers (two research physicians working full time on CTC) and six novice observers (five radiologists, one recently qualified physician). The two experienced observers had seen over 350 CTC examinations verified by colonoscopy (among these the 75 patients included in this study). All novice observers, without any notable prior experience with CTC, had undergone the same learning curve. The learning curve consisted of 50 selected CTC examinations from a publicly available database.\textsuperscript{17} Forty examinations were read using a primary 2D method and 10 using a primary 3D method. The ratio for this distribution was the assumption that detecting lesions in 2D is more difficult than in 3D, although the assessment of a suspected lesion is similar in both review methods. Personal feedback on false negative and false positive findings for polyps 6 mm or larger was provided by a radiology research fellow (more than 500 CTC examinations verified by colonoscopy). The observers were aware of the fact that the actual study was done on FOBT positive patients.

Reference standard
The reference standard was based on the findings of the initial CTC reading, which was double read by two experienced observers (more than 200 CTC) and verified by colonoscopy with segmental unblinding. Colonoscopy was performed within 2 weeks after CTC. A polyp seen during CTC was considered true positive if (1) its appearance resembled the corresponding adenomatous or nonadenomatous polyp at colonoscopy, (2) its segment or adjacent segment corresponded with the segment of the reference standard and (3) the polyp size as estimated by the endoscopist corresponded with the CTC size, considering a margin of error of 50%. Since the colonoscopy measurement is subject to inaccuracy,\textsuperscript{18,19} this criterion could be overruled by the first two criteria. All other annotations were considered false positives.
The relation of polyps to faecal material
To illustrate the influence of faecal material on the visibility of polyps, a research fellow determined whether each polyp was completely covered by faecal material (i.e., completely submerged in both positions), partially covered by faecal material (i.e., not covered in both scan positions but at least partially covered in at least one position) or not covered by faecal material at all.

Power analysis
A power calculation was performed based on an assumed 15% difference between the methods in sensitivity for polyps 6 mm or larger (i.e., 70% versus 85%). The number of visible polyps required to detect a statistically significant difference by using the McNemar test was 75 (p=0.05). As we expected some of the patients to be excluded due to insufficient diagnostic quality, we included a total of 75 examinations of FOBT positive patients that had 84 visible polyps.

Performance
Per polyp
To investigate differences between PU2D and PEC3D, we calculated the mean per-polyp sensitivity for both experienced and novice readers. Statistical differences between the review methods were assessed by using generalized estimating equations (GEE) (SPSS, 15.0, Statistics, Chicago, USA) to revise for data clustering and dependency. In this GEE method, regression analyses were performed to compare the mean sensitivity values of the two methods. Since the per-polyp specificity cannot be calculated because it is a nonexisting entity, we confined the per-polyp results to the number of false positive findings.

Per patient
Other main outcome per-patient parameters were per-patient sensitivity and specificity. Statistical differences in mean per-patient sensitivity and mean specificity measures were assessed with the McNemar test. Both mean per-polyp and per-patient outcome measures were analysed according to cutoff values of 6 and 10 mm. P values <0.05 were considered statistically significant.

Review time
The review time, defined as the time measured with a stopwatch to review a complete examination, was compared for both methods. The review time did not include the time required for processing the images. These procedures are highly dependent on calculation power, are performed semiautomatically and require no reviewer interaction. Differences in mean review time of experienced and novice observers were assessed with a paired Student’s t test. P values <0.05 were considered statistically significant.

Image quality
The image quality of the examinations was rated (after reading) on a four-point Likert scale: diagnostic without artefacts; diagnostic with a small number of artefacts, polyps 6
mm or larger cannot be missed; diagnostic with many artefacts, polyps 6–9 mm can be missed; not diagnostic, polyps 10 mm or larger can be missed.

Firstly, if at least four observers rated the examination as "not diagnostic" the patient was excluded. Secondly, we determined the percentage of PU2D and PEC3D examinations in the various rating categories. The percentage represented the mean rating of all eight observers. Thirdly, we assessed per-observer differences in quality between PU2D and PEC3D using ordinal regression analysis with PU2D as reference standard. A lower relative diagnostic odds ratio (RDOR) implies inferior image quality of the PEC3D compared with the PU2D. Confidence intervals not reaching 1 indicate significant inferiority. Fourthly, each observer determined the presence of artefacts per examination. The impact of each artefact on the "readability" of the examination was assessed on a four-point Likert scale: not disturbing; disturbing, but cannot hinder detection of polyps 6 mm or larger; disturbing, can cover polyps 6–9 mm; and disturbing, can cover polyps 10 mm or larger. We report the number of patients with artefacts observed by at least four observers and the number of patients with artefacts classified by at least four observers as "disturbing, can cover polyps". These were analysed according to cutoff values of 6 and 10 mm.

RESULTS

All 75 patients were scanned between October 2006 and January 2007 and underwent colonoscopy within 9.4 days (SD 6.6 days). We excluded three of the 75 patients because more than four observers rated the diagnostic quality of three PEC3D examinations "not diagnostic". In 2D these examinations were rated by one to three observers as "not diagnostic". The remaining 72 patients consisted of 38 men and 34 women (mean age 59.5 years, SD 6.4 years, range 50–73). Bleeding during polypectomy was reported for three patients, none of whom required reintervention. No adverse events were reported to occur in any of the CT examinations.

A total of 90 polyps 6 mm or larger were detected: 17 polyps were 20 mm or larger (median size 25 mm, range 20–40 mm), 36 polyps were 10–19 mm (median size 11 mm, range 10–17 mm) and 37 polyps were 6–9 mm (median size 7 mm, range 6–9 mm). The histology revealed 82 adenomatous polyps, 4 nonadenomatous polyps and 4 colorectal carcinomas. Polyps 6 mm or larger were found in 50 out of 72 patients (69%) and polyps 10 mm or larger were found in 34 out of 72 patients (47%). As shown by Table 2 a substantial part of most polyps was covered by faecal material.

Performance

Per polyp

Mean per-polyp sensitivity for novices and experienced observers for both review methods are listed in Table 3. Novice observers had a significantly higher mean sensitivity when using PEC3D for polyps 6 mm or larger (+14%, p<0.001), 6–9 mm (+19%, p<0.001) and 10 mm or larger (+9%, p<0.001). Within the group of novice observers there was a considerable difference in sensitivity for both review methods (Tables 3 and 4), despite the
fact that all observers had undergone a similar training protocol. For experienced observers there was no significant difference in mean sensitivity between both methods for polyps 6 mm or larger ($p=0.755$), 6–9 mm ($p=0.170$) and 10 mm or larger ($p=0.207$).

Table 2 Relation of polyps to faecal material

<table>
<thead>
<tr>
<th>Polyp Description</th>
<th>6-9 mm</th>
<th>6-9 mm</th>
<th>≥10 mm</th>
<th>≥10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyps completely covered by faecal material in both scan positions</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Polyps partially covered by faecal material in one or both scan positions or completely covered in one position</td>
<td>13</td>
<td>35</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>Polyps not covered by faecal material at all in both scan positions</td>
<td>18</td>
<td>49</td>
<td>22</td>
<td>42</td>
</tr>
<tr>
<td>In retrospect not visible in both scan positions</td>
<td>5</td>
<td>14</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total number of polyps</td>
<td>37</td>
<td>100</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>

Table shows the number (n) and percentage of visible polyps either completely covered by faecal material, partially covered by faecal material or not covered by faecal material at all in two scan positions. Polyps that are not visible at all are reported as well.

Table 3 Per-polyp sensitivity and false positives rate of experienced observers and novices

<table>
<thead>
<tr>
<th>Observer</th>
<th>Experience</th>
<th>Per-polyp sensitivity</th>
<th>Number of false positives</th>
<th>Number of false positives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥6 mm (95% CI)</td>
<td>≥6 mm (95% CI)</td>
<td>≥6mm (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2D</td>
<td>3D</td>
<td>2D</td>
</tr>
<tr>
<td>2</td>
<td>Experienced</td>
<td>80% (70-87)</td>
<td>65% (47-79)</td>
<td>91% (79-96)</td>
</tr>
<tr>
<td>6</td>
<td>Experienced</td>
<td>78% (69-85)</td>
<td>57% (43-70)</td>
<td>92% (79-98)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>79% (70-86)</td>
<td>61% (46-74)</td>
<td>92% (79-97)</td>
</tr>
<tr>
<td>1</td>
<td>Novice</td>
<td>63% (53-71)</td>
<td>42% (27-58)</td>
<td>77% (66-85)</td>
</tr>
<tr>
<td>3</td>
<td>Novice</td>
<td>59% (50-67)</td>
<td>38% (24-54)</td>
<td>74% (59-84)</td>
</tr>
<tr>
<td>4</td>
<td>Novice</td>
<td>56% (45-66)</td>
<td>27% (14-45)</td>
<td>75% (59-87)</td>
</tr>
<tr>
<td>5</td>
<td>Novice</td>
<td>53% (44-62)</td>
<td>24% (12-42)</td>
<td>74% (61-83)</td>
</tr>
<tr>
<td>7</td>
<td>Novice</td>
<td>29% (21-39)</td>
<td>8% (3-23)</td>
<td>45% (31-57)</td>
</tr>
<tr>
<td>8</td>
<td>Novice</td>
<td>49% (35-64)</td>
<td>22% (9-43)</td>
<td>70% (54-62)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>51%* (44-59)</td>
<td>27%* (17-39)</td>
<td>69%* (59-77)</td>
</tr>
</tbody>
</table>

Individual per-polyp sensitivity is stratified for polyp size; 95% confidence intervals are between brackets.

*Denotes statistically significant difference between the review methods.

Per patient

The per-patient performance characteristics for PU2D and PEC3D are shown in Table 4. Novice observers had a significantly higher mean sensitivity when using PEC3D for polyps.
6 mm or larger (+11%, p<0.001) and 10 mm or larger (+6%, p=0.033) compared with PU2D. For experienced observers there was no significant difference in mean sensitivity between both methods for polyps 6 mm or larger (p=0.549) and 10 mm or larger (p=0.125). Specificity for novice observers when using PEC3D was not significantly lower for polyps 6 mm or larger (p=0.057) and 10 mm or larger (p=0.36) compared with PU2D. For experienced observers there was no significant difference for polyps 6 mm or larger (p=0.5) and 10 mm or larger (p=1.0) as well. Thus, specificity did not significantly differ between both methods in any size category for both experienced and novice observers.

Table 4 Per-patient sensitivity and specificity of experienced observers and novices

<table>
<thead>
<tr>
<th>Observer Experience</th>
<th>Per patient sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2D</td>
</tr>
<tr>
<td></td>
<td>≥6mm (95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>2 Experienced</td>
<td>88% (79-97)</td>
<td>(91-100)</td>
</tr>
<tr>
<td>6 Experienced</td>
<td>84% (74-94)</td>
<td>(91-100)</td>
</tr>
<tr>
<td>Mean values</td>
<td>86% (79-93)</td>
<td>(93-100)</td>
</tr>
<tr>
<td>1 Novice</td>
<td>71% (58-84)</td>
<td>(69-95)</td>
</tr>
<tr>
<td>3 Novice</td>
<td>74% (62-86)</td>
<td>(73-97)</td>
</tr>
<tr>
<td>4 Novice</td>
<td>68% (55-81)</td>
<td>(73-97)</td>
</tr>
<tr>
<td>5 Novice</td>
<td>70% (57-83)</td>
<td>(77-99)</td>
</tr>
<tr>
<td>7 Novice</td>
<td>42% (28-56)</td>
<td>(42-75)</td>
</tr>
<tr>
<td>8 Novice</td>
<td>62% (48-76)</td>
<td>(57-95)</td>
</tr>
<tr>
<td>Mean values</td>
<td>64% (59-70)</td>
<td>(74-86)</td>
</tr>
</tbody>
</table>

Individual per-patient sensitivity and specificity are stratified for polyp size; 95% confidence interval are between brackets) *Denotes statistically significant difference between the review methods

Review time

For novice observers mean review time for PU2D was 8.9 min (range 4.3–12.8 min) compared with 10.8 min (range 6.3–16.1 min) for PEC3D (p<0.001). For experienced observers the review times were respectively 8.4 min (range 7.2–9.6 min) and 9.8 min (range 9.6–9.9 min) (p<0.001). For most observers PU2D was faster. One observer evaluated the examinations faster in primary cleansed 3D method (Table 1).

Diagnostic quality

The mean rating of the diagnostic quality is displayed in Table 5. Figure 3 shows that all observers rated the image quality of PEC3D significantly lower than PU2D, as the confidence intervals did not reach 1. Floating debris (Fig. 4) and holes in the colon wall (Fig. 5) were important causes of artefacts in PEC3D (Table 6). According to the

156
observers, floating debris in particular may hinder the diagnostic accuracy by covering polyps 6 mm or larger. In PU2D virtually no disturbing artefacts were reported.

Table 5 Mean rating of diagnostic quality

<table>
<thead>
<tr>
<th>Image quality of the examinations</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not diagnostic, polyps 10 mm or larger can be missed</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Diagnostic with many artefacts, polyps 6-9 mm can be missed</td>
<td>4%</td>
<td>18%</td>
</tr>
<tr>
<td>Diagnostic with a small number of artefacts, polyps 6 mm or larger cannot be missed</td>
<td>20%</td>
<td>53%</td>
</tr>
<tr>
<td>Diagnostic without artefacts</td>
<td>69%</td>
<td>19%</td>
</tr>
<tr>
<td>Unknown</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table displays the percentage of PU2D and PEC3D examinations in the various rating categories. The percentage represented the mean rating of all eight observers in 72 patients.

Table 6 Number of patients with artefacts

<table>
<thead>
<tr>
<th>Artefacts</th>
<th>Number of patients</th>
<th>Number of patients having artefacts classified as “disturbing, can cover polyps 6 mm or larger”</th>
<th>Number of patients having artefacts classified as “disturbing, can cover polyps 10 mm or larger”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary electronically cleansed 3D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floating debris</td>
<td>55 (76%)</td>
<td>18 (25%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Holes in the colon wall</td>
<td>39 (54%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Windmill artefacts</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ridges</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Primary uncleansed 2D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Windmill artefacts</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Insufficient faecal tagging</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table displays the number of patients with artefacts observed by at least four observers, the number of patients having artefacts classified by at least four observers as “disturbing, can cover polyps 6 mm or larger” and the number of patients having artefacts classified by at least four observers as “disturbing, can cover polyps 10 mm or larger.”
Fig. 3 Image quality assessment showing regression coefficients of primary electronically cleansed 3D (PEC3D). It estimates the change in the log transformed diagnostic odds ratio (DOR) compared with primary uncleansed 2D (PU2D). A lower relative diagnostic odds ratio (RDOR) implies inferior image quality. Confidence intervals not reaching 1 indicate significant inferiority. Thus, this figure shows that all observers rated the image quality of PEC3D significantly less qualitative than PU2D.

Fig. 4 Floating debris (black arrow) as a result of incomplete electronic cleansing of inhomogeneously tagged faecal material (grey arrow on 2D image)
DISCUSSION

This study shows that novice observers (compared with experienced observers) have a higher sensitivity in limited prepared patients when using PEC3D compared with PU2D. The higher sensitivity comes without a statistically significant lower specificity. On average more review time was needed for PEC3D. Paradoxically, despite its superior performance in polyp detection, the image quality of PEC3D was rated significantly less than for PU2D.

Recently, two comparative studies of primary 2D and primary 3D review methods have addressed the merit of both techniques. As in this study, more polyps of 6 mm or larger were detected using primary 3D, although in only one study the difference was statistically significant. The reason for this superior sensitivity may be that abnormalities are visible to the observer for longer. Secondly, polyps that may have a similar appearance to folds on 2D are easier to distinguish from folds in 3D. However, the fact that primary 3D is often not used in CTC is probably based on practical grounds such as long review time and high computer requirements associated with this review technique in the past. Compared with the abovementioned previous studies, in this study patients underwent a limited bowel preparation. There is a risk that the reported superiority of 3D

Fig. 5 Hole in the wall on the 3D image (black arrow). The white arrow indicates the corresponding colon wall in 2D. After electronic cleansing, the colon wall has become so thin that virtual holes appear between two air-containing structures
in polyp detection would be neutralized by the reduction of visible colonic surface. In this study we report a large number of at least partially submerged polyps. This increases the risk of overlooking polyps.\textsuperscript{21,22} This is the reason why electronic cleansing was used in the 3D examinations.

Electronic cleansing has been subject to study for several years now.\textsuperscript{16,23–27} Recently two comparative studies of electronic cleansing were published. In both studies electronic cleansing had an additional value in terms of sensitivity for some observers.\textsuperscript{23,24} In this study we assumed it had an additional value as well: nearly half of the polyps were in at least one position at least partially covered by faecal material (Table 2). Specific artefacts of electronic cleansing are described in the literature\textsuperscript{13} e.g. ridges, pseudopolyps due to partial volume effect and floating debris due to untagged faecal material. These may be the reason that electronic cleansing for primary CTC evaluation has not often been used. The electronic cleansing algorithm we used in this study was specially designed to overcome artefacts of distracting ‘ridges’ emanating from locations where air, soft tissue and tagged material meet.\textsuperscript{16} These ridges were in fact noted by none of the observers in this study. Floating debris, though, was detected in the majority of patients examined in PEC3D (Table 6). An important cause of debris is noise due to heterogeneously or insufficiently tagged stool. The three patients were excluded because of these artefacts. These artefacts stress the fact that more than just a good cleansing algorithm is important in order to achieve good 3D image quality i.e. a good tagging regimen, good patient compliance and good CT parameters. However, the three excluded patients were rated in PU2D by one to three observers “not diagnostic” as well.

This stresses the fact that although 3D is more susceptible to tagging artefacts, 2D suffers from heterogeneous or insufficient tagging as well. Artefacts were seen in the majority of patients reviewed in PEC3D. To be able to easily distinguish artefacts from polyps, it is important to be able to correlate electronically cleansed 3D images with complementary original uncleansed 2D images. This combination has limited the number of false positive findings when using PEC3D (Table 3). Using PEC3D did not statistically decrease specificity for any observer group at any size per-patient threshold i.e. true negative patients were not erroneously classified using PEC3D.

We have not studied a primary 3D reading method without electronic cleansing or primary 2D with electronic cleansing. Although interesting from a methodological point of view, we think that these approaches are not meaningful; the former is not since a large number of (partially) submerged polyps are prevented from being detected because they are otherwise covered by faecal material; the second approach is not since there is no need to electronically remove faecal material that can already be distinguished from colonic structures. However, one study\textsuperscript{23} demonstrated an additional value in terms of polyp detection of cleansing in a 2D approach. An important difference compared with our study is the nature of the preparation: barium instead of iodine and no low-fibre diet. This results in more adherent and solid stool that is “mentally” more difficult to read than the quiet homogeneous fluid levels seen in our patient population. Therefore, electronic cleansing may prevent reader fatigue in this patient population.

The mean difference between PU2D and PEC3D was in accordance with the expected difference between both techniques. However, the expected baseline sensitivity
for polyps 6 mm or larger was higher (70%) than the actual measured sensitivity (51%).
This had consequences for the statistical power of the comparison; however, statistical
significance was still reached for the group of inexperienced readers. The higher per-polyp
sensitivity of PEC3D mainly concerned polyps 6–9 mm (Table 3). The prevalence of
adenomas with advanced features (i.e. villous components or high-grade dysplasia) in this
size category tends to be low.28 The joint guideline of the American Cancer Society, the US
Multi-Society Task Force on Colorectal Cancer and the American College of Radiology
recommends colonoscopy and polypectomy for polyps 6 mm or larger.1 Thus, polyps in
this size category may not be neglected. The novice observers were trained according to
the recommendations of the American College of Radiology and the European Society of
Gastrointestinal and Abdominal Radiology;29,30 50 CTC studies with 20–50% prevalence
with personal feedback on all false positive and negative findings for polyps 6 mm or
larger.29 The response to training, though, is unpredictable and competence cannot be
assumed after 50 cases.31

In this study the two experienced observers (350 CTCs or more) outperformed
the six novice observers. Thus, it is likely that the optimum number of training cases is
more than 50, as suggested earlier.32 However, the difference between these levels of
experience in PEC3D is less than PU2D. So, in the phase of familiarization with CTC
primary cleansed 3D is advantageous. The group of experienced readers consisted of two
observers compared with the group of inexperienced readers that consisted of six
observers. In general, experienced observers show less difference in polyp detection
between review methods33 and will perform better when compared with inexperienced
readers. Therefore, we expected the differences between both review methods to be
insignificant in a very experienced observer group. This was confirmed by the two
experienced reviewers in this study who performed very well using both methods. Thus,
we think that although interesting from a methodological point of view adding four extra
reviewers would not change the conclusion of this study.

A computer-aided detection algorithm has not been used in this study. Its effect
will be twofold when applied to electronically cleansed data: the number of detectable
polyps will increase as well as the number of detected artefacts. Since these effects are
not yet balanced, this will be subject to further research.

This study has limitations. First the prevalence of polyps in this FOBT positive
population was fairly high compared with an asymptomatic screening population. This may
limit the generalization to an average risk screening population. Secondly, in this patient
population we used a low-dose scan protocol combined with sub-millimetre slices. Noise in
the images may have limited the quality of the cleansing since faecal material appeared
less homogeneous. Still, the quality of the images was rated diagnostic in the vast
majority of the cases i.e. only three cases were excluded. Thirdly, all patients had been
prepared with oral iodine tagging resulting in a fairly homogeneously tagged colon
content. Probably any electronic cleansing algorithm will perform optimal with
homogeneously tagged stool.27 Accordingly, we expect the algorithm to be better suited
for removing pools of (iodine) fluid compared with adherent heterogeneous faecal residue
encountered in barium tagging. Fourthly, before this study the experienced observers had
evaluated all patients in the framework of a comparative study of colonoscopy and CTC
(http://rsna2008.rsna.org/event_display.cfm?em_id=6012336). These patients were
evaluated at least 1 year before this study with a primary 2D review method. In the period in between both studies at least 100 other CTC examinations were read. So, it is not likely that this has influenced the performance characteristics of the experienced observers. Fifthly, in this study we have used an enhanced 3D display i.e. the unfolded cube display. The advantage of this technique is that it covers nearly all colonic mucosa without image distortion in a single fly-through,\textsuperscript{15} compared with the conventional 'endoscopic' view that needs a bidirectional fly through to cover nearly all colonic mucosa. Therefore, our approach is a more time efficient method than a conventional 3D technique.\textsuperscript{15} This may limit the generalizability of difference in review time, however not in accuracy.

**Conclusions**
In summary, we conclude that novice observers have a significantly higher sensitivity for the detection of clinically relevant polyps when using primary electronically cleansed 3D compared with primary 2D. For experienced observers, who performed better overall, there is no difference between both methods. Specificity is not affected when using primary electronically cleansed 3D. Therefore we recommend primary electronically cleansed 3D for novice observers in evaluating CTC in patients that have undergone limited bowel preparation.

**Acknowledgments**
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References

CT colonography polyp matching: differences between experienced readers

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ABSTRACT

Purpose: The purpose of this study was to investigate if experienced readers differ when matching polyps shown by both CT colonography (CTC) and optical colonoscopy (OC) and to explore the reasons for discrepancy.

Methods: Twenty-eight CTC cases with corresponding OC were presented to eight experienced CTC readers. Cases represented a broad spectrum of findings, not completely fulfilling typical matching criteria. In 21 cases there was a single polyp on CTC and OC; in seven there were multiple polyps. Agreement between readers for matching was analyzed.

Results: For the 21 single-polyp cases, the number of correct matches per reader varied from 13 to 19. Almost complete agreement between readers was observed in 15 cases (71%), but substantial discrepancy was found for the remaining six (29%) probably due to large perceived differences in polyp size between CT and OC. Readers were able to match between 27 (71%) and 35 (92%) of the 38 CTC detected polyps in the seven cases with multiple polyps.

Conclusions: Experienced CTC readers agree to a considerable extent when matching polyps between CTC and subsequent OC, but non-negligible disagreement exists.
INTRODUCTION

Computed tomography colonography (CTC) is an established diagnostic technique for both symptomatic and screening patients. The diagnostic performance of CTC has generally necessitated comparison between CTC and subsequent optical colonoscopy (OC). Such comparisons are often performed by an experienced radiologist who uses prespecified criteria to match polyps identified by CTC with those found at subsequent OC.

A variety of matching criteria have been described, usually based on the location, size, and morphology of polyps. For example, a correct matching may be assumed when the polyp identified by CTC is found in the same or adjacent colonic segment as the polyp detected by OC. For convenience the colon is usually divided into six segments: caecum, ascending, transverse and descending colon, sigmoid and rectum.

For size matching a frequently described criterion stipulates that the CTC polyp must be within 50% of the diameter measured at colonoscopy. Matching based on general morphology may also be performed. However, observers using identical criteria may nevertheless match different polyps because the matching procedure is subjective and requires interpretation of both CTC and colonoscopy data. Furthermore, variation in the matching criteria stipulated by different researchers hinders comparisons between different studies.

The purpose of our study was to investigate to what extent experienced readers differ when matching polyps between CTC and OC and to explore the reasons underpinning any differences. Ultimately we aimed to develop criteria to minimize matching disagreement with a view to improve study methodology and facilitate interstudy comparisons.

METHODS

Eight highly experienced CTC researchers from six centres in Europe and the USA participated. We administered a questionnaire to document their current criteria for polyp matching. To investigate matching in daily practice, the eight readers were asked to match preselected cases. Reader experience varied from 250 to over 3,000 CTC interpretations and between 100 and 3,000 CTC cases with corresponding OC.

Questionnaire

The questionnaire presented multiple choice questions relating to matching criteria used by readers for their research studies (Table 1). Options were formulated based on descriptions of matching criteria from the literature.

Patients

A radiology researcher (M.L.) selected 28 cases from two research databases of 170 surveillance patients and 240 faecal occult blood test positive patients who had undergone
both CTC and subsequent colonoscopy. These studies had been approved by the local Medical Ethics Committee and informed consent was obtained from all participants. All CTC examinations had been read prospectively by one of four experienced observers, each with at least 100 CTC interpretations with colonoscopic verification. Observers had marked any polyp and indicated the morphology, size, location, and their confidence. Colonoscopy with segmental unblinding was performed subsequently by a gastroenterologist, gastroenterology resident, or gastroenterology nurse under supervision. Maximal polyp diameter was estimated by using an opened biopsy forceps and in some cases with a linear measure probe additionally (Olympus America). All colonoscopies were videotaped starting from the caecum.

Case selection
As the present study aimed at evaluating concordance when matching polyps between CTC and OC, selection was biased towards cases likely to prove challenging. A research fellow experienced in matching (>250 matched CTC and OC studies) selected cases with polyps that failed to meet the typical matching criteria specified by the literature. For example, a polyp at CTC whose location apparently differed two segments or more from the location suggested by colonoscopy. Only technically adequate CTC examinations were selected so as not to confound matching, by insufficient distension, for example.

Twenty-one cases were selected where a single polyp at CTC and OC had to be matched by the experienced reader. To evaluate a broad spectrum of potential matching scenarios, in 13 cases the CTC and colonoscopy data were purposely perturbed so that two different patients were combined. In this way, different morphologies and/or locations could be presented to the reader. Figure 1 illustrates examples of three cases. Seven other cases were selected that had multiple polyps at CTC and/or OC. Again, difficult cases were purposely selected whose polyps could not necessarily be matched using established criteria.

Reviewing matching cases
All readers performed the observations at their own department and were free from clinical commitments during the matching procedure. Readers were free to use their own visualization software to read cases, but a laptop with View Forum software (Version 6.2, Philips, Best, Netherlands) was also available. Polyps initially found by the CTC observer (in the original research study) were presented to the readers by a researcher with information on morphology, size, location, and certainty of diagnosis scored by the observer. The experienced readers were able to remeasure the polyps if they wished. Colonoscopic information was also available to the readers: colonoscopy videos, diameter information, and location and morphology.

Polyp matching
Readers completed a data form for each case. For the 21 single-polyp cases the readers indicated whether they considered the CTC and OC polyp a correct match. If readers believed the two polyps were not the same, the researcher queried their reasoning and classified each mismatch as due to disagreement relating to: (1) diameter; (2) morphology; (3) location.
Table 1. Questionnaire matching

1. What information do you use for the matching procedure? *(more than one answer possible)*
   - Colonoscopy video
   - Colonoscopy report
   - Pictures of colonoscopy polyps
   - Other: .................................................................

2. What information from the gastroenterologist concerning the polyps you need for matching? *(more than one answer possible)*
   - Size of the polyp
   - Segmental location
   - Morphology
   - Distance of endoscope from anus to lesion
   - Information of pathologist about histology
   - Other: .................................................................

3. Do you use morphology criteria for matching CTC polyps with colonoscopy polyps?
   - Yes → go to question 4
   - No → go to question 5

4. If yes, morphology matching is based on *(more than one answer possible)*:
   - The description of the morphology of the gastroenterologist (flat, sessile, pedunculated) resembles the description of the morphology of the CTC observer.
   - The polyp at CTC has a similar appearance/shape as the colonoscopy polyp (judged by the observer that is performing the matching)
   - Other: .................................................................

5. What is the definition you use for flat lesions? *(Please fill in the number of mm)*
   - The width is at least 2 times the height of the lesion
   - The lesion protrudes less than .. mm* from the mucosa
   - The surface of the lesion is flat and not convex
   - Other: .................................................................

6. Do you use size criteria for matching a CTC polyp with a colonoscopy polyp?
   - Yes, the CTC polyp and colonoscopy polyp need to have the same size
   - No, size is no criterion for matching → go to question 8

7. If matching is done according to size range, the size range must be within: *(indicate percentage)*
   - The CTC polyp must be maximally...%* smaller and ...%* larger than the colonoscopy polyp
   - The colonoscopy polyp must be maximally...%* smaller or ...%* larger than the CTC polyp
   - The size of the lesion at CTC can be maximally ...%* smaller than the measured lesion size at colonoscopy or can be any size larger
   - Other: .................................................................

8. Do you use the segmental location for matching the CTC and colonoscopy polyps?
   - Yes → go to question 9
   - No

9. If yes, the location matching is based on:
   - The CTC polyp must be in the same segment (e.g. cecum, ascending, transverse or descending colon, sigmoid or rectum) as the colonoscopy polyp
   - The CTC polyp must be in the same or most nearby half of the adjacent segment as the colonoscopy polyp
   - The CTC polyp must be in the same or adjacent segment as the colonoscopy polyp
   - The CTC polyp must be in the same or next 2 adjacent segments as the colonoscopy polyp
   - The CTC polyp must be in the same or next ... adjacent* segments as the colonoscopy polyp *(please indicate number)*
   - Other: .................................................................

In the seven multiple-polyp cases, readers were invited to indicate which of the polyps presented to them matched and which they believed did not. Again, reasons for mismatching were explored.
Fig. 1 a Case 2; CTC polyp: caecum, 7.1 mm, sessile. OC polyp: ascending colon, 3 mm, sessile. From left to right: 2D image, 3D image, colonoscopy image. In this case all eight readers indicated a match. b Case 15; CTC polyp: sigmoid, 5.2 mm, sessile. OC polyp: ascending colon, 6 mm, sessile. In this case only one reader indicated a match. c Case 19; CTC polyp: descending colon, 17.9 mm, pedunculated. OC polyp: pedunculated, 6 mm, pedunculated. Four of the eight readers indicated a match

**Statistical analysis**

Because cases were preselected, only descriptive statistics were performed. A per case analysis was performed for the 21 single-polyp cases; for each case the number of the eight observers reporting a match was determined. For size and location matching we determined the number of instances in which a reader did not adhere to their own matching criteria, prespecified by them in the questionnaire. Of the seven multiple-polyp cases, the number of matched polyps per size category (≥10 mm, 6 to <10 mm, or <6 mm) was counted per case and summarized per observer. Reference diameter was colonoscopic excepting nonmatched CTC polyps.
RESULTS

Questionnaire
All readers stated that they normally use colonoscopy reports or a case record form completed during colonoscopy for polyp matching. Seven readers used video stills of colonoscopic polyps; four readers also used colonoscopy videos; two readers also employed pathology reports for polyp diameter information. All readers normally required endoscopic information relating to segmental location, size, and morphology. Six readers defined a flat lesion as one whose width must be at least twice its height; two also stated that the polyp must protrude less than 3 mm from the mucosa. The remaining two readers exclusively used this latter definition for flat lesions. Three readers wished to have information about the distance of the polyp from the anus and two wished to have histology information to facilitate matching. Table 2 details the different criteria described by readers for matching.

Single-polyp cases
Agreement amongst readers could concern agreement on the presence of a match as well as the lack of presence of a match in a case, both important aspects in matching. Disagreement amongst readers in a case means that about half of the readers concern the presence of a match and the other half not.

In the 21 cases with a single polyp, readers considered a match between CTC and OC to be present in between 13 (62%) and 19 (90%) of cases, i.e., there was some disagreement as to whether a match between CTC and OC was possible or not due to a perceived unacceptable discrepancy for one or more of the typical matching criteria (size, location, and morphology).

Table 2 Different matching criteria indicated by eight readers in the questionnaire

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Size</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CTC polyp needs to have a similar appearance/shape as the colonoscopy polyp (8)</td>
<td>-Size of the CTC polyp has to be within 50% of the colonoscopy polyp size (4)</td>
<td>-Polyps are in the same or adjacent segment (6)</td>
</tr>
<tr>
<td>-And description of morphology by the gastroenterologist resembles that of the CTC observer (6)</td>
<td>-Size of the CTC polyp can be maximally 50% smaller or 100% larger than the colonoscopy polyp (1)</td>
<td>-Polyps are in the same segment (1)</td>
</tr>
<tr>
<td>-Size of the colonoscopy polyp has to be within 50% (1) or 40% (1) of the CTC polyp size</td>
<td>-Polyps are within a reasonable distance (judged by the CTC radiologist who is performing the matching) (1)</td>
<td></td>
</tr>
</tbody>
</table>

The numbers within parentheses indicate how many readers use the specific matching criterion

To evaluate the magnitude of this disagreement we analyzed the per case agreement or disagreement. We then found that the readers agreed completely or almost completely in 15 of 21 cases with respect to the presence or lack of a match of CTC and
Complete agreement was present in five cases in whom all eight readers agreed on a match. Almost complete agreement on matching (i.e., seven of eight readers indicated a match) was present in seven cases, whereas almost complete agreement on the lack of matching was present in three cases. In six of the 21 cases, however, a considerable disagreement in matching was found. In five cases only four readers indicated a match, and in one case five readers indicated a match. Figure 2 indicates how many cases readers agreed and disagreed in matching the CTC and colonoscopy polyp.

To explore the rationale underpinning this disagreement we evaluated data separately for cases with location, size, and morphology discrepancies. In the five cases that were selected for segmental location difference between the CTC and colonoscopy polyp, there was a high matching agreement across readers. Nearly all readers refused to match polyps where the CTC and colonoscopy location differed by three or more adjacent segments. Regarding the ten cases where diameter disagreements ostensibly prevented matching between the CTC and colonoscopy, in five cases nearly all readers in practice ignored diameter discrepancies of more than 100% between the CTC and colonoscopy polyp. In the other five cases, while diameter discrepancies of more than 100% again existed between polyps, only four of eight readers (in four cases) and five of eight readers (in one case) found matching possible, indicating poor agreement existed. In cases with different morphology, agreement for matching was high except for a single case; case 21 demonstrated a faecal residue at CTC and a polyp at colonoscopy in which only four of eight readers performed a match between the faecal residue and a polyp.

Overall, 55 polyps (mean 6.9 polyps per reader) were matched by readers despite individual polyps not fulfilling the criteria for matching on the basis of diameter prespecified by each reader. Overall, 12 polyps (mean 1.5 polyps per reader) were matched despite not fulfilling criteria prespecified by readers for segmental location. Two polyps were matched despite not fulfilling both diameter and segmental criteria.

**Fig. 2** Agreement and disagreement amongst readers in matching 21 single polyp cases. At the x-axis agreement or disagreement in matching is presented. The number of cases is given on the y-axis. In the ideal situation, all readers agree on the presence (8/8) or the lack (0/8) of a match; this means complete matching agreement (gray bar). When only half the readers agree on a match and the other half do not agree (4/8) this is complete matching disagreement (gray bar). When only seven of eight readers indicate a match or no match there is almost complete matching agreement (black bar).
### Table 3
Number of matched polyps per reader in the multiple-polyp cases

<table>
<thead>
<tr>
<th>Reader</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Case 2</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Case 5</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Case 6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Case 7</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31</strong></td>
<td><strong>34</strong></td>
<td><strong>33</strong></td>
<td><strong>31</strong></td>
<td><strong>33</strong></td>
<td><strong>27</strong></td>
<td><strong>32</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

The numbers of matched polyps (all sizes) are indicated per reader. The total number of matches per reader is presented in the last row.

### Multiple-polyp cases

The seven cases with multiple polyps had 11 CTC polyps and 12 colonoscopy polyps of 10 mm or larger, 18 CTC and 12 colonoscopy polyps of 6–9 mm, and nine CTC and 20 colonoscopy polyps smaller than 6 mm. The total number of polyps matched per reader varied from 27 to 35 (Table 3). In case 3, for example, one reader matched five polyps on CTC with OC, while another reader matched nine. For CTC polyps of 10 mm or larger, the number of matches per reader showed less variation, between 9 and 11 (Table 4). For polyps smaller than 6 mm the inter-reader variability was larger, with the number of matches varied from 7 to 14. The number of false negative CTC polyps of 10 mm or larger per reader ranged from one to three and the number of false positive CTC polyps of 10 mm or larger ranged from zero to two. Reasons for not matching CTC and colonoscopy polyps were mismatching due to location, size, and morphology.

### Table 4
Numbers of true positive, false positive, and false negative CTC polyps per size category per reader in the multiple-polyp cases

<table>
<thead>
<tr>
<th>Reader</th>
<th>TP ≥10mm</th>
<th>TP 6-9mm</th>
<th>TP &lt;6mm</th>
<th>FN ≥10mm</th>
<th>FN 6-9mm</th>
<th>FN &lt;6mm</th>
<th>FP ≥10mm</th>
<th>FP 6-9mm</th>
<th>FP &lt;6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Case 2</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Case 3</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Case 4</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Case 5</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Case 6</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Case 7</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

TP true positive polyp, i.e., a CTC polyp that was matched with a colonoscopy polyp; FN false negative polyp for CTC, i.e., a colonoscopy polyp that was not matched with a CTC polyp; FP false positive polyp for CTC, i.e., a CTC polyp that was not matched with a colonoscopy polyp. Reader 2 had interpreted one case wrongly and this case was therefore excluded.
Observations
Six readers remeasured polyps on CTC when a large diameter difference was apparent between it and the OC polyp. To resolve this, four readers disagreed with the diameter recorded by the colonoscopist and reinterpreted the size of the OC polyp shown on video. To determine polyp location precisely, two readers thoroughly examined the colonoscopic video to clarify the colonic segment or location of the polyp compared to a fold. Four readers occasionally scrutinized the morphology of the polyp at video, especially in pedunculated cases (e.g., to determine stalk length) and cases with flat polyps.

DISCUSSION
We have investigated if disagreement exists between experienced readers when attempting to match polyps identified by CTC and subsequent colonoscopy. Eight experienced CTC researchers apparently used similar matching criteria, based on polyp location, size, and morphology. Readers largely agreed when matching cases with single polyps. We found, however, substantial disagreement in a minority but non-negligible proportion of cases. Disagreement was also present in cases with multiple polyps but predominantly for the least relevant polyps, i.e., those smaller than 6 mm.

The CTC literature describes various matching criteria, based on expert opinion rather than an evidence-based approach. Evidence-based matching criteria are difficult to formulate because a robust reference standard for matching corresponding CTC and colonoscopy polyps poses very substantial methodological difficulties. We did not aim to validate matching criteria. Rather, we investigated how readers matched in practice and the level of disagreement between them. While we found substantial agreement there was also non-negligible disagreement, predominantly due to a large perceived diameter difference between CTC and OC. This was not a constant observation, however, because some cases with similar discrepancies were matched by most readers. The reasons underpinning this observation were unclear, despite us asking readers for their rationale.

Discrepancy was also noted in those cases with multiple polyps. For the most clinically important polyps ($\geq 10$ mm), we observed minimal disagreement. In populations with a low prevalence of polyps, matching is less problematic because few polyps need be matched. However, when the number of polyps per patient increases, matching will likely become less straightforward and we have demonstrated inter-reader disagreement. After case matching, readers were asked for their matching criteria via a questionnaire. All readers reported practically identical matching criteria (described in the Introduction).

While these criteria are apparently straightforward, in practice there are several problems. Difficulties when matching location exist because anatomical borders are ill-defined and colonoscopists frequently cannot locate the endoscope tip with precision. In our study almost all readers took this into account and were prepared to match polyps that were not within the same or adjacent colonic segments. Another problem exists when matching based on polyp diameter. Colonoscopic estimation of diameter is imprecise. We found that most readers remeasured CTC polyps and often redefined the colonoscopist’s assessment
of diameter from the video provided. Hence apparently large diameter differences between polyps did not always preclude a match. Matching of polyps based on morphology also differed between readers because judgment of morphology is subjective. While definitions of lesion morphology are clearly described,\textsuperscript{15} we found that readers often used different definitions for flat lesions at CTC.

Because we found that experienced readers did not always adhere to established matching criteria, we propose that disagreement is best resolved by consensus. At the very least, two readers would then have to consider whether a match between a polyp imaged by both CTC and OC was possible, which is likely to reduce error and uncertainty. Such an approach is inevitably time consuming and an alternative is to perform consensus matching only when polyps do not satisfy generally accepted criteria for matching. However, as we have stated, these criteria are not evidence-based and our study was not designed to provide such a base. However, we do propose a matching procedure (Fig. 3) suggesting consensus matching by at least two experienced readers where cases do not satisfy conventional matching criteria. Optimally, at least one observer should be a radiologist and the other a colonoscopist since both have different attributes.

A potential limitation of our study is that we did not present pathology reports or the histological diameter of excised polyps. It is however questionable whether these data would provide useful additional information since polyps often shrink after polypectomy due to electrosurgical tissue effects and vascular collapse.\textsuperscript{16} Another limitation is that our cases were purposely biased towards difficult cases. This was done to magnify any inter-reader variation in a pragmatic manner. Although this approach was efficient, as a consequence it was impossible to calculate meaningful metrics applicable to real-world scenarios.

![Matching procedure of CTC and colonoscopy polyps](image)

\textsuperscript{1}6 colonic segments are considered: caecum, ascending, transverse and descending colon, sigmoid and rectum. \textsuperscript{2}Consensus matching must be performed with at least two experienced persons, preferably one radiologist and one gastroenterologist. \textsuperscript{3}CTC and colonoscopy polyp have a similar appearance/shape (judged by the observer who is performing the matching).
Conclusions
In summary, we found that experienced CTC readers agree to a considerable extent when matching polyps detected by CTC to those found at subsequent OC in difficult cases, but non-negligible disagreement exists. Such disagreement may explain data variation of some studies on the diagnostic accuracy of CTC. We suggest using a consensus to minimize disagreement when matching those cases that do not satisfy established matching criteria.
References

Summary of findings and implications
SUMMARY OF FINDINGS AND IMPLICATIONS

In this thesis several aspects of CT colonography have been discussed. All cohort studies reported in this thesis have included patients with a positive faecal occult blood test (FOBT). In these patients different minimal bowel preparations with iodine contrast agent were tested. We evaluated the accuracy of polyp detection and triage with CT colonography, assessed the learning curve of novice readers and different viewing methods, and evaluated radiation dose and matching of polyps by expert readers.

When the bowel preparation for a colonic examination is very burdensome, patient compliance for the ingestion of the preparation might be reduced. An advantage of CT colonography compared to colonoscopy is that cathartic agents are not necessary; a contrast agent that ‘tags’ the faeces is sufficient. One then needs to find a balance between patient burden and image quality, one that is adequate and leads to an optimal polyp detection. Cathartic agents will cause a liquid consistency of the faeces and/or will reduce the amount of faeces in the colon. A tagging agent mixes with the residual faeces, facilitating differentiation between the colon wall, polyps and faeces. An iodine contrast agent is often hyperosmotic and can result in diarrhoea just like the cathartic preparations. This makes it necessary to assess the patient burden for this preparation.

In the study reported in chapter 2 a one-day and a two-day preparation scheme with an iodine faecal tagging agent (meglumine ioxithalamate, 300 mg I/ml) were compared in 100 patients. We found that when using a one-day preparation consisting of four times 50 ml of contrast agent and a low-fibre diet, the patient burden from diarrhoea was lower than when using the two-day preparation, while image quality remained excellent. The density of the tagged faecal residues was high and comparable in both preparation groups and also the homogeneity did not differ between both groups. When results of polyp detection in both preparation groups were compared we found no significant differences. The conclusion of this study was that a one-day preparation is preferred over a two-day preparation.

In studies that use tagging only bowel preparations often a low-fibre or low-residue diet is prescribed. The hypothesis is that fibres are not digested and cause an inhomogeneous mixing with the oral contrast agent which results in untagged stool particles. Yet no study had shown that a specific diet is necessary for an optimal tagging. In chapter 3 a study is described that compared 2 groups of 25 patients; one group used a tagging only preparation with a low-fibre diet, while the other group used the same tagging preparation but without a diet before the CT colonography. In the second group we found more untagged pieces of stool and a trend towards a decreased tagging quality. Because of these reasons, the number of false positive findings can increase, and it can possibly affect the sensitivity for polyp detection. No significant differences in sensitivity between groups were found, but this was probably due to the relatively low number of patients per group.
Our findings in this study suggest that a low-fibre diet is necessary to optimize image quality in a tagging-only iodine bowel preparation.

In chapter 2 we showed that a one-day preparation with four times a 50 ml dose of iodine contrast agent resulted in an excellent tagging quality. Subsequently we investigated if a lower amount of iodine contrast agent would also be sufficient for optimal tagging while further decreasing patient burden. In the study reported in chapter 4 we compared three groups of 15 patients who received different doses of iodine contrast; group 1 received three times a 50 ml dose of iodine, group 2 received four times a 25 ml dose and group 3 received three times a 25 ml dose. We found that group 1 had the best tagging quality; in group 2 and 3 more untagged stool pieces and more adherent faeces was found. The homogeneity and homogeneity ratio (=homogeneity/density) were higher in group 2 and 3, resulting in a decreased tagging quality. Three times a 50 ml iodine dose was thus considered the best preparation, despite the higher patient burden.

Overall, we showed in chapter 2 to 4 that an oral iodine contrast agent ingested the day before the examination can give an excellent image quality with a significant decrease in patient burden, compared to the cathartic preparation of the colonoscopy. When the dose of this iodine contrast agent is lowered from 350 ml to 150 ml the image quality decreases, but in most patients the colon can still be evaluated properly. A problem is that, when using only 75 ml, in some colonic segments the faeces is not homogenously tagged and untagged stool particles remain. The addition of barium may improve the image quality, as barium tags the solid components of the faeces. We did not test the combination of an iodine and barium preparation, as has been used in some other studies, because we wanted to keep the instructions to the patients as simple as possible. Another option to improve the image quality is to use a cleansing algorithm that subtracts the (inhomogenously) tagged stool. The problem is that insufficiently tagged faecal residues are not subtracted by the cleansing algorithms that are currently available and visibility on the colon wall is hampered, especially at 3D views. With the development of improved cleansing algorithms, even less extensive bowel preparations could be used, leading to a decrease in patient burden while maintaining image readability.

Screening for colorectal carcinoma can reduce the mortality from colorectal cancer. Several screening methods exist. The most simple and least expensive test shown to reduce the mortality of colorectal carcinoma is the faecal occult blood test (FOBT). A disadvantage of this test is that it has a relatively low sensitivity and a low positive predictive value resulting in a large number of false positives. These false positive patients will receive a colonoscopy without any benefit. One option to reduce the number of unnecessary colonoscopies is to use CT colonography as a triage test after a positive FOBT, in an effort to select only those patients that have relevant colonic lesions. This strategy has been evaluated in chapter 5. We found that CT colonography is unlikely to be an efficient triage technique in a first round of FOBT screening. Reasonably high positive predictive values but relatively low negative predictive values were obtained. The burden from the CT colonography was rated as less than that of the colonoscopy. Due to the high lesion prevalence in FOBT positive patients, a high number of patients would have
to undergo two examinations – both CT colonography and colonoscopy – if CT colonography was to be used as a triage technique. We conclude that CT colonography cannot be used efficiently as a triage technique in this first round FOBT population screening.

An explanation for the low negative predictive value of CT colonography is that the effectiveness of triage has to be evaluated based on size. As the goal of screening has been defined as the detection of cancer and large adenomatous polyps, we used a lesion size cut-off at CT colonography to decide whether or not to refer patients for colonoscopy. Only patients with at least one lesion of a certain size – 10 mm, or 6 mm or larger - were considered as CT colonography positives. When the size of the lesion measured at CT colonography was below this cut-off, say 5 mm, the patient was considered a CT colonography negative. It is possible that in this case the same lesion, when found at colonoscopy, would measure 6 mm. If so, the patient would have been classified as a false negative for CT colonography. If the method of polyp matching had been used to determine the accuracy (thus allowing a certain difference in size between CT colonography and colonoscopy), this same patient would be considered a true positive for CT colonography.

Another important reason for the low negative predictive value was that the number of FOBT positive patients with relevant lesions was very high; half of the patients had at least one lesion of 10 mm and larger. Consequently a relatively small number of true negative patients remained which resulted in a lower negative predictive value than would have been in a population with a lower lesion prevalence. Because of these reasons CT colonography does not seem useful in a first round FOBT population screening. But in second or third rounds where the lesion prevalence is possibly lower, CT colonography might become more useful as a triage test. To investigate this, future research should be performed.

In the study described in chapter 6 the detection of advanced neoplasia with CT colonography in an FOBT positive population was evaluated. In this study we used the method of matching polyps between CT colonography and colonoscopy to estimate sensitivity and specificity. We found that CT colonography has a high diagnostic accuracy for the detection of colorectal neoplasia in an FOBT positive screening population. Even with the use of a limited bowel preparation, the sensitivity of CT colonography in the detection of large adenomas and carcinomas was similar to that of colonoscopy. Furthermore we found that double reading and additional 3D reading increased the sensitivity of CT colonography. Although CT colonography should not be used as a triage test in a first round FOBT positive population, it could be used in FOBT positive patients that cannot or are not willing to undergo colonoscopy. Our results on the sensitivity and specificity for detection of colorectal carcinomas and adenomas equal that of studies that evaluated CT colonography in screening and in symptomatic patients.

When CT colonography is used for screening purposes the risks of complications should be kept at a minimum. One of the risks associated with CT colonography is the development
of radiation induced cancer. A higher effective radiation dose will increase the mortality from radiation induced cancer. It is therefore important to minimize the radiation dose as much as possible, although it is still unclear what the exact risks of radiation are. Not only screening participants will benefit from a lower radiation dose, but also patients receiving CT colonography examinations in daily practice. Chapter 7 presents a dose evaluation study among all research institutions with publications on CT colonography between January 2004 and January 2007. We found that radiation doses of scan-protocols used for screening (median dose 5.7 mSv) were significantly lower than that of daily practice protocols (median dose 9.1 mSv). Although the median effective doses were quite low, the range of different doses among institutions was very wide (range 2.8-22.0 mSv). Some institutions used an effective dose ten times higher then the dose in other institutions. This suggests that awareness of the possibility to decrease the effective dose should be extended among institutions that perform CT colonography. Even very low doses, e.g. 2 to 3 mSv, can be sufficient for an optimal visualisation of the colon and colonic polyps. It would be interesting to investigate in the next few years whether the effective doses of CT colonography have decreased further in these institutes.

In previous studies it has been shown that novice CT colonography readers have a lower sensitivity and specificity in polyp detection than experienced readers. Some CT colonography training studies have been performed but after 100 examinations readers were still not trained well enough to reach an accuracy identical to that of experienced readers. Up till now it remained unclear how many cases should be practiced to obtain a sufficient sensitivity and specificity. We performed a CT colonography learning curve study among radiographers and physicians using 200 CT colonography datasets with colonoscopic verification in chapter 8. We found that after an average number of 164 cases the novice readers were capable to read a CT colonography with a high sensitivity for detection of lesions of 6 mm and larger. Three of nine readers however did not reach a sufficient sensitivity after 200 cases. All novice readers, except one, had an average specificity higher than 80% for lesions 6 mm and larger, and no learning in specificity was observed during the training program. From these results we can conclude that most novice readers will reach an adequate level of polyp detection within 175 CT colonography training cases. When the desired level is not reached after this number of cases, additional training will be necessary. Because the number of cases in our study was limited to 200, we do not how many cases these readers will additionally need to practice to reach a level of sufficient polyp detection. It is also possible that these readers might even not be able to reach this level at all. Furthermore we evaluated only one training program with a certain prevalence of lesions. A training program with, for example, a higher lesion prevalence or a more extensive pitfalls training might result in different outcomes.

Specialized software for reading CT colonography exists that can visualize the colon in a three-dimensional view (3D view). Two reading strategies for reading a CT colonography are available: a primary 3D read with a 2D problem solving or a primary 2D read with 3D problem solving. An automatic subtraction of the tagged faeces can be done by specific ‘cleansing’ software so that at the 3D images faecal material cannot obscure polyps. We investigated which of the two reading paradigms, primary 2D or primary cleansed 3D,
resulted in the best outcomes for novice and experienced readers (Chapter 9). We found that for experienced readers there was no difference between 2D or 3D reading. In contrast, novice readers had a significantly better sensitivity with 3D reading compared to 2D reading. There were no significant differences in specificity.

A likely explanation for a better 3D detection of lesions is increased lesion conspicuity. This does not seem to affect experienced readers however. One advantage of 2D reading compared to 3D reading is that reading times are shorter both for inexperienced and experienced readers. Therefore, in large screening cohorts, the 2D reading paradigm can be more cost-effective. When a 2D read is combined with a secondary computer aided detection (CAD) read, sensitivity will probably increase, but so will reading times, to some extent. In our study the added value of a CAD system for 2D and 3D reading was not tested because the CAD algorithm generated too many false positives in the 3D cleansed images because of artefacts. When CAD systems are optimized for inhomogenous tagged stool or insufficiently cleansed examinations, their added value in a 2D and cleansed 3D paradigm should be tested. If so, differences with novice readers in reading 2D versus 3D may decrease. Further developments are mandatory before using CAD and cleansing algorithms in (very) low dose CT-colonography.

For calculating the sensitivity and specificity in CT colonography research, polyps found at CT colonography have to be compared with the polyps found at colonoscopy. This is often referred to as the ‘matching’ procedure. An experienced CT colonography reader judges if the polyp found at CT colonography is the same polyp as the polyp found at colonoscopy. Three aspects of the polyps are then taken into account: their size, the segmental location and the morphology of the polyps. When this matching procedure is performed differently by different readers, this will have influence on the outcomes of accuracy of studies. In chapter 10, we investigated how eight highly experienced readers performed the matching procedure in a set of 27 cases. We found that there were differences in the process of matching, especially for the smaller polyps. Furthermore we found that the matching criteria that readers used were not identical. This made us to develop uniform matching criteria. In cases that do not fit these standard criteria, a second expert reader has to be invited to perform a consensus read. Despite these small differences in matching, readers in our study agreed to a considerable extent when matching cases. The number of readers in this study was quite large, but the number of CT colonography cases was too low to draw statistically significant conclusions. To investigate if differences in matching result in significantly different estimates of sensitivity and specificity, a large unselected dataset should be presented to several readers. In that case the matching criteria, presented in our study, could be used by the readers and differences could be calculated.
CONCLUSIONS

1. Based on our studies on bowel preparation we conclude that CT colonography can be performed with a minimal bowel preparation using an iodine contrast agent only. The dose of the iodine contrast agent used (meglumine ioxithalamate), can be reduced to three times 50 ml. This benefits the patient burden and eventually will also improve the patient compliance for ingesting the preparation. A low-fibre diet in combination with the iodine contrast agent is necessary to remain an optimal tagging quality.

2. CT colonography has a high accuracy, which equals that of colonoscopy in detecting relevant lesions in FOBT positive screening participants. However, when CT colonography is used as a triage method to select only those patients that need colonoscopy, it does not seem an efficient strategy in a first round of FOBT population screening. Because of the high lesion prevalence, too many patients would have to undergo two examinations: a CT colonography followed by a colonoscopy.

3. The median radiation dose used for CT colonography imaging among institutions all over the world is relatively low, especially when CT colonography is used for screening purposes. The range in the effective radiation dose used is however very wide in the same institutions. We should increase the awareness of radiation induced risks and of the possibilities to reduce the effective dose using the newest scanners available.

4. Training is necessary for reading CT colonography. After 175 cases most readers are able to reach a sensitivity that equals that of experienced readers.

5. When novice readers interpret CT colonography images, it is preferable that they use a 3D reading paradigm with cleansed images instead of a 2D reading paradigm. Experienced readers can either use 2D reading or 3D reading.

6. When matching CT colonography and colonoscopy polyps, standard matching criteria should be used. In cases that do not fit these standard criteria, a second expert reader has to be invited to perform a consensus read.
Samenvatting van bevindingen en implicaties
SAMENVATTING VAN BEVINDINGEN EN IMPLICATIES

In dit proefschrift worden meerdere aspecten van de CT-colografie behandeld. Alle cohort studies die in dit proefschrift zijn vermeld bevatten patiënten die een positieve fecaal occult bloed test (FOBT) hadden. In deze patiënten hebben we verschillende minimale darmvoorbereidingen met jodiumcontrast getest. Verder hebben we de accuratesse van poliep detectie en triage met CT-colografie geëvalueerd, een leercurve van onervaren lezers en verschillende reading paradigma’s getest en een evaluatie gedaan van stralingsdosis en het matchen van poliepen door ervaren lezers.

Als de darmvoorbereiding voor een darmonderzoek erg belastend is, kan dit invloed hebben op de navolging van het schema van de darmvoorbereiding door de patiënt. Een voordeel van CT-colografie in vergelijking met coloscopie is dat er geen laxerende middelen gebruikt hoeven te worden; slechts een contrastmiddel dat de feces aankleurt ('tagging') is voldoende. Er moet dan een balans gevonden worden tussen patiëntbelasting en beeldkwaliteit, zodanig dat deze laatste goed is en leidt tot een optimale poliepdetectie. Laxerende middelen zorgen voor een vloeibare consistentie van de feces en/of reduceren de hoeveelheid feces in de dikke darm (het colon). Een oraal contrastmiddel vermengt zich met de residu feces waardoor de differentiatie tussen de colonwand, poliepen en feces wordt vergemakkelijkt ('tagging'). Een jodiumcontrastmiddel is vaak hyperosmotisch en kan leiden tot diarree net als bij de laxerende darmvoorbereidingen. Dit maakt het noodzakelijk de patiëntbelasting voor deze darmvoorbereiding te evalueren.

In het onderzoek in hoofdstuk 2 wordt een darmvoorbereiding van één dag inname van een jodiumcontrastmiddel (meglumine ioxithalamaat, 300 mg I/ml) vergeleken met de inname van twee dagen van dit contrastmiddel in 100 patiënten. We vonden dat wanneer een eendaagse darmvoorbereiding wordt gebruikt die bestaat uit vier keer 50 ml contrastmiddel en een vezelarm dieet, de patiëntbelasting door diarree minder was dan wanneer de tweedaagse voorbereiding werd gebruikt, terwijl de beeldkwaliteit gelijk bleef. De dichtheid van het getagde fecale residu was hoog en gelijk in beide voorbereidingsgroepen. Ook was er geen verschil in de homogeniteit tussen de twee groepen. Wanneer de resultaten van de poliepdetectie in beide groepen werden vergeleken vonden we geen significante verschillen. De conclusie van deze studie was dat een eendaagse voorbereiding superieur is aan een tweedaagse darmvoorbereiding.

In studies waarbij darmvoorbereidingen met enkel een oraal contrastmiddel worden gebruikt, wordt daarbij vaak een vezelarm dieet of een minimaal residu dieet voorgeschreven. De hypothese is dat vezels niet worden verteerd en niet homogeen mengen met het orale contrastmiddel in de darm, wat resulteert in ongetagde stukken feces. Tot nu toe was er nog geen studie die had aangetoond dat een specifiek dieet nodig is voor een optimale tagging. In hoofdstuk 3 wordt een studie beschreven die 2 groepen van 25 patiënten vergeleek; één groep kreeg een oraal jodium contrastmiddel en een vezelarm dieet voorgeschreven, terwijl de andere groep hetzelfde contrastmiddel kreeg.
maar dan zonder dieet. In de tweede groep vonden we meer ongetagde stukken feces en een trend richting een afgenomen tagging kwaliteit. Daardoor kan het aantal fout positieve bevindingen toenemen, en wordt mogelijk de sensitiviteit van de poliepdetectie beïnvloed. We vonden geen significante verschillen in de sensitiviteit tussen groepen, maar dat kwam waarschijnlijk door het relatief lage aantal patiënten per groep. Onze bevindingen in deze studie suggereren dat een vezelarm dieet nodig is om de beeldkwaliteit te optimaliseren in een darmvoorbereiding met alleen een jodium contrastmiddel.

In hoofdstuk 2 hebben we aangetoond dat een eendaagse darmvoorbereiding met vier keer een dosis van 50 ml jodiumcontrastmiddel resulteerde in een excellence tagging kwaliteit. Vervolgens hebben we onderzocht of een lagere hoeveelheid contrastmiddel ook voldoornde zou zijn voor het verkrijgen van een optimale tagging kwaliteit met daarbij een vermindering van de patiëntbelasting. In het onderzoek dat in hoofdstuk 4 wordt beschreven hebben we drie groepen van 15 patiënten met verschillende doses jodium contrastmiddel vergeleken; groep 1 kreeg drie keer een 50 ml dosis jodium contrastmiddel, groep 2 kreeg vier keer een 25 ml dosis en groep 3 kreeg drie keer een 25 ml dosis. De CT-colografieën uit groep 1 hadden de beste tagging kwaliteit; in groep 2 en 3 werden meer ongetagde stukken ontlasting en adherente ontlasting gevonden. De homogeniteit en homogeniteit ratio (=homogeniteit/densiteit) waren hoger in groep 2 en 3, wat betekent dat de tagging kwaliteit minder was. Drie keer een dosis van 50 ml jodium is dus de beste darmvoorbereiding ondanks dat dit wel een hogere patiëntbelasting geeft.

In de hoofdstukken 2, 3 en 4 hebben we aangetoond dat een oraal jodium contrastmiddel dat enkel de dag voor het onderzoek wordt ingenomen een goede beeldkwaliteit geeft met een significant lagere patiëntbelasting vergeleken met de darmvoorbereiding van de coloscopie. Wanneer de dosis van dit jodium contrastmiddel wordt verlaagd van 350 ml naar 150 ml neemt de beeldkwaliteit af, maar in de meeste patiënten kan de dikke darm nog steeds goed beoordeeld worden. Wanneer echter maar 75 ml contrastmiddel wordt gebruikt is echter het probleem dat in sommige darmsegmenten de feces niet homogen wordt getagd en dat ongetagde stukken ontlasting overblijven. De toevoeging van barium kan mogelijk de beeldkwaliteit verbeteren omdat barium de vaste bestanddelen van de ontlasting aankleurt. We hebben echter niet de combinatie van een jodium en barium darmvoorbereiding uitgetest, zoals in enkele andere studies gedaan werd, omdat we de instructies voor de patiënten zo eenvoudig mogelijk wilden houden. Een andere mogelijkheid om de beeldkwaliteit te verbeteren is het gebruik van een cleansing algoritme dat de (inhomogene) getagde ontlasting extraheert. Het probleem is dat onvoldoende getagde fecale residuen niet geëxtraheerd worden door de cleansing algoritmes die nu beschikbaar zijn. Daardoor wordt de zichtbaarheid op de darmwand beperkt, vooral op de 3D beelden. Met de ontwikkeling van verbeterde cleansing algoritmes, zouden zelfs minder uitgebreide darmvoorbereidingen gebruikt kunnen worden zodat de patiëntbelasting afneemt, terwijl de leesbaarheid van de beelden gelijk blijft.

Screening op colorectaal carcinoom kan de mortaliteit aan darmkanker reduceren. Er bestaan verschillende screening methoden. De meest eenvoudige en goedkoopste test die heeft aangetoond dat de mortaliteit aan colorectaal carcinoom wordt verminderd door
screening is de fecaal occult bloed test (FOBT). Een nadeel van deze test is dat het een lage sensitiviteit heeft en een lage positief voorspellende waarde wat resulteert in een groot aantal fout positieve patiënten. Deze fout positieve patiënten zullen daarom een onnodige coloscopie krijgen. Een optie om het aantal onnodige coloscopenieën te verminderen is om CT-colografie te gebruiken als triage techniek om alleen de patiënten met relevante colonische laesies te detecteren. Dit werd geëvalueerd in hoofdstuk 5. We vonden dat CT-colografie geen efficiënte triage techniek is in een eerste ronde FOBT screening. Relatief hoge positief voorspellende waarden werden gevonden terwijl de negatief voorspellende waarden van de CT-colografie laag waren. De patiënten vonden de CT-colografie minder belastend dan de coloscopie. Door de hoge laesie prevalentie in de FOBT positieve patiënten, zou een hoog aantal patiënten twee onderzoeken moeten ondergaan – een CT-colografie en een coloscopie – als de CT-colografie als triage techniek gebruikt zou worden. We concluderen dat CT-colografie niet efficiënt als triage techniek gebruikt kan worden in een eerste ronde van een FOBT populatie screening.

Een verklaring voor de lage negatieve voorspellende waarde van de CT-colografie als triage techniek is dat de effectiviteit van triage geëvalueerd wordt op basis van poliepgrootte. Omdat het doel van screening gedefinieerd is als de detectie van kanker en grote adenomateuze poliepen, gebruikten we een afkapwaarde voor de grootte van de laesie bij CT-colografie om te bepalen of patiënten wel of niet naar coloscopie verwezen moeten worden. Alleen patiënten met tenminste een laesie van een bepaalde grootte – 10mm, of 6 mm of groter – werden beschouwd als CT-colografie positief. Wanneer de grootte van de laesie op CT-colografie beneden deze afkapwaarde is, bijvoorbeeld 5 mm, werd de patiënt beschouwd als CT-colografie negatieve. Het is mogelijk dat in dit geval dezelfde laesie bij coloscopie 6 mm werd gemeten. Als dit het geval was, dan werd de patiënt geclassificeerd als fout negatief voor CT-colografie. Als de methode van poliep matching gebruikt zou worden om de accuratesse te bepalen (dus er wordt een bepaald verschil in grootte tussen de CT-colografie en coloscopie laesie toegestaan), dan zou deze zelfde patiënt als terecht positief voor CT-colografie beschouwd worden.

Een andere belangrijke reden voor de lage negatieve voorspellende waarde was dat het aantal FOBT positieve patiënten met relevante laesies erg hoog was; de helft van de patiënten had tenminste één laesie van 10 mm en groter. Als gevolg bleef er maar een klein aantal terecht negatieve patiënten over waardoor er een lagere negatief voorspellende waarde resulteert in vergelijking met een populatie met een lagere laesie prevalentie. Omwille van deze redenen lijkt CT-colografie niet bruikbaar in een eerste ronde FOBT populatie screening. Maar in een tweede of derde ronde waar de laesie prevalentie mogelijk lager is, zou CT-colografie mogelijk wel bruikbaar zijn als triage test. Om dit te evalueren is verder onderzoek nodig.

In de studie beschreven in hoofdstuk 6 werd de detectie van advanced neoplasia met CT-colografie in een FOBT positieve populatie geëvalueerd. In deze studie gebruikten we de methode van het matchen van poliepen gevonden bij CT-colografie en coloscopie om de sensitiviteit en specificiteit te bepalen. We vonden dat CT-colografie een hoge
diagnostische accuratesse heeft voor het detecteren van colorectale neoplasie in een FOBT positieve screening populatie. Zelfs met het gebruik van een beperkte darmvoorbereiding is de sensitiviteit van de CT-colografie voor de detectie van grote adenomen en carcinomen gelijk aan die van coloscopie. Verder vonden we dat double reading en additionele 3D reading de sensitiviteit van CT-colografie vergrootten. Ook al moet CT-colografie niet gebruikt worden in een eerste ronde FOBT positieve populatie, het zou wel gebruikt kunnen worden in FOBT positieve patiënten die geen coloscopie kunnen of willen ondergaan. Onze resultaten van de sensitiviteit en specificiteit voor detectie van carcinomen en adenomen zijn gelijk aan die van studies die CT-colografie in screening en symptomatische patiënten evalueerden.

Wanneer CT-colografie wordt gebruikt voor screeningsdoeleinden moeten de risico’s op complicaties tot het minimum worden beperkt. Een van de risico’s die geassocieerd is met CT-colografie is de ontwikkeling van stralingsgeïnduceerde kanker. Een hogere effectieve stralingsdosis zal de mortaliteit aan stralingsgeïnduceerde kanker doen toenemen. Daarom is het belangrijk om de stralingsdosis zo laag mogelijk te maken. Niet alleen deelnemers aan screening met CT-colografie zullen profijt hebben van een lagere stralingsdosis, maar natuurlijk ook patiënten die om andere redenen een CT-colografie krijgen (symptomatische of surveillance patiënten). In hoofdstuk 7 beschrijven we een dosisevaluatie studie. Deze evaluatie werd uitgevoerd onder alle onderzoeksinstituten met publicaties over CT-colografie tussen januari 2004 en januari 2007. We vonden dat de stralingsdoses van scanprotocollen die werden gebruikt voor screening (mediane dosis 5.7 mSv) significant lager waren dan van de scanprotocollen voor de dagelijkse praktijk (mediane dosis 9.1 mSv). Ondanks dat de mediane effectieve doses vrij laag waren, was de range aan verschillende doses onder instituten erg groot (range 2.8-22.0 mSv). Sommige instituten gebruikten een effectieve dosis die tien keer hoger was dan de dosis in andere instituten. Dit geeft aan, dat onder de instituten die CT-colografie uitvoerden, de kenbaarheid over de mogelijkheid om de effectieve dosis te verlagen vergroot zou moeten worden. Zelfs kleine lage doses, bijv. 2 tot 3 mSv, zijn voldoende voor een optimale visualisatie van de dikke darm en de dikke darmpoliepen. Het zou interessant zijn om te onderzoeken of de effectieve doses van CT-colografie in de komende jaren verminderen in deze instituten.

In voorgaande studies is aangetoond dat onervaren CT-colografie lezers een lagere sensitiviteit en specificiteit voor poliepdetectie hebben dan ervaren lezers. Er zijn een aantal CT-colografie studies uitgevoerd, maar daaruit bleek dat na 100 CT-colografie onderzoeken een lezer nog steeds niet goed genoeg getraind is om een accuratesse te bereiken die vergelijkbaar is met die van een ervaren lezer. Tot nu toe was het niet duidelijk hoeveel cases er getraind zouden moeten worden om een voldoende sensitiviteit en specificiteit te bereiken. In hoofdstuk 8 beschrijven we een CT-colografie training studie onder artsen en röntgenlaboranten met 200 CT-colografie datasets waarbij coloscopie verificatie aanwezig was. We vonden dat na gemiddeld 164 CT-colografie cases de onervaren lezers de CT-colografieën beoordeelden met een hoge sensitiviteit voor detectie van laesies van 6 mm en groter vergelijkbaar aan die van ervaren lezers. Drie van de negen lezers haalden echter niet een voldoende hoge sensitiviteit na 200 cases. Acht

193
van de negen onervaren lezers hadden een specificiteit van 80% of hoger voor laesies van 6 mm en groter, en er was geen leercurve voor de specificiteit tijdens het trainingsprogramma. Uit deze resultaten kunnen we concluderen dat de meeste onervaren lezers een adequaat niveau van poliepdetectie kunnen bereiken na beoordeling van 175 CT-colografie training cases. Als het gewenste niveau niet gehaald wordt na dit aantal cases dan zal extra training nodig zijn. Omdat het aantal cases in onze studie beperkt was tot 200 weten we niet hoeveel cases deze lezers extra hadden moeten oefenen om een voldoende hoog niveau van poliepdetectie te bereiken. Het is ook mogelijk dat deze lezers zelfs nooit dit niveau kunnen halen. Bovendien hebben we maar één training trainingsprogramma geëvalueerd met een bepaalde laesie prevalentie. Een trainingsprogramma met bijvoorbeeld een hogere laesie prevalentie of een intensievere fout positieve training kan mogelijk resulteren in andere uitkomsten.

Voor het lezen van CT-colografie bestaat gespecialiseerde software die de dikke darm kan visualiseren op een driedimensionale manier (3D view). Er zijn twee strategieën beschikbaar voor het bekijken van een CT-colografie: primair 3D lezen met 2D ‘problem solving’ of een primaire 2D lezing met 3D ‘problem solving’. Een automatische subtractie van de getagde feces kan gedaan worden door speciale ‘cleansing’ software zodat het fecale materiaal op de 3D beelden het niet de poliepen kan maskeren. We hebben onderzocht welke van de twee lezing strategieën, primair 2D of primair 3D gecleansed, resulteerde in de beste uitkomsten voor onervaren en ervaren lezers (hoofdstuk 9). We vonden dat er bij ervaren lezers geen verschil was tussen 2D of 3D beoordeling. In tegenstelling hadden de onervaren lezers wel een significant betere sensitiviteit met 3D lezing in vergelijking met 2D lezing.

Een mogelijke verklaring voor een beter detectie van de laesies wanneer 3D wordt gelezen is dat de laesies langer in beeld zijn tijdens een 3D beoordeling. Dit blijkt echter niet de sensitiviteit van ervaren lezers te beïnvloeden. Een voordeel van 2D lezing in vergelijking met 3D lezing is dat de leestijd korter is voor zowel onervaren als ervaren lezers. Daardoor zal in grote screeningscohorten de 2D lezing het meest kosteneffectief zijn. Wanneer een 2D lezing wordt gecombineerd met computer aided detection (CAD) als ‘second read’, zal de sensitiviteit waarschijnlijk toenemen maar daarnaast ook enigszins de beoordelingstijd. In de gerapporteerde studie hebben wij niet de toegevoegde waarde van een CAD systeem bij 2D en 3D lezing getest omdat het CAD algoritme te veel fout positieven genereerde door artefacten in de 3D gecleansde beelden. Als de CAD systemen worden geoptimaliseerd voor inhomogene getagde ontlasting of onvoldoende gecleansde CT-colografieën, zou de toegevoegde waarde van het CAD bij 2D en een 3D gecleansde beelden getest kunnen worden. Hierdoor zouden mogelijk verschillen in 2D en 3D lezing door onervaren lezers verminderd kunnen worden. Verdere ontwikkelingen zijn noodzakelijk voordat de CAD en cleansing algoritmes gebruikt kunnen worden in CT-colografieën met (zeer) lage dosis.

Voor de berekening van de sensitiviteit en specificiteit in CT-colografie onderzoek moeten de poliepen die gevonden worden bij de CT-colografie vergeleken worden met de poliepen
gevonden bij coloscopie. Dit wordt ook wel de ‘matching’ procedure genoemd. Een ervaren CT-colografie lezer beoordeeld of de poliep die gevonden wordt bij de CT-colografie dezelfde poliep is als de poliep die gevonden is bij de coloscopie. Er worden dan drie kenmerken van de poliep in acht genomen: de grootte, in welk darmsegment deze zich bevindt en de morfologie van de poliep. Wanneer deze matching procedure verschillend wordt gedaan door verschillende beoordelaars dan kan dit invloed hebben op de accuratesse uitkomsten van studies. In hoofdstuk 10 hebben we onderzocht hoe acht zeer ervaren CT-colografie beoordelaars in 27 cases de matching procedure uitvoerden. We vonden dat er verschillen waren in de manier van matchen, vooral voor de kleinere poliepen. Verder vonden we dat de matching criteria die de beoordelaars gebruikten niet identiek waren. Dit heeft er toe geleid dat we uniforme matching criteria hebben ontwikkeld. In cases die niet aan de matching criteria voldoen moet een tweede expert gevraagd worden zodat een consensus kan plaatsvinden. Ondanks de kleine verschillen in matching waren de beoordelaars in onze studie het toch voor het grootste deel eens bij het matchen van cases. Het aantal lezers in deze studie was redelijk groot, maar het aantal CT-colografie cases was te klein om voor statistisch significante conclusies. Om te onderzoeken of verschillen in matching resulteren in een verschillende sensitiviteit en specificiteit, moet een grote ongeselecteerde dataset met CT-colografieën aan verschillende lezers gepresenteerd worden. In dat geval kunnen de matching criteria die in onze studie gepresenteerd zijn gebruikt worden door de lezers en kunnen eventuele verschillen in sensitiviteit en specificiteit worden berekend.
CONCLUSIES

1. Uit onze studies over darmvoorbereiding kunnen we concluderen dat CT-colografie uitgevoerd kan worden met een minimale darmvoorbereiding waarbij alleen een jodiumcontrastmiddel (meglumine ioxithalamaat) gebruikt wordt. De gebruikte dosis van het jodiumcontrastmiddel, kan gereduceerd worden tot drie keer 50 ml. Dit komt ten goede aan de patiëntbelasting en zal uiteindelijk ook de inname van de voorbereiding door patiënten verbeteren. Een vezelarm dieet in combinatie met het jodiumcontrastmiddel is nodig om een optimale tagging kwaliteit te krijgen.

2. CT-colografie in FOBT positieve screening deelnemers heeft een hoge accuratesse voor de detectie van relevante laesies die overeenkomt met die van coloscopie. Echter, wanneer CT-colografie gebruikt wordt als triage methode om alleen de patiënten te selecteren die coloscopie nodig hebben blijkt het niet een efficiënte strategie in een eerste ronde van FOBT populatie screening. Vanwege de hoge laesie prevalentie moeten te veel patiënten twee onderzoeken ondergaan; een CT-colografie gevolgd door een coloscopie.

3. De mediane stralingsdosis voor CT-colografie in instituten over de hele wereld is relatief laag, vooral wanneer CT-colografie voor screening doeleinden wordt gebruikt. De range in effectieve stralingsdosis is echter erg groot in deze instituten. Het is daarom belangrijk om de kenbaarheid te vergroten ten aanzien van de risico’s van straling en ten aanzien van de mogelijkheden om de effectieve dosis te verlagen met de nieuwste scanners.

4. Training is noodzakelijk voor het goed leren interpreteren van CT-colografie. Na 175 cases zijn de meeste readers in staat om een sensitiviteit te bereiken die gelijk is aan die van ervaren lezers.

5. Wanneer onervaren lezers CT-colografie gaan beoordelen heeft het de voorkeur dat ze 3D lezen in plaats van 2D. Ervaren lezers kunnen zowel een 2D als 3D lezing doen met hetzelfde resultaat.

6. Wanneer CT-colografie poliepen met coloscopie poliepen gematched worden moeten standaard matching criteria gebruikt worden. In de gevallen waaraan niet aan deze matching criteria kan worden voldaan moet een tweede ervaren beoordelaar gevraagd worden zodat consensus kan plaatsvinden.
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Voorwerk'; jullie studies waren een basis voor het onderzoek wat ik heb uitgevoerd. Daarnaast zal ik alle leuke congressen en etentjes zeker niet vergeten!

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Sebastiaan en Jasper, ik heb erg veel gelachen om jullie grappen en miste jullie aanwezigheid op de afdeling nadat jullie klaar waren met onderzoek. Ondanks dat Sebastiaan nu in een ander ziekenhuis werkt hoop ik je nog vaak te zien en met je te kunnen samenwerken. We gaan gewoon nog een keer naar die 'gay-friendly Inn' in Boston, toch?

Frank, erg leuk dat je vanuit het OLVG bij ons in het AMC bent gekomen om onderzoek te doen. Je bent erg voortvarend van start gegaan en ik wens je veel succes met je verdere promotie.

Ik wens ook de nieuwe colon-onderzoekers, Margriet en Thierry, veel succes met hun verdere onderzoek.

Sinds de tijd dat ik mijn onderzoek op G1 ben begonnen zijn er een heleboel collega's gegaan en gekomen. Toen ik net begon waren er nog maar een paar onderzoekers; Ayso, Karin en Adrienne. Zij hebben me in de onderzoekswereld ingewijd. Al snel kwamen Jochem, Roos, Sandra en Sanna ons versterken en inmiddels zijn we met een grote groep; Anneloes, Chris, Esther, Françelien, Frank, Joppe, Manon, Marije, Margriet, Marjolein (L...) en Thierry. Bedankt voor alle gezellige momenten die even afleiding geven van het soms toch wel wat eentonige werk!

Tijdens mijn onderzoeksperiode waren er een aantal studenten die mij hebben geholpen bij mijn studies. Katherina, Cornelia, Kelly en Wouter, bedankt voor het invoeren van die vele data en het bijwonen van eindeloze coloscopieën!

Het grootste deel van mijn onderzoek had niet kunnen plaatsvinden zonder de hulp van een aantal laboranten. In het bijzonder dank aan Martin die de CT-colografieën perfect kan uitvoeren en altijd bereid was mee te helpen om het onderzoek te verbeteren. Daarnaast ook dank aan Dominique, Cindy en Roel die naast scannen een groot deel van hun vrije tijd hebben gestoken in het beoordelen van CT-colografieën voor mijn leercurve studie.

Naast de afdeling Radiologie in het AMC, was de afdeling Gastroenterologie zeer betrokken bij mijn onderzoek. Met Anne ben ik de inclusies voor mijn eerste grote studie begonnen. Zonder jouw inzet Anne was mijn inclusie zeker een stuk lager geweest! Daarna heeft Maaike het stokje overgenomen en ook zij heeft veel kunnen betekenen voor inclusies en coloscopieën. Naast Anne en Maaike natuurlijk ook alle artsen en verpleegkundigen op de afdeling bedankt die de coloscopieën bij de patiënten van mijn onderzoek hebben uitgevoerd. Ook wil ik graag alle mensen bedanken van de afdelingen Radiologie en
Gastroenterologie van het Erasmus MC en het UMCN Radboud die hebben bijgedragen aan mijn onderzoek.

Gelukkig was er naast mijn onderzoek nog genoeg vrije tijd over om leuke dingen te doen met alle lieve vrienden. Avondjes eten en uitgaan met Janine, Anoek en Marije en natuurlijk Marleen, mijn paranimf. Verder hadden we veel gezellige beachvolleyavondjes met Eveline en Hans (de revanche op de 5-0 in komt helaas pas ergens in de zomer...).

Met Esther en Tijs zit een weekendje zeilen waarschijnlijk er volgend jaar niet meer in, maar vast genoeg momenten om samen van onze baby’s te genieten! Daarnaast hoop ik met alle andere vrienden ook de komende jaren genoeg tijd te kunnen besteden om leuke dingen te doen; de Maastricht en Curaçao meiden, Eveline en Diane en natuurlijk mijn beach-maatjes Marijke en Petra.

En als (bijna) laatste mijn paranimfen, ik heb jullie tussen de regels door al even genoemd, maar ik wil jullie hier nog even speciaal bedanken.

Marleen, je bent een lieve vriendin die naast het doen van veel gezellige dingen ook altijd erg geïnteresseerd was in mijn onderzoek. Ik vind het knap hoe je met je eigen onderzoek bezig bent, en ik weet zeker dat daar een heel mooi proefschrift uit gaat komen! Naast werk zijn er natuurlijk heel veel andere dingen om over te kletsen en om samen te doen. We kennen elkaar nu 10 jaar en we kunnen terugkijken naar veel mooie herinneringen. Ik hoop dat we de komende jaren net zo kunnen voortzetten!

Ayso, jij was degene die me inwijdde in de wereld van de CT-colografie. Bedankt voor al die CT-colografieën die je voor mijn studies hebt bekeken, ze zullen op een gegeven moment wel je neus uit zijn gekomen... Naast het werk vond ik het erg leuk dat je altijd in was voor wat ontspanning, zoals de rondjes hardlopen in Malmo, Boston, Berlijn en Wenen. Naast hardlopen was er natuurlijk ook tijd voor een feestje, vooral niet te vergeten de memorabele ‘mojito-avond’ op je verjaardag in de Sky-bar in Wenen!

Lieve pap en mam, bedankt voor jullie onvoorwaardelijke steun en liefde. Overal kwamen jullie mij opzoeken; van Maastricht, Leeds, Curaçao, Utrecht, Breda, Amsterdam tot Vianen... altijd staan jullie voor mij klaar. We gaan denk ik een hele leuke en bijzondere tijd tegemoet met jullie eerste kleinkind.

Lieve Linde, door jou wordt het me elke keer weer duidelijk dat er meer is dan werken, sporten, afspraken enzovoort... Lachen, dansen en plezier maken is toch eigenlijk het allerbelangrijkste wat er is? Dank je voor al de leuke momenten tot nu toe en ik hoop dat er nog heel veel meer van deze komen!

Lieve Martijn, door jou voel ik me al vier jaar gelukkiger dan ooit. Ik geniet er zo van om met jou samen te zijn; samen uit eten te gaan, sporten, vakantie vieren. De afgelopen vier jaar zijn voorbij gevllogen en dat is hopelijk nog maar het begin van alle mooie dingen die ons nog te wachten staan...
CURRICULUM VITAE

Marjoleijn Henrieke Liedenbaum was born on November 25th 1981 in Terneuzen. She followed high school at ‘de Rede’ in Terneuzen and graduated in 1999 (cum laude). After her graduation she moved to Maastricht to study medicine at the University of Maastricht. Other than studying she became an active rower at the student rowing club ‘Saurus’. Furthermore she took part in several committees of her rowing club. In the last years of her study she was involved in research at the department of Neurosciences at the University of Maastricht. Furthermore she followed several internships abroad; in Leeds (UK), Curacao and Gent she followed respectively paediatrics, surgery and ophthalmology. After receiving her MD degree in September 2005 she started working as a resident at the Surgery department of the Amphia Hospital in Breda. After working there for eight months, she applied for a PhD project of Professor J. Stoker at the Radiology department of the Academic Medical Centre in Amsterdam. From June 2006 till January 2010 she was a PhD student on ‘CT colonography in FOBT positives’ at this department. She presented her research at national and international congresses. In February 2010 she started her radiological training as resident at the Academic Medical Centre.

Marjolein lives together with Martijn in Vianen. They expect their first child at the end of March 2010.


PROPOSITIONS
belonging to the thesis
CT COLONOGRAPHY IN FAECAL OCCULT BLOOD TEST POSITIVES
by M.H. Liedenbaum

1. CT colonography has a performance equal to that of colonoscopy for the detection of lesions larger than 10 mm in people with a positive faecal occult blood test result. - this thesis -

2. CT colonography is not well suited to use as a triage method in the first round of faecal occult blood test screening because of the high prevalence of lesions in this population. - this thesis -

3. The bowel preparation for CT colonography can be limited to the intake of an iodine based contrast agent for a single day. - this thesis -

4. The radiation dose used for CT colonography can be reduced to a dose which is comparable with the annual background radiation. Unfortunately many institutions use a higher dose. - this thesis -

5. Novice CT colonography readers obtain a sensitivity for polyp detection equal to that of an experienced reader after practising an average of 164 CT colonographies. - this thesis -

6. Better student selection regarding professional behaviour should take place during the study of medicine so that the number of 'rude' doctors might decrease.

7. It is safer in a chemical plant than in a hospital. - R. Willems, Shell -

8. A strange folklore: While women abroad experience a painless childbirth in hospitals, we put the bed on blocks, cook pans of hot water and, in a very mediaeval manner, midwives appear. - Herman Pleij -

9. Finishing a thesis is like running a marathon; hard times are experienced and it demands perseverance but there are also moments of victory.

10. Strength does not come from physical capacity. It comes from an indomitable will. - Mahatma Gandhi -

11. "Never enjoy with moderation." - Loesje -
CT-colografie is net zo goed als coloscopie in het detecteren van laesies groter dan 10 mm in mensen met een positieve uitslag van de test op fecaal occult bloed.

CT-colografie kan beter niet als triagemethode worden gebruikt in een eerste ronde van screening met een test op fecaal occult bloed, vanwege de hoge prevalentie van afwijkingen in deze populatie.

De darmvoorbereiding voor CT-colografie kan worden beperkt tot slechts een dag inname van een contrastmiddel op basis van oraal jodium.

De stralingsdosis voor CT-colografie kan worden beperkt tot een dosis die vergelijkbaar is met de jaarlijkse achtergrondstraling. Helaas gebruiken nog veel instituten een hogere dosis.

Onervaren CT-colografiebeoordelaars bereiken na gemiddeld 164 CT-colografieën een sensitiviteit voor poliepdetectie die vergelijkbaar is met die van ervaren beoordelaars.

Tijdens de geneeskundestudie moet een betere selectie plaatsvinden onder toekomstige artsen op professioneel gedrag, zodat het aantal 'lompe' dokters verminderd wordt.

In een chemische fabriek is het veiliger dan in een ziekenhuis.

Een curieuze folklore. Waar vrouwen elders pijnloos in het ziekenhuis bevallen, zetten wij het bed op klossen, rukken pannen met kokend water aan en duiken, heel middeleeuws, de vroedvrouwen op.

Promotieonderzoek doen is net een marathon lopen; het vereist een enorm doorzettingsvermogen en er zijn momenten van afzien, maar ook van overwinning.

Strength does not come from physical capacity. It comes from an indomitable will.

Geniet nooit met mate.