CT colonography as surveillance technique for patients at increased risk for colorectal cancer
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Sebastiaan Jensch
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CT Colonography as Surveillance Technique for Patients at Increased Risk for Colorectal Cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boon
ten overstaan van een door het college voor promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel op
vrijdag 16 oktober 2009, te 10.00

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Sebastiaan Jensch

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Faculteit der Geneeskunde
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Introduction and Outline of the Thesis
Chapter 1

Introduction

Colorectal cancer is the second leading cause of cancer related deaths in the Western World. In the year 2006, 11231 new patients were diagnosed with colorectal cancer in the Netherlands and 4709 patients died of the disease [1]. The life-time risk to develop colorectal cancer is approximately five percent [2]. The proportional rise in the ageing population and growth of the population will result in a rise of new cases in the near future [3]. In fact, it is estimated that the incidence of colorectal cancer in the Netherlands will increase with forty-two percent between 2005 and 2025 [4].

The prognosis of patients with early stages of the disease has improved because of early detection and follow-up of patients with colorectal polyps or cancer. Nonetheless, still forty to fifty percent of patients with colorectal cancer will die within five years of diagnosis. This is mainly due to the fact that at first presentation about forty percent of patients have advanced stages of disease because of the relatively late occurrence of symptoms [5].

Current data indicates that over ninety-five percent of colorectal cancers arise in adenomatous polyps which develop and grow slowly in the colon and take approximately ten to fifteen years to turn into a carcinoma, this is called the adenomatous-carcinoma sequence (figure 1) [6, 7, 8].

Figure 1. Adenoma-Carcinoma Sequence

The adenoma-carcinoma sequence is a well-described pathway of mutational events that characterize the transition from normal colon epithelium to premalignant adenoma and then invasive adenocarcinoma. This process may take up to 10 to 15 years.
Although the occurrence of adenomas is relatively frequent (twenty to thirty percent) in individuals fifty years and older [9], it has been estimated that only a small proportion of adenomas will eventually develop into a carcinoma [10]. Size is an important predictor of malignancy (table 1) [11-14].

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20</td>
<td>30^1,2,3</td>
</tr>
<tr>
<td>≥10</td>
<td>10^1,2,3</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1^4</td>
</tr>
<tr>
<td>&lt;6</td>
<td>0.1^4</td>
</tr>
</tbody>
</table>

^4Waye JD et al. Am J Gastroenterol 1988; 83:120-122

Some studies have indicated that polyps smaller than 10 mm have little to no clinical relevance in intermediate and long-term follow-up [12, 15], other investigators however advocate removal of all polyps regardless of size [16]. Agreed upon is that adenomas larger than 10 mm are clinically significant and associated with an increased-risk for developing cancer [17]. There is compelling evidence that detection and removal of these benign precursors of colorectal cancer will decrease the incidence and cancer-related mortality of colorectal cancer [18, 19]. Also, detection of colorectal cancer in an early and localized stage improves survival dramatically [20]. Therefore, evidence-based guidelines have recommended surveillance of increased-risk patients (i.e. patients with a personal or familial history of colorectal polyps or carcinoma) [21-23] and screening of average-risk individuals (i.e. asymptomatic individuals with an age fifty years or older) [24].

In the Netherlands, increased-risk patients are in general under surveillance by a gastroenterologist. These patients undergo an optical colonoscopy once in the 3 or 6 years for the detection of adenomatous polyps and early carcinoma [25]. By inserting a colonoscope into the colon, optical colonoscopy allows for a complete inspection of the colon mucosa. This technique is considered the gold standard for the detection of polyps and carcinoma, although a miss rate of about five percent for colorectal cancer is reported [26]. An advantage of optical colonoscopy is that polyps can be removed in a single session. Disadvantages are that it is an invasive test that is associated with complications as bleeding and perforation in case of polypectomy.
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[27]. Sedation is often needed to reduce pain. Furthermore to clean the colon, a cathartic bowel preparation is required prior to optical colonoscopy.

Despite guidelines for surveillance of increased-risk patients and awareness of patients that they have an above average risk for colorectal cancer, several studies have reported unsatisfactory low utilization rates of colon surveillance in this population [28-30]. Potential deterrents for individuals not to participate in a surveillance/screening program are fear of pain, discomfort and embarrassment associated with the examination [30-34]. Furthermore, the cathartic bowel preparation that is required for many imaging modalities is burdensome and often considered very unpleasant by patients [35].

**Figure 2. Reconstructed three-dimensional CT colonography image**

Computed tomography (CT) colonography is a relatively new imaging technique that was first described in 1994 by Vining et al. [36]. Through a thin flexible tube the colon is insufflated with carbon dioxide. The patient is scanned in supine and prone position with a multi-slice CT scanner. Two-dimensional and reconstructed three-dimensional “fly-through” images of the entire colon are generated (figure 2). The examination can be reviewed on a dedicated workstation with specialized CT colonography software. The ability of CT colonography to detect cancer or large polyps (≥ 10 mm) in high-risk and average-risk patients is well established and comparable to detection rates in optical colonoscopy [37-40].
Data on accuracy in a population at increased-risk for colorectal cancer is however sparse and reported detection rates vary considerably [41-42]. The relatively high prevalence of flat polyps (figure 3) in surveillance patients is of major concern because these lesions are difficult to detect at CT colonography [43]. Flat lesions may have an innate higher prevalence in patients at increased-risk, may have blossomed from small to large lesions after being overlooked at prior colonoscopy or may have developed from polyp remnants after prior incomplete polypectomy [44].

A wide range of reader performance might also explain why detection rates in CT colonography are not consistently reproduced. One explanation for poor reader performance is inadequate training or experience [45, 46]. In addition, high volumes of data and low disease prevalence could play a role as this leads to reader’s fatigue [41]. A double-reading strategy might be used to limit interobserver variability and improve sensitivity. Double interpretation by two radiologists however is time-consuming, increases costs, and may not be feasible in every radiology department. Possible alternative scenarios are the deployment of trained radiographers or the use of a computer aided detection (CAD) algorithm as second readers [47-51]. Further study on how to improve diagnostic accuracy for CT colonography in an increased risk population is warranted as patients may benefit greatly from a pre-select non-invasive imaging technique.

![Figure 3. Example of two flat adenomatous polyps](image)

Two lesions of flat morphology (arrows) that were missed at CT colonography and not visible in retrospect. Flat morphology is defined as a height less than 3 mm or a height that is less than two times the length.

An important advantage of CT colonography is that this technique is well tolerated by the majority of patients. Although some studies have reported less procedural pain and a future preference for optical colonoscopy [52-54], most studies conclude the
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opposite [32,35, 55-61]. What most studies agree upon is that the cathartic bowel preparation that is required for both tests is the most unpleasant part of the examination. For example, in a five week follow-up study Van Gelder et al. compared CT colonography to optical colonoscopy with regard to patient acceptance in population at increased risk [35]. Their data showed that five weeks later at home, 63% of patients indicated that the cathartic bowel preparation was the most burdensome event to undergo; 35% of patients pointed towards optical colonoscopy and just 2% of patients considered CT colonography the most burdensome event (Figure 4). In this study an average of four litres poly-ethylene glycol solution was used to prepare patients for same-day CT colonography and optical colonoscopy.

In 2001 the possibility to prepare patients with a less extensive bowel preparation (i.e. limited bowel preparation) for CT colonography was introduced by using faecal tagging [62]. With faecal tagging any faecal material in the colon is labelled so that colorectal cancer or polyps can be distinguished from faecal material. Three types of tagging agents are available: barium, non-ionic and ionic iodinated contrast. Furthermore, a variety of mild laxatives, e.g. bisacodyl sodium or magnesium citrate, can be added in order to reduce the amount of faeces in the colon [63, 64, 65]. To date, no consensus exists about which contrast agent should be used and whether mild cathartics should be added to the tagging regimen, and if so, in what dose [66, 67].
Several feasibility studies have reported promising results for CT colonography with a limited preparation with regard to image quality, diagnostic value and patient acceptance [62-65, 68-73]. In addition, a large accuracy study without catharsis by Iannaccone et al. reported a polyp sensitivity of 90% and a specificity of 92% in a heterogeneous population (mix of high-, increased- and average-risk patients) [74]. These results are similar or superior to accuracy studies in which a cathartic bowel preparation was used [39-42, 75-77]. This is important because if no extensive bowel cleansing is necessary, this approach might increase patient compliance with surveillance guidelines [78-80]. To date however, no study investigating accuracy or acceptance for CT colonography with a limited bowel preparation has been published in a homogeneous increased-risk population.

A point of concern for CT colonography is the use of ionizing radiation. Risks imposed by diagnostic imaging are generally very low, but scanning high numbers of patients, as in surveillance or screening settings, will inevitably increase the number of radiation-induced cancer deaths related to medical imaging [81-85]. Although CT colonography can be performed with relatively low radiation doses because of the inherent high contrast difference between air and bowel wall, the use of modern multi-slice scanners with thin collimation might give rise to a substantial increase in dose [86-88]. Therefore, it is important to understand the radiation doses that are associated with CT colonography because in that way potential health risks of its large-scale application can be estimated.

**Outline of the Thesis**

In this thesis, CT colonography was investigated in a population at increased-risk for colorectal cancer. We focused on a limited bowel preparation for CT colonography with regard to image quality, diagnostic value and patient acceptance. Furthermore, performance characteristics of radiographers and of a computer aided diagnosis algorithm were evaluated in cathartic CT colonography. Finally, radiation doses that are currently used for CT colonography around the world were determined by means of a survey.

In chapter 2 image quality and patient acceptance parameters of CT colonography were compared between four faecal tagging regimens with increasing levels of mild...
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catharsis, using bisacodyl and magnesium citrate as laxative agents. The aim of the
study was to determine the optimal dosage of mild laxatives for a limited bowel
preparation. Chapter 3 addressed the diagnostic value of CT colonography with a
limited bowel preparation in an increased-risk population. Sensitivity and specificity
for the depiction of polyps were prospectively evaluated in 168 consecutive patients,
using colonoscopy as the reference standard. In chapter 4 we hypothesized that CT
colonography with a limited bowel preparation leads to a better patient acceptance in
comparison to optical colonoscopy with a cathartic preparation. In this five-weeks
follow-up study intra-individual experience and preference were assessed for both
techniques. Chapter 5 discusses the reader performance of trained radiographers in
comparison with radiologists in the evaluation of CT colonographic images. As double
reading might improve detection rates in CT colonography, we also determined if
sensitivity increased when results were combined for the radiographers and the
radiologists. A possible alternative that can serve as a second reader is the use of a
computer aided detection algorithm (CAD). Therefore in chapter 6 we determined
whether CAD in a second read paradigm could improve the performance
characteristics of experienced readers in a practical setting. Chapter 7 provides a
temporal overview of scan protocols for CT colonography in the literature. Effective
doses were estimated from these protocols. In addition, research institutions were
contacted for their current scan protocols. In this way, we could calculate up-to-date
effective doses and determine the potential radiation-induced health risk associated
with CT colonography.
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Image Quality and Patient Acceptance of Four Regimens with Different Amounts of Mild Laxatives for CT Colonography

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Ayso H. de Vries
Dennis Pot
Jan Peringa
Shandra Bipat
Jasper Florie
Rogier E. van Gelder
Jaap Stoker

Abstract

**Purpose:** The purpose of our study was to prospectively evaluate image quality and patient acceptance of CT colonography (CTC) with fecal tagging using different levels of catharsis.

**Methods:** Forty consecutive increased-risk patients were randomized. Group 1 received orally 20 mg of bisacodyl, group 2 received 30 mg of bisacodyl, group 3 received 20 mg of bisacodyl and 8.2 g of magnesium citrate, and group 4 received 30 mg of bisacodyl and 16.4 g of magnesium citrate. All patients used a 2-day low-fiber diet and received diatrizoate meglumine and barium for fecal tagging. One reviewer blindly scored subjective image quality (fecal tagging, amount of residual feces [liquid or solid], luminal distention, and image readability) on a 5- to 6-point scale using a 2D review technique. The mean and SD of attenuation of tagging were measured as well as the relative SD as a measure of homogeneity. Furthermore, patient acceptance (burden related to diarrhea, abdominal pain, flatulence, and overall burden) was evaluated. Ordinal regression, generalized estimating equations, and parametric and nonparametric tests were used for analysis.

**Results:** Image readability was evaluated as good or excellent in all examinations except one in group 2 (non-diagnostic) and two in group 3 (moderate). Group 2 contained more feces than group 4 ($p = 0.04$). With regard to mean attenuation and homogeneity of tagging, no significant differences were observed between groups. Group 4 experienced more severe diarrhea than groups 1 and 2 and higher overall burden than groups 1 and 3 ($p < 0.042$).

**Conclusion:** The mildest preparation with 20 mg of bisacodyl provided good image quality of CTC images. Increasing the amount of laxatives did not improve image quality or tagging characteristics but was associated with a lower patient acceptance.
Introduction

CT colonography (CTC) is being investigated as a possible screening technique for the detection of colorectal polyps and cancer [1–5]. However, the requisite cathartic bowel preparation, which is often described by patients as the most burdensome aspect of colonic examinations [6–8], might diminish patients’ willingness to participate in a screening program [9–11]. Labeling of fecal material with a contrast agent (fecal tagging) has enabled the use of limited bowel preparation regimens containing no or only limited amounts of laxatives [12]. So far, feasibility studies investigating CTC with reduced catharsis have shown promising results with regard to image quality and patient acceptance [13–17]. In addition, one large accuracy study that used no cathartics has been published that reported excellent results with regard to polyp detection [18].

For labeling fecal material, three types of tagging agents are available: barium and nonionic and ionic iodinated contrast agents. Barium is traditionally used for solid fecal matter tagging and iodinated contrast agents are used to tag residual fluid. Furthermore, a variety of mild laxatives, for example, bisacodyl sodium or magnesium citrate [13, 14], can be added to reduce the amount of fecal matter in the colon. At present, no consensus exists about which contrast agent should be used and whether mild cathartics should be added to the tagging regimen, and if so, in what dose [19].

We hypothesized that a higher level of catharsis would improve image quality but reduce patient acceptance. Our objective was to determine the optimal dosage of laxatives for CTC with limited bowel preparation with regard to both image quality and patient acceptance. Therefore, we compared image quality and patient acceptance between four regimens with increasing levels of mild catharsis, using bisacodyl and magnesium citrate as laxative agents. Although some studies have compared image quality of CTC with and without laxatives [20, 21], to our knowledge, our study is the first that has investigated the effect of different amounts of mild laxatives in CTC.

Materials and Methods

Study population

Forty consecutive adult patients with an increased risk for colorectal cancer (i.e., a personal or family history of colorectal polyps or cancer) were included in this study.
between October 2004 and January 2005. All patients were scheduled to undergo a conventional colonoscopy for polyp detection at the endoscopic departments of the Academic Medical Center or the Onze Lieve Vrouwe Gasthuis. Exclusion criteria were a personal history of inflammatory bowel disease or familial adenomatous polyposis, prior allergic reaction to an iodine-containing contrast agent, colorectal polyps or cancer at prior endoscopy that were not removed, or participation in a research project that involved ionizing radiation within 12 months preceding the CTC examination. On the day of the CTC examination, patients were asked to indicate whether they had symptoms of colorectal disease (i.e., abdominal pain, hematochezia, or altered bowel habits) and if so, which symptoms were present. No formal power calculation was performed in this feasibility study and, for practical reasons, 40 patients were studied. The institutional review board of both hospitals gave approval for this feasibility study of 40 patients. All patients gave written informed consent.

*Bowel Preparation*

A low-fiber diet was prescribed for all patients for 2 days before the CTC examination. No specific meal kit was used. Through a customized computer program, patients were randomized into one of four groups using a randomization lock design (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Barium Sulphatea (mL) (40% w/v)</th>
<th>Diatrizoate Meglumineb (mL) (200 mgI/mL)</th>
<th>Bisacodylc (mg)</th>
<th>Magnesium Citrateb (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>80</td>
<td>110</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>80</td>
<td>110</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>80</td>
<td>110</td>
<td>20</td>
<td>8.2</td>
</tr>
<tr>
<td>IV</td>
<td>80</td>
<td>110</td>
<td>30</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Note—Dash (—) indicates not applicable.

*aDosage: 2 days before CTC, 20 mL at dinner and 1 day before CTC, 20 mL at breakfast, lunch, and dinner.*

*bDosage: 1 day before CTC, 10 mL at breakfast and 20 mL at lunch and dinner; on the day of CTC, 60 mL at breakfast.*

*cDosage: 16 hours before CTC, 10 mg of orally administered bisacodyl for groups 1 and 3 and 20 mg for groups 2 and 4; on the day of CTC, all groups received 10 mg of bisacodyl orally at breakfast.*

*dDosage: 18 hours before CTC, groups 3 and 4 received magnesium citrate in the displayed dose.*

Preparations contained solely orally administered bisacodyl or bisacodyl in combination with magnesium citrate (LoSo Prep, E-Z-EM) as laxative agents, and the
extent of catharsis gradually increased from group 1 to group 4. We did not include a laxative-free regimen because such regimens have been shown to result in insufficient image quality [20, 21]. The most extensive preparation (group 4) contained a combination of bisacodyl and magnesium citrate in a dosage that is commercially available as a preparation kit for CT colonography (LoSo Prep) and is considered a mild preparation [13, 14]. Tagging consisted of barium sulfate, 40% weight per volume (Tagitol V, E-Z-EM) and diatrizoate meglumine with an iodine concentration of 200 mg/mL. Patients were not informed of the content of the other regimens.

**CT Colonography**

The CTC examination was performed in the supine and prone positions on an Mx8000 4-MDCT scanner (Philips Medical Systems) with the following parameters: 120 kV; collimation, 4 × 2.5 mm; rotation time, 0.75 second; pitch, 1.25; slice thickness, 3.2 mm; and reconstruction interval, 1.6 mm. Patients with a circumference < 103 cm were scanned with 50 mAs (n = 15); patients with a circumference > 103 cm, with 70 mAs (n = 25). A total of 20 mg of butylophenolamine bromide (Buscopan, Boehringer Ingelheim) (n = 22) or, if contraindicated, 1 mg of glucagon hydrochloride (GlucaGen, Novo Nordisk) (n = 17) was administered IV immediately before scanning. In one patient neither was administered because of contraindications. On average, 4 L of carbon dioxide (CO2) was insufflated via an automatic insufflator (PROTOCO2L, E-Z-EM) to achieve adequate distention. The time that patients spent in the CT room was recorded with a stopwatch.

**Conventional Colonoscopy**

Colonoscopy was performed 4–30 days (mean, 17 days) after CTC. Bowel preparation for colonoscopy consisted of 3 (n = 2), 4 (n = 36), or 6 L (n = 2) of polyethylene glycol–electrolyte solution (Klean-Prep, Helsinn Birex Pharmaceuticals) administered the day before the examination. Patients received midazolam (n = 28), fentanyl (n = 20), or alfentanil (Rapifen, AstraZeneca) (n = 6) on request. Buscopan was administered IV to all patients. The colonoscopy was performed either by an experienced gastroenterologist or surgeon or by a resident under the direct supervision of a staff member. During the examination, a research nurse involved in our study was present.
Outcome Parameters

Subjective image quality

The CTC data were evaluated by a research fellow in CTC who was blinded to all clinical data, including the bowel preparation used. The reviewer had a prior experience of 150 non-tagged cathartic-prepared CTC examinations with colonoscopic verification.

A primary 2D evaluation technique (axial views) was applied using multiplanar reformatted (MPR) images and 3D endoluminal views for problem solving (ViewForum 5.1, Philips Medical Systems). No electronic cleansing software was
applied. The reviewer filled out a standardized questionnaire for every examination with regard to image quality. Table 2 displays the scoring system used by the reviewer. The image quality parameters of fecal tagging (Fig. 1), luminal distention, amount of fecal residue (combined estimation for liquid and solid feces), and image readability were scored by the reviewer for the complete (supine and prone together) examination. This evaluation was considered the subjective image quality assessment on a per-patient basis. The same image quality parameters were again evaluated on a per-segment basis. To this end, the colon was divided in six segments: cecum; ascending, transverse, descending, and sigmoid colon; and rectum. Fecal tagging and the amount of fecal material were evaluated only with the patient in the supine position because we presumed these parameters would not be influenced by a position change. However, because alteration of the position of the patient might substantially influence distention of different colonic segments [22, 23], luminal distention and segmental image readability were again evaluated with the patient in the prone position. Furthermore, to examine the effect of increasing catharsis on the consistency of fecal material, the reviewer scored the ratio between feces with a solid consistency and feces with a liquid consistency. This was performed on a per-segment basis with the patient in the supine position. A 5-point scale was applied: 1, 0–20% solid; 2, 21–40% solid; 3, 41–60% solid; 4, 61–80% solid; and 5, 81–100% solid. If no stool was present in a segment, no evaluation of consistency was performed for that particular segment.

**Numeric evaluation of degree and homogeneity of tagging**

To evaluate the quality of fecal tagging, the mean and SD of attenuation of tagged material (in Hounsfield units) were measured on seven separate slices that were randomly selected by a computer program (Windows Excel 2002, Microsoft) for every patient. To this end, a resident in the fourth year of training, who was blinded as to the preparation used, placed a region of interest (ROI) of at least 60 mm² in the area that contained the most fecal material on the randomly picked axial slices. The resident recorded whether the ROI was placed in liquid stool, stool adherent to the colon wall, or solid stool. The mean and SD of attenuation values within the ROIs were then calculated by our CTC software (ViewForum 5.1) (Fig. 2). If not enough fecal material was present to draw an ROI, the randomization program provided another slice for evaluation. The SD of attenuation values of tagged material is a measure of homogeneity. However, because the mean attenuation of tagging can vary considerably among patients, we considered the relative SD (SD / mean) to be
a better measure of homogeneity. After all, by adapting the window width when viewing images, tagging with a larger mean attenuation value and a large SD may have a similar visual appearance to tagging with a smaller attenuation value and a proportionally smaller SD. Furthermore, separate assessments were performed for solid, adherent, and liquid feces.

**Interpretation time**

The time needed to interpret a complete examination for polyp detection, excluding report time and image quality evaluation, was recorded with a stopwatch by the reviewer. Because of the limited number of patients and the expected low prevalence of polyps in our cohort, performance characteristics were not part of our study design and are not discussed in this article.

**Patient experience**

Patients were asked to fill out a questionnaire on the day of the CTC examination with regard to the burden and side effects of the CTC preparation—that is, flatulence, abdominal pain, and diarrhea—as well as the discomfort caused by the intake of contrast material and laxative agents on a 5-point scale (Table 2). To understand if the everyday bowel habits of patients were of influence on image quality parameters, patients were asked to fill out their normal frequency of defecation: 1, more than one defecation per day; 2, once per day; 3, once per 2 days; 4, once in 3 days; 5, less than one defecation per 3 days; and 6, less than one defecation per 5 days. On the
### Table 2. Scales Used by Observer to Rate Image Quality and by Patients to Rate Burden and Preference

<table>
<thead>
<tr>
<th><strong>Observer</strong></th>
<th><strong>Scale</strong></th>
</tr>
</thead>
</table>
| Fecal tagging<sup>a</sup> | a = Poor, not interpretable  
| | b = Moderate, diagnostic with untagged feces < 10 mm  
| | c = Good, diagnostic with untagged feces < 6 mm  
| | d = Very good, diagnostic without limitations  
| Presence of feces<sup>a</sup> | a = Large amount of feces, segment fully filled  
| | b = Moderate amount of feces, ≈ 50% of lumen filled  
| | c = Small amount of feces  
| | d = Only layer on wall  
| | e = No feces at all  
| Luminal distention<sup>a,b</sup> | a = Collapsed  
| | b = Poorly distended  
| | c = Only moderately distended, but segment is distended over its full length  
| | d = Good  
| | e = Very good  
| Image readability<sup>a,b</sup> | a = Poor, not diagnostic  
| | b = Moderate, diagnostic for lesions ≥ 10 mm  
| | c = Good, diagnostic for lesions ≥ 6 mm  
| | d = Excellent, no limitations  

<table>
<thead>
<tr>
<th><strong>Patients</strong></th>
<th><strong>Scale</strong></th>
</tr>
</thead>
</table>
| Burden caused by intake of bisacodyl, magnesium citrate, barium sulfate, diatrizoate meglumine | a = None  
| | b = Mild  
| | c = Moderate  
| | d = Severe  
| | e = Extreme  
| Side effects: diarrhea, flatulence, abdominal pain, overall burden | a = None  
| | b = Mild  
| | c = Moderate  
| | d = Severe  
| | e = Extreme  
| Most burdensome preparation | CT colonography (CTC) or conventional colonoscopy  
| Most burdensome examination | CT colonography (CTC) or conventional colonoscopy  
| Most burdensome event | Bowel preparation prior to conventional colonoscopy  
| | Limited bowel preparation prior to CTC  
| | CTC examination  
| | Conventional colonoscopy examination  
| Preference for CTC or conventional colonoscopy examination in the future | Definitely CTC  
| | Probably CTC  
| | Possibly CTC  
| | Indifferent  
| | Possibly conventional colonoscopy  
| | Probably conventional colonoscopy  
| | Definitely conventional colonoscopy  

---

<sup>a</sup>Subjective image quality parameters were scored per patient and per segment in the supine position.  
<sup>b</sup>Luminal distention and image readability were again evaluated on a per-segment basis in the prone position.
day of the colonoscopy, patients filled out a questionnaire with regard to the burden associated with the bowel preparation for colonoscopy (Table 2).

**Patient preference**
Five weeks after colonoscopy, patients were sent a questionnaire in which they were asked which preparation had been most burdensome (CTC or conventional colonoscopy) and which examination (CTC or conventional colonoscopy) they would prefer in the future, and they were asked to indicate the most burdensome event of both examinations (Table 2). The patient preference and experience questionnaires were designed by the department of social medicine and had previously been used in two studies that were performed in our institution [7, 24].

**Statistical Analysis**

**Subjective image quality**
With regard to the per-patient analysis, possible differences in image quality parameters between the four preparations were assessed using ordinal regression analysis. In this analysis, first the preparation with the highest regression coefficient was determined; this was subsequently used as the reference group. With regard to the per-segment analysis, ordinal regression analysis was applied using generalized estimating equations (GEE) to revise the data clustering and dependency [25]. This was done because more than one segment was obtained from each patient. The link function was set at log link, and an independent working correction matrix was used. Furthermore, associations between normal defecation frequency and subjective image quality parameters were tested with the chi-square test. If significant associations were present, additional ordinal regression analyses using GEE for revising the patient’s normal defecation frequency were performed. Associations between the subjective image quality parameters (e.g., association between fecal tagging and the amount of residual feces) within each group were assessed using the chi-square test.

**Numeric evaluation of degree and homogeneity of tagging**
Because more than one measurement of Hounsfield units and SD was obtained from each patient, linear regression analysis was applied using GEE to revise the data clustering and dependency. Furthermore, ROIs were placed at random and were not evenly distributed among segments. This might have resulted in differences in measured homogeneity because of the physiologic variation of mean tagging
Laxative regimes for CT colonography

attenuation within a given patient due to the normal dehydrating action of the colon. Therefore, the GEE analysis was adjusted to correct for this segmental distribution. Furthermore, because liquid material tends to be more homogeneously tagged than solid material, the GEE analysis was adjusted to correct for stool consistency (solid, adherent, or liquid feces). For each group, estimates of means with corresponding standard errors could be calculated from the results (intercept and slopes) obtained by the analysis.

Patient experience and preference
Differences in patient experience (burden) were analyzed using ordinal regression analysis and the preparation with the lowest regression coefficient (most burdensome) as the reference group. The chi-square test was used to test for significant differences in patients’ indications of the most burdensome preparation and examination (CTC or conventional colonoscopy) between groups. Patient preference for either CTC or colonoscopy was tested using the chi-square test after the data were first dichotomized as preference for CTC versus preference for colonoscopy.

Interpretation time
Differences in interpretation times for the different preparations were tested for significance using the independent samples Student’s t test. Statistical analyses were performed with SPSS version 12.0.2 for Windows (SPSS) and SAS version 8.02 for Windows (SAS Institute). The Proc Genmod command was used to apply the generalized estimating equations. A p-value of < 0.05 was considered to indicate a statistically significant difference.

Results
All patients included in this study accepted randomization. Eleven patients were randomized into group 1, 10 patients into group 2, 10 patients into group 3, and nine patients into group 4. Twenty-seven patients were men (67.5%) and 13 patients were women (32.5%), with an average age of 62 years (age range, 40–83 years). Fourteen (35%) patients had symptoms (abdominal pain, 6; hematochezia, 4; and altered bowel habits, 4), and 26 (65%) patients were asymptomatic. Thirty-three (83%) patients had a personal history of colorectal polyps (n = 21), cancer (n = 6), or both (n = 6). A total of 11 patients had undergone surgery for a colorectal cancer:
right-sided hemicolectomy \((n = 1)\), transverse colectomy \((n = 2)\), low anterior resection \((n = 7)\), total mesorectal excision \((n = 1)\). Thirty of 38 patients who filled out the questionnaire with regard to bowel frequency had a defecation frequency of one defecation or more per day, five patients had a defecation frequency of once in 2 days, two patients (groups 2 and 3) had a frequency of once in 3 days, and one patient had a bowel frequency of once in 3–5 days (group 2). Because one patient had undergone a hemicolectomy, a total of 476 bowel segments were available for analysis (per position: group 1, 66 segments; group 2, 58; group 3, 60; and group 4, 54 segments). The average room examination time for CTC was 15 minutes.

**Subjective image quality**

On a per-patient basis \((n = 40)\), no significant differences were found between groups with regard to image quality. All examinations were evaluated as good (diagnostic for lesions \(\geq 6\) mm) or excellent (diagnostic with no limitations) image readability. Only one examination (group 2) was of nondiagnostic value (because of poor distention) and two examinations (group 3) were of moderate image readability (because of moderate fecal tagging) (Table 3). Within each group, a higher degree of homogeneity was significantly associated with better image readability \((p < 0.006)\).

<table>
<thead>
<tr>
<th>Group</th>
<th>Excellent; No Limitations</th>
<th>Good; Diagnostic for Lesions (\geq 6)mm</th>
<th>Moderate; Diagnostic for Lesions (\geq 10)mm</th>
<th>Poor; Not Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ((n=11))</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 ((n=10))</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 ((n=10))</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4 ((n=9))</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note—Data are number of examinations that were subjectively evaluated by the reviewer.*

For group 2, poorer distention was associated with decreased image readability \((p = 0.002)\). On a per-segment basis, significantly more residual feces was present in group 2 in comparison with group 4 \((p = 0.04)\). No other significant differences in image quality were found between groups (Fig. 3). Fecal material was significantly more liquid in group 4 in comparison with groups 1, 2, and 3 \((p = 0.004, p = 0.002,\)
and \( p < 0.001 \) (Fig. 4). A significant association was observed between daily bowel habits and the amount of residual feces in the colon for groups 2 and 3 \( (p < 0.0001) \). In other words, a lower defecation frequency in normal life was associated with a higher amount of residual feces in our study. Subsequently, when the normal defecation frequency of patients was included in the GEE analysis, the finding that group 2 contained more residual feces than group 4 was no longer significant \( (p = 0.160) \).

**Numeric evaluation of degree and homogeneity of tagging**

The degree of tagging, expressed as the mean attenuation of tagged material, decreased when more laxatives were used (Table 4); however, this decrease was not statistically significant \( (all \ p \geq 0.253) \). A gradual decrease in mean SD of pixel values was also found from group 1 to group 4. This decline, however, was not significant between groups \( (all \ p \geq 0.067) \). Furthermore, the relative SD \( (SD/mean) \) did not differ significantly among groups \( (all \ p \geq 0.157) \), indicating no difference in homogeneity of tagging among groups.

**Figure 3.** Graphs show subjective image quality scores on per-segment basis

<table>
<thead>
<tr>
<th>Fecal Tagging</th>
<th>Amount of Feces</th>
<th>Distension</th>
<th>Diagnostic Readability</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of segments</td>
<td>% of segments</td>
<td>% of segments</td>
<td>% of segments</td>
</tr>
<tr>
<td>group I</td>
<td>group II</td>
<td>group III</td>
<td>group IV</td>
</tr>
<tr>
<td>poor</td>
<td>moderate</td>
<td>good</td>
<td>very good</td>
</tr>
</tbody>
</table>

Fecal tagging and amount of feces were scored on supine images (for group 1, 66 segments; group 2, 58 segments; group 3, 60 segments; and group 4, 54 segments). Distention and diagnostic readability were scored on supine and prone images (132, 120, 210, and 108 segments, resp.). Group 2 performed significantly poorer with regard to amount of residual feces in comparison with group 4 \( (p = 0.04) \).
Regardless of the preparation, the relative SD was significantly higher for solid feces (0.22) versus adherent (0.16) or liquid (0.14) feces, showing that tagging was less homogeneous for solid feces than for adherent stool ($p = 0.008$) or liquid feces ($p = 0.001$) (Table 5).

**Interpretation time**

The mean interpretation time for group 1 was 16 minutes, for group 2 was 24 minutes, for group 3 was 26 minutes, and for group 4 was 21 minutes (all $p \geq 0.107$).

**Patient Experience**

All patients experienced diarrhea except for three patients in group 2. The burden of diarrhea was evaluated as none or mild by six patients (55%) in group 1, six patients (60%) in group 2, four patients (40%) in group 3, and one patient (11%) in group 4. Diarrhea was considered significantly more burdensome in group 4 than in groups 1 ($p = 0.042$) and 2 ($p = 0.031$) but not compared with group 3 ($p = 0.179$).

With regard to abdominal pain and flatulence, no significant differences were found among groups. With regard to abdominal pain ($n = 37$), one patient in group 4 had severe abdominal pain, and two patients (groups 2 and 4) had moderate abdominal pain. The remaining patients had little ($n = 6$) or no ($n = 28$) pain. With regard to flatulence ($n = 37$), one patient in group 4 experienced a severe burden, one patient in group 2 had a moderate burden, and the other patients experienced little ($n = 5$) or no ($n = 30$) burden.
The total burden of the bowel preparation was rated as none or mild by all patients (100%) in group 1, nine (90%) in group 2, eight (80%) in group 3, and five (55%) in group 4—a significantly higher total burden in group 4 than in groups 1 ($p = 0.002$) and 3 ($p = 0.02$). No significant difference ($p = 0.082$) was found between groups 2 and 4, most likely because one patient in group 2 rated the CTC bowel preparation as extremely burdensome. This patient stated, before the CTC preparation, an explicit preference for the colonoscopy preparation because in his opinion that preparation was simpler and shorter. Excluding this patient, a significantly lower overall burden ($p = 0.04$) was found for group 2 in comparison with group 4. Most patients experienced no or only a mild burden with regard to the intake of barium (32/34),

### Table 4. Estimates of Mean Attenuation and Mean SD of Fecal Material

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Fecal Material</th>
<th>Liquid Consistency</th>
<th>Adherent Consistency</th>
<th>Solid Consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation 1</td>
<td>(n=77)</td>
<td>720</td>
<td>106</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>(71%)</td>
<td>683</td>
<td>98</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(19%)</td>
<td>803</td>
<td>115</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>(10%)</td>
<td>1030$^a$</td>
<td>215$^b$</td>
<td>0.18</td>
</tr>
<tr>
<td>Preparation 2</td>
<td>(n=66)</td>
<td>686</td>
<td>97</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(60%)</td>
<td>710</td>
<td>74</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>(14%)</td>
<td>636</td>
<td>89</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>(26%)</td>
<td>634</td>
<td>140</td>
<td>0.21$^c$</td>
</tr>
<tr>
<td>Preparation 3</td>
<td>(n=70)</td>
<td>654</td>
<td>80</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(60%)</td>
<td>684</td>
<td>73</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>(29%)</td>
<td>677</td>
<td>103</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(11%)</td>
<td>485</td>
<td>74</td>
<td>0.25$^c$</td>
</tr>
<tr>
<td>Preparation 4</td>
<td>(n=60)</td>
<td>557</td>
<td>62</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>(90%)</td>
<td>509</td>
<td>56</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>(10%)</td>
<td>685</td>
<td>94</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Note—Numbers in parentheses are the number of measurements. Percentages in parentheses refer to the percentage of measurements in the indicated form of fecal material. NA = not applicable.

$^a$Significantly higher mean value for solid consistency in comparison with liquid ($p = 0.003$) or adherent ($p=0.046$) consistency within preparation group 1.

$^b$Significantly higher SD value for solid consistency in comparison with liquid ($p = 0.025$) or adherent ($p = .008$) consistency within preparation group 1.

$^c$Significantly higher relative SD value for solid consistency in comparison with liquid consistency within preparation group 2 ($p = 0.006$) and within preparation group 3 ($p = 0.011$).
diatrizoate meglumine (36/40), bisacodyl (34/37), or magnesium citrate (9/15), with no significant differences between the groups.

### Table 5. Tagging characteristics for stool consistency regardless of the preparation

<table>
<thead>
<tr>
<th>Stool Consistency</th>
<th>Mean (HU)</th>
<th>SD</th>
<th>Relative SD (SD/mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid consistency (n=32)</td>
<td>737</td>
<td>143a</td>
<td>0.22b</td>
</tr>
<tr>
<td>Adherent consistency (n=50)</td>
<td>688</td>
<td>97</td>
<td>0.16</td>
</tr>
<tr>
<td>Liquid consistency (n=191)</td>
<td>631</td>
<td>79</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Note**—Data in parentheses are number of measurements.

a SD was significantly higher for solid than for adherent ($p = 0.041$) or liquid ($p = 0.005$) feces.

b Relative SD was significantly higher for solid than for adherent ($p = 0.008$) or liquid ($p = 0.001$) feces.

### Table 6. Most Burdensome Event for 40 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>CTC Bowel Preparation</th>
<th>CTC Examination</th>
<th>Conventional Colonoscopy Bowel Preparation</th>
<th>Conventional Colonoscopy Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

**Note**—Appraisal by patients 5 weeks after CT colonography (CTC) and conventional colonoscopy. Most patients (n = 30) indicated the bowel preparation for colonoscopy as the most burdensome event regardless of the bowel preparation used for CTC.

### Patient Preferences

Except four patients (one in group 2 and three in group 3), all patients found colonoscopy a more burdensome examination than CTC. If patients were asked what examination they would prefer in the future, most patients (30/40) indicated a preference for CTC, two patients were indifferent, and eight patients preferred conventional colonoscopy (Fig. 5). The reasons patients preferred colonoscopy were: direct polypectomy ($n = 4$), shorter preparation time ($n = 2$), false-positive CTC ($n = 1$), and no particular reason ($n = 1$). No significant differences in preference were observed among the groups. All (100%) patients in group 1, nine (90%) patients in group 2, eight (80%) in group 3, and seven (78%) patients in group 4 preferred CTC bowel preparation over the polyethylene glycol preparation, with no significant differences among groups ($p = 0.054$). In all groups, most patients evaluated the
bowel preparation for colonoscopy \((n = 30)\) or colonoscopy itself \((n = 5)\) as the most burdensome event, with no significant differences among the groups (Table 6).

**Figure 5.** Patient preference 5 weeks after colonoscopy

Graph shows patient preference 5 weeks after colonoscopy. Patients \((n = 40)\) indicated whether they preferred CT colonography (CTC) or colonoscopy (CC) as colorectal examination in the future. Most patients \((n = 30)\) preferred CTC.

**Discussion**

In this feasibility study regarding image quality and patient acceptance, we investigated four different dosages of mild laxatives, consisting of bisacodyl (a bowel stimulant) and magnesium citrate (a hyperosmotic saline laxative), to prepare patients for CTC. Our results showed good to excellent image readability of CTC examinations \((37/40)\) regardless of the preparation used. Increasing the amounts of laxatives did not lead to a higher attenuation of tagging or to more homogeneous tagging, and subjective image quality did not show significant improvement. A higher dosage of laxatives was significantly associated with a higher burden of diarrhea and a higher overall burden of the bowel preparation. Nevertheless, irrespective of the amount of laxatives for CTC, the majority of patients \((35/40)\) preferred the bowel preparation for CTC over the cleansing laxative bowel preparation (polyethylene glycol) for colonoscopy.

In two previous studies, the same or a higher dose of magnesium citrate (without bisacodyl) as used in our group 4, was used; both reported significantly better image quality of CTC images compared with images made without the use of laxatives [20, 21]. Magnesium citrate liquefies residual feces and decreases the amount of remaining feces. This is associated with better readability [21] and can be expected to lead to increased homogeneity of tagged material. In concordance with these
studies, we expected that image quality would gradually improve in our study and be best with group 4.

In our study, however, a higher level of catharsis resulted in neither better image quality nor improvement of tagging characteristics (subjective or numeric). Our data showed that residual feces in group 4 was more liquefied compared with the other groups (all $p \leq 0.004$), but the relative SD (SD / mean) did not decrease, indicating that homogeneity did not improve. A decline, although not significant ($p \geq 0.253$), of the mean attenuation of the tagged material from group 1 to group 4 was observed that we did not anticipate. The lower attenuation values in groups with more catharsis might be explained because lower concentrations of contrast agent were present as a result of dilution caused by the hyperosmotic effect of magnesium citrate.

Regardless of the preparation, solid feces was less homogeneously tagged than liquid stool. However, we believe that homogeneity of solid feces was still satisfactory in all groups. Attenuation of solid feces was high (group 1, 1,030 H; group 2, 634 H; and group 3, 485 H) with relatively small SDs (215, 140, and 74, respectively) and nearly constant relative SDs (0.18, 0.21, and 0.23, respectively). As a result, the lowest attenuation value of tagged solid material was still well above soft-tissue density in all groups.

Most segments (88%) contained no or only small amounts of feces. Furthermore, no decrease in the amount of fecal material was observed using a higher dose of laxatives. This is in contrast with the results of Dachman et al. [21], who found no feces in only 65% of segments using magnesium citrate. That we used a combination of barium and diatrizoate meglumine for tagging purposes instead of only barium might explain this difference. Probably the laxative side effect of diatrizoate meglumine combined with (small amounts of) laxatives caused relatively clean colons with good homogeneity of tagged feces.

Increasing the amounts of laxatives did not improve subjective image quality but did increase the burden perceived by patients. In our study, most patients experienced diarrhea, regardless of the preparation used. These observations are not in line with the previously discussed study by Zalis et al. [20]. In that study, only one of 22 patients reported mild transient diarrhea after preparation with magnesium citrate. Two important differences between the studies may explain this discrepancy. First, we used ionic iodinated contrast material, which is known to have a strong osmotic effect, instead of a nonionic contrast agent. Second, in our study, all patients
received bisacodyl, whereas in the Zalis et al. study, no bisacodyl was administered at all. It is likely that a combination of both factors led to some degree of diarrhea. Although diarrhea was present in all preparations, the burden of diarrhea and the overall burden of the preparation significantly increased with higher doses of laxatives. In fact, one could argue whether laxatives should be added at all to the preparation if ionic contrast agents are used in high concentrations. At the time of the writing of this article, we no longer add any form of laxatives to the preparation, and we believe this has not impaired the image quality of CTC.

An interval of 5 weeks was applied after colonoscopy to ask patients about their preference because the memory of adverse reactions may decrease over time [7, 8, 24]. The majority of patients (75%) preferred CTC as a colorectal examination and considered the polyethylene glycol–electrolyte solution for colonoscopy the most unpleasant factor (75%). In our institution, this bowel preparation is used by the gastroenterologists for all patients because it is safe to use and rigorously cleans the colon. Other bowel preparations for colonoscopy, such as an osmotic laxative ([sodium phosphates solution] Phospho-soda, Fleet), are considered more patient-friendly [26, 27]. Had these been used in our study, they might have caused a shift in patient preference toward colonoscopy. A disadvantage of Phospho-soda is that it can cause electrolyte imbalance and is contraindicated in patients with congestive heart failure or renal failure [28, 29].

Several limitations of our study must be considered. A limited cohort of 40 patients, randomized into four groups, participated in this study. Despite the relatively low numbers of patients per group, we did find a significantly higher patient burden with increasing laxative dosage. With regard to image quality, no trend of improvement in quality was observed with more catharsis. However, in group 2, segments contained significantly more feces compared with group 4. This was mainly attributed to the fact that two of the three patients in our study with a relatively low defecation frequency in normal life were placed in group 2. Despite more feces present in the colon, image readability of the examinations was not significantly affected. Although our data are limited, this might suggest that with adequate tagging, patients with bowel habits of one defecation in 3–5 days can be prepared with minimal amounts of laxatives without affecting image quality. Furthermore, all patients without diarrhea (n = 3) were in group 2. Patients were not asked about compliance with the preparation. Because non-compliance could have contributed to more residual feces in group 2 but could also provide a possible explanation for the moderate image quality in two patients in group 3, we considered that a limitation of our study.
Furthermore, only one observer subjectively evaluated all data on image quality. It is possible that another observer would rate the data differently. Another possible qualifier is that we did not include a full catharsis regimen as a reference standard to which the studied preparations were compared. However, we believe that for this study a clinically relevant scoring system was constructed with regard to image quality of the examinations: using classifications as not diagnostic, diagnostic for all lesions, diagnostic for lesions $\geq 6$ mm, or only diagnostic for lesions $\geq 10$ mm.

The experience of the reviewer before our study consisted of 150 cathartic CTC examinations, and consequently image quality of these examinations served as a reference standard for the reviewer. With regard to patient experience, the bowel preparation used for colonoscopy in our study was a full cathartic bowel preparation using a polyethylene glycol–electrolyte solution that can also be used for CTC. Most patients in all groups indicated the colonoscopy preparation as more burdensome when compared with the CTC bowel preparation.

We used an iodine-based contrast medium for fecal tagging in addition to barium. Some investigators prefer using only barium because of the side effects and possible adverse reactions to iodine-based contrast agents [10]. However, we believe that a combination of both contrast agents resulted in adequate tagging of both solid and liquid feces as stated in other studies [2, 29]. Although the laxative side effect of an iodine-based contrast agent will probably increase the patient burden in some way, an advantage is that CTC images are easier to interpret and a possible cleansing algorithm might be more effective [20, 30]. Finally, in our study we focused on image quality. Polyp conspicuity was not investigated. So far, one larger study without catharsis has reported an excellent sensitivity of 90% and specificity of 92% for patients with polyps of any size [18]. Although further research is warranted, these results underscore our findings that good image quality can be obtained with small amounts of laxatives.

We conclude that CTC with limited bowel preparation, using barium and ionic iodinated contrast agents for fecal tagging, requires only minimal doses of laxatives—in our study only 20 mg of bisacodyl—to obtain good image quality and minimize patient burden. This is important because a mild bowel preparation will undoubtedly increase patient willingness to participate in a screening program.
Laxative regimes for CT colonography

Acknowledgments

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Chapter 2


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Chapter 3

CT Colonography with Limited Bowel Preparation: Performance Characteristics in an Increased-Risk Population

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Jaap Stoker

Radiology 2008; 247:122-132
Abstract

Purpose: To prospectively evaluate the sensitivity and specificity of computed tomographic (CT) colonography with limited bowel preparation for the depiction of colonic polyps, by using colonoscopy as the reference standard.

Methods: Institutional review board approval and written informed consent were obtained. Patients at increased risk for colorectal cancer underwent CT colonography after fecal tagging, which consisted of 80 mL of barium sulfate and 180 mL of diatrizoate meglumine. Bisacodyl was added for stool softening. A radiologist and a research fellow evaluated all data independently by using a primary two-dimensional approach. Discrepant findings for lesions 6 mm or larger in diameter were solved with consensus. Segmental unblinding was performed. Per-patient sensitivity and specificity, per-polyp sensitivity, and number of false-positive findings were found (for lesions $\geq 6$ mm and $\geq 10$ mm in diameter). Per-patient sensitivities (blinded colonoscopy versus CT colonography) were tested for significance with McNemar statistics. Interobserver variability was analyzed per segment (prevalence-adjusted bias-adjusted $\kappa$ values [$\kappa_p$]).

Results: One hundred fourteen of 168 patients (105 men, 63 women; mean age, 56 years) had polyps, with 56 polyps 6 mm or larger and 17 polyps 10 mm or larger. Per-patient sensitivities were not significantly different for CT colonography (consensus reading) and colonoscopy ($P \geq 0.070$). Sensitivity of CT colonography for patients with lesions 6 mm or larger and 10 mm or larger was 76% and 82%, respectively, and specificity of CT colonography was 79% and 97%, respectively. Blinded colonoscopy depicted 91% (lesions $\geq 6$ mm) and 88% (lesions $\geq 10$ mm) of disease in patients. Per-polyp sensitivity for CT colonography was 70% (lesions $\geq 6$ mm) and 82% (lesions $\geq 10$ mm). Number of false-positive findings was 42 (lesions $\geq 6$ mm) and six (lesions $\geq 10$ mm). $\kappa_p$ Was 0.88 (lesions $\geq 6$ mm) and 0.96 (lesions $\geq 10$ mm).

Conclusion: CT colonography with limited bowel preparation has a sensitivity of 82% and specificity of 97% for patients with polyps 10 mm or larger.
Introduction

As with other colonic examinations, computed tomographic (CT) colonography requires a clean colon for optimal assessment of the bowel wall [1–5]. However, the necessary cathartic bowel preparation is often described by patients as the most burdensome part of colonic examinations [6–9]. This might negatively affect patients' willingness to participate in a screening program. In 2001, limited bowel preparation for CT colonography with iodine- or barium-based contrast material for fecal tagging was introduced [10]. With fecal tagging, any fecal material in the colon is labeled so that colorectal polyps or cancer can be distinguished from fecal material. Because no extensive bowel cleansing is necessary, this approach might increase patient compliance in a screening setting [11–13].

Feasibility studies with limited bowel preparation have revealed promising results [14–18]. In addition, results of one large diagnostic accuracy study by Iannaccone et al [19] showed a sensitivity of 90% (71 of 79) and specificity of 92% (114 of 124) for patients with polyps, regardless of polyp size. These results are similar or superior to those of accuracy studies in which a cathartic bowel preparation was used [1–5].

To our knowledge, no confirmatory study on limited bowel preparation has been published since that of Iannaccone et al [19]. Therefore, the aim of our study was to prospectively evaluate the sensitivity and specificity of CT colonography with limited bowel preparation for the depiction of colonic polyps, by using colonoscopy as the reference standard.

Materials and Methods

This study received grant support from the Dutch Cancer Society (Koningin Wilhelmina Fonds) (No. CKTO 2003-02). The authors retained control of all aspects of the study.

Patients

Patients with a personal or family history of colorectal polyps or cancer were invited to participate from January 10, 2004, until November 10, 2005. All patients were scheduled to undergo routine colonoscopy at the endoscopy department of the Academic Medical Center or the Onze Lieve Vrouwe Gasthuis. Exclusion criteria were age younger than 18 years, a personal history of inflammatory bowel disease or familial adenomatous polyposis, prior allergic reaction to an iodine-containing contrast
agent, known colorectal polyps that were not removed at prior endoscopy, or participation in a research project that involved ionizing radiation within 12 months preceding CT colonographic examination. The institutional review boards of both hospitals approved the study. All patients gave written informed consent. Information about radiation associated with the examination was given to all patients before written consent was obtained.

<p>| Table 1. Bowel preparation for CT Colonography |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Instruction and Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days before CT colonography</td>
<td>Avoid fiber rich food 20 ml Barium Sulphate at dinner</td>
</tr>
<tr>
<td>1 day before CT colonography</td>
<td>Three doses of 20 mL barium sulphate and three doses of diatrizoate meglumine, once at breakfast, lunch and dinner Only liquids after dinner 20 mg bisacodyl (oral) 18 hours prior to CT colonography</td>
</tr>
<tr>
<td>day of examination</td>
<td>60 mL diatrizoate meglumine and 10 mg bisacodyl (oral) at breakfast 60 mL diatrizoate meglumine 1 hour before CT colonography</td>
</tr>
</tbody>
</table>

*Barium Sulphate (40% w/v, 30%w/w), Diatrizoate Meglumine (200mgI/ml).

Diagnostic Procedures

Bowel preparation

Patients were instructed not to eat high-fiber foods for 2 days before the examination. A combination of 80 mL of barium sulfate suspension (Tagitol V; E-Z-Em, Westbury, NY) and 180 mL of diatrizoate meglumine (200 milligrams of iodine per milliliter, prepared by hospital pharmacy, Academic Medical Center) was prescribed for fecal tagging (Table 1). Bisacodyl (30 mg, prepared by hospital pharmacy, Academic Medical Center) was given to soften fecal material for optimal contrast material and feces mixing and to avoid solid, sticky stool.

CT colonographic image analysis

CT colonographic data were evaluated for colorectal polyps and carcinoma independently by two observers who were blinded to clinical data. Observer 1 (J.P.) had 5 years of experience as an abdominal radiologist and had received training consisting of 50 cathartic untagged and 20 limited preparation tagged CT
colonographic cases with colonoscopic verification. Observer 2 (A.H.d.V.) was a research fellow who had evaluated 100 cathartic untagged and 20 limited preparation tagged CT colonographic cases with colonoscopic verification as part of his fellowship in CT colonography. Evaluation of data was performed with a dedicated CT colonographic workstation (Viewforum; Philips Medical Systems) by using a primary two-dimensional evaluation technique, with instant onscreen correlation with multiplanar reformation images and three-dimensional endoluminal views for problem solving. Standard window settings were applied (window width, 1250 HU; window level, –50 HU), but observers were free to adjust these settings.

**Figure 1. Flow-chart shows patient participation**

- 468 pt at increased risk for colorectal cancer (316 [blinded]; 152 [blinded])
- 85 not requested
  - Reasons: organizational, 25
  - unreachable, 60
- 383 requested
- 203 refused
- 180 participated
- 6 patients declined later on
  - second thoughts, 3
  - reported allergic reaction, 2
  - claustrophobia, 1
- CTC
- 6 patients excluded for analysis
  - no segmental unblinding, 1
  - no colonoscopy, 1
  - inadequate bowel preparation, 4
- 174 underwent CTC
- 168 patients for analysis
Stool subtraction software was not used, and routine endoluminal fly-through was not performed. The observers classified CT colonographic polyps with regard to size, morphology (sessile, pedunculated, or flat [ie, height < 3 mm]), and location (cecum, ascending colon, transverse colon, descending colon, or sigmoid colon and rectum) by using the same classification as our gastroenterologists. Consensus reading, or a double-read strategy, was performed in case one observer found a lesion 6 mm or larger in diameter but the other did not or if both observers found the same lesion but disagreed on morphology, size, or location. Agreement forms were completed after each examination for polyps 6 mm or larger in diameter and included two-dimensional and three-dimensional images of the polyp at CT colonography, with the location marked in the three-dimensionally rendered colon. The research nurse (A.H.) used these agreement forms to provide feedback for segmental unblinding during colonoscopy. Interpretation times, with the exclusion of reporting time and evaluation of extracolonic findings, were recorded for each examination by both observers.

**CT colonographic stool-tagging analysis**
A questionnaire was filled out by observer 1 to subjectively assess the adequacy of stool tagging for every examination. A four-point scale was used in which a score of 1 indicated good tagging (homogeneous, diagnostic for all lesions); a score of 2, adequate tagging (fairly homogeneous and diagnostic for all lesions); a score of 3, poor tagging with untagged solid stool less than 6 mm (diagnostic for lesions ≥6 mm); and a score of 4, poor tagging with untagged solid stool 6 mm or larger (not diagnostic for lesions ≥6 mm).

### Table 2. Baseline patient characteristics (n=168)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-female ratio</td>
<td>105:63</td>
</tr>
<tr>
<td>Age (y)</td>
<td>56 (24-79)</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
</tr>
<tr>
<td>Academic Medical Center / Onze Lieve Vrouwe Gasthuis</td>
<td>119 /49</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Without polyps</td>
<td>54</td>
</tr>
<tr>
<td>With polyps (all sizes)</td>
<td>114</td>
</tr>
<tr>
<td>With a polyp ≥10mm</td>
<td>17</td>
</tr>
<tr>
<td>History of colorectal polyps or cancer</td>
<td>108</td>
</tr>
<tr>
<td>Family history of colorectal polyps or cancer</td>
<td>60</td>
</tr>
</tbody>
</table>

Note.-unless otherwise indicated, data are numbers of patients.
Colonoscopy
An experienced staff member (a gastroenterologist \(n = 15\) or a gastrointestinal surgeon \(n = 4\) with an average experience of 11 years; range, 1–26 years) or a gastroenterology fellow with direct supervision (including E.D., J.F.B., L.C.B.) performed the colonoscopic examinations with a standard colonoscope (CF-140L; Olympus, Tokyo, Japan). Patients received 2.0–10.0 mg midazolam (Dormicum; Roche, Basel, Switzerland) and 0.05–0.1 mg fentanyl (Fentanyl-Janssen; Janssen Pharmaceuticals, Beerse, Belgium) on request. The examination was recorded on videotape. Segmental location, morphology, and size of polyps were documented on a case-record form by the attending research nurse (A.H.). Polyp size was measured with open biopsy forceps (8 mm in length). Segmental unblinding was performed only for lesions 6 mm or larger that both observers agreed on (independently or through consensus). Histological findings were obtained at colonoscopy, except in those cases in which it was technically not possible or when material was lost in the colonic lumen during the procedure.

Determination of lesion status
Colonoscopy after unblinding of the CT colonographic findings served as a reference standard. For CT colonography, a polyp was considered true-positive if (a) the segment or adjacent segment corresponded with the reference standard segment and (b) the polyp size as estimated by the endoscopist corresponded with size as measured at CT colonography, considering a margin of error of 50%. Polyps 10 mm or larger at colonoscopy that were not identified by either observer were reevaluated with knowledge of the colonoscopic findings by an independent radiologist with experience in the evaluation of more than 1000 CT colonographic studies. This reevaluation was performed to differentiate between technical errors (polyps obscured by technical failure [e.g., inhomogeneous tagging]), perception errors (polyps visible in retrospect), and occult lesions (polyps not visible in retrospect). This classification was also used by MacCarty et al [20]. Furthermore, a research fellow in CT colonography (S.J.) who was not involved in evaluation of the CT colonographic assessed the nature of false-positive findings 10 mm or larger (eg, untagged stool or haustral folds).

Patient experience and preference
To evaluate patient experience, we asked patients to fill out a questionnaire on the day of the CT colonographic examination. Patients were asked if they had
experienced diarrhea as a side effect and graded it on a five-point scale (none, mild, moderate, severe, extreme, with 0 indicating none and 5 indicating extreme). Furthermore, the overall burden of the complete preparation was evaluated on the same scale. Patient preference was assessed 5 weeks after colonoscopy. This, like adverse reactions to tests, tends to temper with time [7,8], and the attitude at that time point will better reflect the attitude toward future screening. Patients were asked if they had experienced the bowel preparation for CT colonography or that for colonoscopy as most burdensome and if they would prefer CT colonography or colonoscopy in the future as the colonic examination of choice.

**Statistical Analysis**

**Outcome parameters**

Observers were instructed before the start of the study that only polyps at CT colonography that were matched to true polyps (i.e., adenomatous, hyperplastic, or hamartomatous polyps) on the basis of the histological report or, if histological findings were not acquired, on the basis of the endoscopic report would be considered true-positive findings. All other lesions at CT colonography that were matched to polypoid lesions at colonoscopy that have no malignant potential (e.g., lipomas or pseudopolyps) would be classified as false-positive findings. For CT colonography, a patient was considered to have a true-positive finding if CT colonography depicted at
least one polyp seen at colonoscopy, on the basis of the location and size criteria described previously. A patient was considered to have a false-negative finding if CT colonography depicted no polyps or only those of a lower size category in comparison to those depicted with the reference standard. Sensitivity, specificity, and positive and negative predictive values were calculated for CT colonography on a per-patient basis and were stratified according to polyp size (all sizes, ≥6 mm, ≥7 mm, ≥8 mm, ≥9 mm, and ≥10 mm, as well for the size range 6–9 mm). Per-patient sensitivity was calculated for blinded colonoscopy. For calculation of the per-polyp sensitivity for CT colonography and blinded colonoscopy, generalized estimating equations (GEE) were used to revise the data clustering and dependency (21) because some patients had more than one polyp. For CT colonography, the number of false-positive findings was calculated on a per-lesion basis. For the per-polyp sensitivity and false-positive findings, data were also stratified according to polyp size (all sizes, ≥6 mm, ≥7 mm, ≥8 mm, ≥9 mm, and ≥10 mm, as well for the size range 6–9 mm).

<table>
<thead>
<tr>
<th>Table 3. Histology and morphology of polyps at colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyps 6-9mm (n=39)</strong></td>
</tr>
<tr>
<td>No histology finding</td>
</tr>
<tr>
<td>Histology finding</td>
</tr>
<tr>
<td>Hyperplastic</td>
</tr>
<tr>
<td>Adenomatous*</td>
</tr>
<tr>
<td>tubulovillous</td>
</tr>
<tr>
<td>tubular</td>
</tr>
<tr>
<td>serrated</td>
</tr>
<tr>
<td>non-specified</td>
</tr>
<tr>
<td>Hamartomatous</td>
</tr>
<tr>
<td>Morphology</td>
</tr>
<tr>
<td>Sessile</td>
</tr>
<tr>
<td>Pedunculated</td>
</tr>
<tr>
<td>Flat</td>
</tr>
</tbody>
</table>

Note- Data are number of polyps.
*No specification of the degree of dysplasia is provided by the pathologist in our institution.
Chapter 3

**Diagnostic value**
We used the McNemar test to compare per-patient sensitivity values between blinded conventional colonoscopy, consensus reading, and observer 1 and observer 2 (colonoscopy vs consensus reading, colonoscopy vs observer 1, colonoscopy vs observer 2, consensus reading vs observer 1, consensus reading vs observer 2, and observer 1 vs observer 2). We also used the McNemar test to compare per-patient specificity values between consensus reading and both observers (consensus reading vs observer 1, consensus reading vs observer 2, and observer 1 vs observer 2). With the GEE model, we took into account the comparison of per-polyp sensitivities between blinded colonoscopy, consensus reading, and both observers (colonoscopy vs consensus reading, colonoscopy vs observer 1, colonoscopy vs observer 2, consensus reading vs observer 1, consensus reading vs observer 2, and observer 1 vs observer 2).

**Interobserver variability**
Per-segment agreement and prevalence-adjusted bias-adjusted $\kappa$ values ($\kappa_p$ values) were calculated (22,23) for lesions 6 mm or larger and lesions 10 mm or larger. Observers were considered to agree if both recorded corresponding lesion(s) in the same segment or if both recorded no findings. Values were interpreted as those for the regular Cohen $\kappa$ statistic: $\kappa_p \leq 0.20$ indicated poor agreement; $\kappa_p = 0.21–0.40$, fair agreement; $\kappa_p = 0.41–0.60$, moderate agreement; $\kappa_p = 0.61–0.80$, good agreement; and $\kappa_p = 0.81–1.00$, very good agreement.

**Interpretation time**
Mean interpretation times and 95% confidence intervals are provided. Differences in evaluation time between the observers were tested for significance by using the paired Student $t$ test.

GEE analyses were performed with software (SPSS 15 for Windows; SPSS, Chicago, Ill). All other analyses (per-patient sensitivity, per-patient specificity, and interpretation time) were performed with software (SPSS for Windows, version 12.0.2; SPSS).

$P$ values less than .05 were considered to indicate statistically significant differences.
Results

Patients

Of 468 eligible patients who were scheduled to undergo colonoscopy during the inclusion period, 180 participated in the study. Twelve (7%) of 180 patients were excluded for different reasons, which left 168 patients for analysis (Fig 1, Table 2).

Table 4. Per-Patient Sensitivity and Specificity according to Polyp Size

<table>
<thead>
<tr>
<th></th>
<th>All sizes</th>
<th>6-9 mm</th>
<th>≥6mm</th>
<th>≥7mm</th>
<th>≥8mm</th>
<th>≥9mm</th>
<th>≥10mm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>a 109/114</td>
<td>b 26/28</td>
<td>c 41/45</td>
<td>32/35</td>
<td>21/23</td>
<td>15/17</td>
<td>15/17</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>93</td>
<td>91</td>
<td>91</td>
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<td>(82-100)</td>
<td>(80-100)</td>
<td>(73-100)</td>
<td>(73-100)</td>
</tr>
<tr>
<td>Consensus</td>
<td>n/a</td>
<td>20/28</td>
<td>34/45</td>
<td>29/35</td>
<td>20/23</td>
<td>14/17</td>
<td>14/17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71</td>
<td>76</td>
<td>83</td>
<td>87</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(55-88)</td>
<td>(63-88)</td>
<td>(70-95)</td>
<td>(73-100)</td>
<td>(64-100)</td>
<td>(64-100)</td>
</tr>
<tr>
<td>Observer 1</td>
<td>70/114</td>
<td>21/28</td>
<td>34/45</td>
<td>28/35</td>
<td>19/23</td>
<td>13/17</td>
<td>13/17</td>
</tr>
<tr>
<td></td>
<td>61 (52-70)</td>
<td>75</td>
<td>76</td>
<td>80</td>
<td>83</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>59 (59-91)</td>
<td>61</td>
<td>64</td>
<td>69</td>
<td>74</td>
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<td>59 (43-79)</td>
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<tr>
<td>Observer 2</td>
<td>67/114</td>
<td>17/28</td>
<td>29/45</td>
<td>24/35</td>
<td>17/23</td>
<td>12/17</td>
<td>12/17</td>
</tr>
<tr>
<td></td>
<td>59 (50-68)</td>
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<td>64</td>
<td>69</td>
<td>74</td>
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</tr>
<tr>
<td></td>
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<td>(43-79)</td>
<td>(50-78)</td>
<td>(53-84)</td>
<td>(56-92)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consensus</td>
<td>n/a</td>
<td>113/140</td>
<td>97/123</td>
<td>119/133</td>
<td>136/145</td>
<td>145/151</td>
<td>146/151</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81</td>
<td>79</td>
<td>89</td>
<td>94</td>
<td>96</td>
<td>97</td>
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<td>(72-86)</td>
<td>(84-95)</td>
<td>(90-98)</td>
<td>(93-99)</td>
<td>(94-100)</td>
</tr>
<tr>
<td>Observer 1</td>
<td>18/54</td>
<td>111/140</td>
<td>98/123</td>
<td>118/133</td>
<td>134/145</td>
<td>144/151</td>
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<td>33 (21-46)</td>
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<td>(73-87)</td>
<td>(83-94)</td>
<td>(88-97)</td>
<td>(92-99)</td>
<td>(95-100)</td>
</tr>
<tr>
<td>Observer 2</td>
<td>26/54</td>
<td>116/140</td>
<td>98/123</td>
<td>116/133</td>
<td>129/145</td>
<td>140/151</td>
<td>142/151</td>
</tr>
<tr>
<td></td>
<td>48 (35-61)</td>
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<td>87</td>
<td>89</td>
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</tr>
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<td>(73-87)</td>
<td>(82-93)</td>
<td>(84-94)</td>
<td>(89-97)</td>
<td>(90-98)</td>
</tr>
</tbody>
</table>

Note - Data are number of patients and sensitivity with in parenthesis 95% confidence intervals.
a colonoscopy detected significant more patients with lesions of all sizes than observer 1 and 2 (p<0.001, p<0.001).
b colonoscopy detected significant more patients with lesions 6-9mm compared to observer 2 (p=0.012).
c colonoscopy detected significant more patients with lesions ≥6mm than observer 2 (p=0.008).

Colonoscopy

Blinded and unblinded colonoscopic results revealed that 45 (27%) of 168 patients had a polyp 6 mm or larger and 17 (10%) patients had a polyp 10 mm or larger. Table 3 shows results of histological and morphological characterization, subdivided for lesions 6–9 mm and 10 mm or larger. No colorectal carcinomas were found.
Blinded colonoscopy revealed a lesion 6 mm or larger in 41 (91%) of 45 patients and a polyp 10 mm or larger in 15 (88%) of 17 patients (Table 4).

**CT colonography**
The mean scanner-room examination time for patients was 21 minutes (range, 13–48 minutes). Buscopan was administered in 144 patients, glucagon was administered in 21, and three patients received no spasmolytic agent. Eighty-eight patients were scanned with 50 mAs, and 80 patients were scanned with 70 mAs. The average amount of carbon dioxide insufflated was 3.9 L (range, 2.0–8.0 L). No complications occurred.

**Interpretation time**
Observer 1 needed significantly more time to evaluate a complete study than observer 2: a mean interpretation time of 18 minutes (95% confidence interval: 17, 18 minutes) versus a mean interpretation time of 13 minutes (95% confidence interval: 12, 14 minutes) (P < .001).

**Figure 3. Missed lesions ≥ 10 mm at CT colonography**

Figure shows two flat adenomatous polyps (arrows, left and middle image) and a sessile adenomatous polyp (arrow, right image) that were missed by the reviewers. These polyps were not visible in retrospect on the CTC images.

**Per-patient analysis**
No patient had more than one polyp 10 mm or larger. The consensus reading resulted in 34 (76%) of 45 patients with a lesion 6 mm or larger, 20 (71%) of 28 patients with a 6–9-mm lesion, and 14 (82%) of 17 patients with a lesion 10 mm or larger (Table 4, Fig 2). Specificity was 79% (97 of 123) for the identification of
patients with a lesion 6 mm or larger, 81% (113 of 140) for the identification of patients with lesions 6–9 mm, and 97% (146 of 151) for the identification of patients with a lesion 10 mm or larger (Table 4).

Table 5. Per-Patient Negative and Positive Predictive Values at CT colonography according to Polyp Size

<table>
<thead>
<tr>
<th></th>
<th>6-9mm</th>
<th>≥6mm</th>
<th>≥7 mm</th>
<th>≥8 mm</th>
<th>≥9 mm</th>
<th>≥10mm</th>
</tr>
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<tbody>
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<td><strong>Negative Predictive Value</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consensus</td>
<td>113/121</td>
<td>97/108</td>
<td>119/125</td>
<td>136/139</td>
<td>145/148</td>
<td>146/149</td>
</tr>
<tr>
<td></td>
<td>(89-98)</td>
<td>(84-96)</td>
<td>(91-99)</td>
<td>(95-100)</td>
<td>(96-100)</td>
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<td>(84-96)</td>
<td>(90-98)</td>
<td>(94-100)</td>
<td>(95-100)</td>
<td></td>
</tr>
<tr>
<td>Observer 2</td>
<td>116/127</td>
<td>98/114</td>
<td>116/127</td>
<td>129/135</td>
<td>140/145</td>
<td>142/147</td>
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</tr>
<tr>
<td>Consensus</td>
<td>20/47</td>
<td>34/60</td>
<td>29/43</td>
<td>20/29</td>
<td>14/20</td>
<td>14/19</td>
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<td>34/59</td>
<td>28/43</td>
<td>19/30</td>
<td>13/20</td>
<td>13/17</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Observer 2</td>
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<td>24/41</td>
<td>17/33</td>
<td>12/23</td>
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<td>(34-69)</td>
<td>(32-73)</td>
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</table>

No significant differences in detection rates were observed between the consensus reading (CT colonography) and colonoscopy (all P values, ≥.070). Colonoscopy did help identify significantly more patients with a lesion of any size than did observers 1 (P < .001) and 2 (P < .001) and significantly more patients with a lesion 6–9 mm (P = .012) or 6 mm or larger (P = .008) than did observer 2. No other significant differences in detection rates were found between colonoscopy and separate observers (all P values, ≥.057). Furthermore, no significant differences in sensitivities or specificities were observed between consensus reading and observers (sensitivity: all P values, ≥.063; specificity: all P values, ≥.092) or between separate observers (sensitivity: all P values, ≥.267; specificity: all P values, ≥.115). The consensus reading resulted in 34 (76%) of 45 patients with a polyp 6 mm or larger, in comparison to 29 (64%) of 45 patients for observer 2 (P = .267); no increase was
observed compared with observer 1. With regard to larger lesions, the consensus reading resulted in the identification of 14 (82%) of 17 patients with a polyp 10 mm or larger, in comparison to 13 (76%) of 17 patients for observer 1 (P > .99) and 12 (71%) of 17 patients for observer 2 (P = .50). Table 5 shows negative and positive predictive values.

Per-polyp analysis
With regard to the three missed lesions 10 mm or larger (two flat polyps—one in the transverse and one in the ascending colon—and one sessile polyp in the ascending colon), no perception or technical errors were observed for the consensus reading (Table 6, Fig 3). Two (33%) of the six false-positive findings for lesions 10 mm or larger were matched to polypoid lesions at colonoscopy: an inverted appendix stump (Fig 4) and a mucosal bleb (cecum); one finding proved to be a lipomatous ileocecal valve, and three findings were attributed to poorly tagged stool. In general, detection rates for colonoscopy were better for lesions 6 mm or larger and 6–9 mm lesions (Table 6).

Figure 4. False-positive finding ≥10mm at CTC

Figure displays a false-positive finding (arrow) at CTC (axial image right and 3D image in the middle) that had a true polypoid morphology at endoscopy (left) but proved to be an inverted appendix stump.

For the other size thresholds, no significant differences in per-polyp sensitivity were found between CT colonography (consensus or observer 1 or observer 2) and colonoscopy (all P values, ≥.101), except for observer 2, whose detection rates were lower for lesions 7 mm or larger (P = .016). All data on per-polyp sensitivity values, with significant corresponding P values for all comparisons (colonoscopy vs consensus reading, colonoscopy vs observer 1, colonoscopy vs observer 2, consensus reading vs
Accuracy of limited prepped CT colonography

observer 1, consensus reading vs observer 2, and observer 1 vs observer 2), are provided in Table 6.

Interobserver agreement

Observers 1 and 2 recorded lesion(s) 10 mm or larger in 19 and 23 segments, respectively: Concordant findings were reported in 11 segments. No findings 10 mm or larger were recorded in 966 segments by both observers.

### Table 6. Polyp Sensitivity and Number of False-Positive Findings according to Size

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<tr>
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<th>All sizes</th>
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<td><strong>Sensitivity (%)</strong></td>
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</table>

Note - Data are number of patients and sensitivity with in parenthesis 95% confidence intervals.

- Colonoscopy detected significant more lesions of all sizes than observer 1 and 2 (p<0.001, p<0.001).
- Observer 1 detected significant more lesions of all sizes than observer 2 (p=0.008).
- Colonoscopy detected significant more lesions 6-9mm than consensus, observer 1 and 2 (p=0.006, p=0.007, p<0.001).
- Colonoscopy detected significant more lesions ≥6mm than consensus, observer 1 and 2 (p=0.008, p=0.008, p<0.001).
- Colonoscopy detected significant more lesions ≥7mm than observer 2 (p<0.001).
- Colonoscopy detected significant more lesions ≥8mm than observer 2 (p=0.003, p=0.024).
- Colonoscopy detected significant more lesions ≥9mm than observer 2 (p=0.016, p=0.010).
Chapter 3

This resulted in a per-segment agreement of 98% (977 of 1000 segments) and a corresponding very good $\kappa_p$ value of 0.96. For lesions 6 mm or larger, the per-segment agreement was 94% (940 of 1000 segments), with an associated $\kappa_p$ value of 0.88.

*Image quality*

Four (2%) of 172 evaluated studies were considered non-diagnostic because of poor tagging and were therefore excluded from analysis (Fig 1). The radiologist evaluated stool tagging as good in 160 (95%) of the 168 included studies and as adequate in seven (4%) of 168 studies. In one (1%) of 168 studies, image quality was rated as poor, with untagged solid stool less than 6 mm. Figure 5 shows different tagging examples.

| Table 7. Burden of diarrhea and overall burden of the bowel preparation (n=168) |
|-----------------|--------|--------|--------|--------|--------|
| Burden of diarrhea* | None  | Mild   | Moderate | Severe  | Extreme |
| 17               | 48     | 44     | 23      | 20      |
| Overall burden#  | 54     | 69     | 28      | 12      | 3       |

*11 patients experienced no diarrhea, 5 patients did not fill out the questionnaire with regard to the burden of diarrhea.

*2 patients did not fill out the questionnaire with regard to the overall burden of the bowel preparation.

*Patient experience and preference*

Diarrhea was present in 152 (93%) of 163 patients who filled out the questionnaire with regard to diarrhea (Table 7). From among the 165 patients who returned the questionnaire after 5 weeks, 144 (87%) rated the bowel preparation for colonoscopy as more burdensome than the bowel preparation for CT colonography. With regard to patient preference, 114 (70%) of 164 patients preferred CT colonography to colonoscopy, 13 (8%) were indifferent, and 36 (22%) favored colonoscopy as a colonic examination.
Our study results had a sensitivity for the consensus reading of 76% (34 of 45) and 82% (14 of 17) for patients with a colorectal polyp 6 mm or larger and those with a polyp 10 mm or larger, respectively. Detection rates were higher for colonoscopy, foroth patients with a polyp 6 mm or larger (41 [91%] of 45) and patients with a lesion 10 mm or larger (15 [88%] of 17), than those at CT colonography, but this
difference was not statistically significant. CT colonography correctly depicted 97 (79%) of 123 patients without polyps 6 mm or larger and 146 (97%) of 151 patients without polyps 10 mm or larger. For these size thresholds, negative predictive values were 90% (97 of 108) and 98% (146 of 149), and positive predictive values were 57% (34 of 60) and 74% (14 of 19) for polyps 6 mm or larger and polyps 10 mm or larger, respectively. Interobserver agreement per segment was 94% (940 of 1000) and 98% (977 of 1000) for lesions 6 mm or larger and lesions 10 mm or larger, respectively.

Our ability to identify patients with lesions 6 mm or larger and those with lesions 10 mm or larger was not as good as in the study by Iannaccone et al [19], in which sensitivity ranged from 90% (44 of 49) for patients with a polyp 6 mm or larger to 100% (24 of 24) for patients with a polyp 10 mm or larger. These differences in accuracy could be explained by interpretation problems, but could also possibly be at least partly explained by visualization problems. An argument in favor of an interpretation problem is that the observers in our study were less experienced (70 and 120 cases) than those in the other study (100, 200, and 300 cases, respectively, for the three observers). Although we believe that a higher level of experience might have improved the detection of medium-size (6–9-mm) polyps, this is not an adequate explanation for the difference with regard to the detection rates of lesions 10 mm or larger. Namely, no lesions 10 mm or larger that were missed at the consensus reading were visible in retrospect. Therefore, the problem with the identification of polyps 10 mm or larger seems to be a visualization rather than an interpretation problem.

There are two major differences between both studies that can possibly explain these visualization errors. First, we used a different bowel preparation with a lower dose of diatrizoate meglumine but added barium and bisacodyl. In theory, inhomogeneous tagging might result in the masking of true lesions. However, stool tagging was considered good in 160 (95%) of 168 of the studies, including the cases with missed lesions, and only four studies were excluded because of poor stool tagging. Therefore, we do not believe that our tagging regimen was the cause of the visualization errors. Second, we investigated only patients at increased risk for colorectal cancer, while the other study had a mixed population, of which 106 (52%) of 203 were high-risk patients. Recently, MacCarty et al [20] suggested that patients at increased risk who regularly undergo colonoscopy tend to have lesions that are hard to detect with CT colonography because easy-to-see lesions are detected and removed at previous colonoscopic examinations, while less conspicuous lesions
Accuracy of limited prepped CT colonography

remain in situ. Van Gelder et al [5], who studied a patient group comparable to ours, found one-third (14 of 48) of polyps 10 mm or larger to be flat, and 71% (10 of 14) of these flat polyps were missed at CT colonography. In our study, four (24%) of the 17 polyps that were 10 mm or larger were flat, and two (50%) of these were missed. Our results underscore the findings of MacCarty et al; this indicates that CT colonography with fecal tagging might therefore perform better in screening populations (e.g., patients at average risk who have not previously undergone screening with colonoscopy). The relatively high number of 42 false-positive findings by using 6 mm as a size threshold was somewhat disappointing because fecal tagging is supposed to be associated with a lower rate of false-positive findings because stool is not mistaken for polyps [15,17,24]. The actual polyp size threshold for colonoscopy referral in a screening setting is still debated, but many institutions consider a size threshold of 6 mm clinically relevant.

An explanation for our high number of false-positive findings in this category is that although stool tagging was homogeneous, the average volume-rendering effect at a section thickness of 3.2 mm might have caused small (6- or 7-mm) pieces of stool to look like small polyps. This explains the sharp decline in the number of false-positive findings at a size threshold of 8 mm or larger, which can be deduced from the fact that only 13 false-positive findings 8 mm or larger were observed, and six of these were 10 mm or larger. Furthermore, the observers were relatively inexperienced, which, in our opinion, undoubtedly contributed to the number of false-positive findings. As mentioned before, we did not use stool subtraction software, which might have helped lower the number of false-positive findings. Despite the high number of medium-sized false-positive findings, specificity was 79% (97 of 123) for patients with a lesion 6 mm or larger and increased to 94% (136 of 145) at a size threshold of 8 mm. Furthermore, negative predictive values were high (lesions ≥6 mm, 90% [97 of 108]; lesions ≥10 mm, 98% [146 of 149]). We applied a double-reading strategy (consensus reading for discrepant lesions) for lesions 6 mm or larger. Although this is a time-consuming and costly strategy, it has been suggested to improve sensitivity [4]. Although a higher detection rate for the consensus reading compared with that for the separate observers was observed, no significant improvement was found by using double reading (P ≥.063). Alternatives to a double reading by radiologists are computed-aided detection [25,26] or the deployment of radiographers [27,28].

The radiologist needed significantly (P < .001) more time to review the cases in comparison to the radiology fellow (18 vs 13 minutes). An explanation is that the research fellow had more experience in CT colonography prior to the study than the
radiologist (120 vs 70 cases). However, the longer review time might also reflect a more careful evaluation of the data by the radiologist. This can be substantiated by the fact that higher sensitivities were calculated for the radiologist than for the research fellow. Some limitations of our study should be considered. A cohort of 168 patients at increased risk for colorectal carcinoma was evaluated in our study. Our results can therefore not be extrapolated to a screening setting of patients at average risk for developing colorectal cancer. Two observers were used in our study, and although interobserver variability was high, the use of two observers might limit generalizibility of our data. Relatively short training of 70 cases for the radiologist and 120 cases for the radiology fellow was applied, and this is probably not enough to achieve a high level of competence with a primary two-dimensional evaluation method [29]. We used a section thickness of 3.2 mm with our four-section CT scanner to enable scanning in one breath hold, and thin collimation is associated with better accuracy in the clean colon [30–32]. Presumably, thin collimation is also important in the limitedly prepared colon because inhomogeneously tagged stool can be better differentiated from polyps, which subsequently lowers false-positive rates and improves detection of particularly flat polyps. Finally, a disadvantage of using a limited bowel preparation for CT colonography in comparison to using a cathartic bowel preparation is that same-day colonoscopy for polyp removal cannot be performed.

In conclusion, we report that CT colonography with limited bowel preparation in a population at increased risk for colorectal cancer had a sensitivity and specificity of 82% (14 of 17) and 97% (146 of 151), respectively, for patients with polyps 10 mm or larger. These results are in line with those of performance studies with extensive bowel preparation [4,5]. Because a cathartic bowel preparation could potentially be a deterrent to screening, we believe that limited bowel preparation can be of value for the implementation of CT colonography as a screening technique for colorectal polyps and cancer.

Acknowledgments

The authors thank Jasper Florie, MD, Karin Horsthuis, MD, and Henk W. Venema, PhD, for their critical review of the manuscript. We thank C. Yung Nio, MD, for his critical review of the CT colonographic cases with missed lesions and Koos A. H. Zwinderman, PhD, for his valuable contribution with regard to the statistical analyses (GEE) of our data.
Reference list

Chapter 4

CT Colonography with Limited Bowel Preparation: Prospective Assessment of Patient Experience and Preference in comparison to Optical Colonoscopy with Cathartic Bowel Preparation

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Shandra Bipat
Jan Peringa
Ayso H. de Vries
Anneke Heutinck
Evelien Dekker
Lubbertus C. Baak
Alexander D. Montauban van Swijndregt
Jaap Stoker

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Abstract

**Purpose:** The purpose of this study was to prospectively compare participant experience and preference of limited preparation CTC with full-preparation colonoscopy in a consecutive series of patients at increased risk of colorectal cancer.

**Methods:** CTC preparation comprised 180ml diatrizoate meglumine, 80ml barium and 30mg bisacodyl. For the colonoscopy preparation four litres of polyethylene-glycol solution was used. Participants' experience (pain, embarrassment, discomfort) and preference were compared using Wilcoxon signed rank test and the Chi-squared test respectively. Associations between preference and experience parameters were determined by logistic regression.

**Results:** Data of 173 participants were included. Diarrhoea occurred in 94% of participants during CTC preparation. This side-effect was perceived as severely or extremely burdensome by 29%. Nonetheless, the total burden was significantly lower for the CTC preparation than for colonoscopy (9% rated the CTC preparation as severely or extremely burdensome compared with 59% for colonoscopy; p<0.001). Participants experienced significantly more pain, discomfort and total burden with the colonoscopy procedure than with CTC (p<0.001). After 5 weeks, 69% preferred CTC, 8% were indifferent and 23% preferred colonoscopy (p<0.001). A burdensome colonoscopy preparation and pain at colonoscopy were associated with CTC preference (p<0.04).

**Conclusion:** Participants’ experience and preference were rated in favour of CTC with a limited bowel preparation compared to full-preparation colonoscopy.
Patient acceptance of limited prepped CT colonography

Introduction

Computed Tomography (CT) colonography is an established and widely used imaging technique in patients with symptoms of colorectal cancer. In addition, it has been identified as an effective instrument for screening average-risk individuals [1-4]. For CT colonography a cathartic bowel preparation is required. The cathartic bowel preparation is, however, burdensome and often considered the most unpleasant part of the examination [5, 6]. This is important for clinical examinations, but especially for screening where participation rates are important determinants of effective screening [7].

Several studies have reported promising results for CT colonography with a less extensive bowel preparation with regard to image quality and accuracy [8-12]. Data on acceptance of these limited bowel preparation schemes are however sparse. To our knowledge, three feasibility studies and one accuracy study have investigated patient acceptance of a limited preparation with favourable results [13-16]. To date, no comprehensive data on patient acceptance and preference in a larger cohort have been published.

Therefore, the purpose of our study was to assess intra-individual experience and preference for CT colonography with a limited preparation in comparison to optical colonoscopy with a cathartic preparation in a population at increased risk of colorectal cancer.

Materials and Methods

Study population

Patients with a personal or family history of colorectal polyps or cancer were invited to participate in our study [17]. All patients were scheduled for a routine optical colonoscopy at the endoscopy departments of the Academic Medical Center (AMC) or the Onze Lieve Vrouwe Gasthuis (OLVG). Exclusion criteria were: age under 18 years, previous reaction to iodine-containing contrast agent, inflammatory bowel disease, familial adenomatous polyposis or previous participation in a research project that involved ionising radiation within 12 months preceding the CT colonography examination. The institutional review board of both hospitals approved the study. All patients gave written informed consent.
Chapter 4

Questionnaires

Participants filled out six questionnaires at different time points with regard to (appendix A):

1. Pre-test appraisal and post-test experience with the preparation for CT colonography and the preparation for optical colonoscopy.
2. Pre-test appraisal and post-test experience with the CT colonography and optical colonoscopy procedures.
3. Preference for their future examinations.

Participants’ pre-test appraisal was based on previous knowledge of the examinations and on information provided by us (in writing and by phone) and was filled out two weeks before CT colonography.

Participant’s experience with the preparation and the procedure was rated using a five-point scale (none, mild, moderate, severe, extreme) and filled out on the day of the examination. Furthermore, after completing both tests participants indicated which event was most burdensome to undergo (CT colonography preparation, the CT colonography procedure, optical colonoscopy preparation, or the optical colonoscopy procedure).

Participants’ preference for CT colonography or optical colonoscopy was rated using a seven-point scale (definitely, probably, possibly CT colonography; indifferent; possibly, probably, definitely optical colonoscopy) and based on the presumption that in 20% of CT colonography examinations a significant lesion would be found that would result in optical colonoscopy referral for polyp removal. Because adverse reactions to tests tend to temper in time and the attitude at that later time point will better reflect the attitude towards future screening, the preference was again assessed five weeks later at home. The questionnaires were designed by the Department of Social Medicine [6, 18].

**Figure 1.** Limited bowel preparation for CT colonography

<table>
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<th>Start low-fibre diet</th>
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<td>3 x 20 ml diatrizoate meglumine</td>
<td>2 x 60 ml diatrizoate meglumine</td>
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<tr>
<td>1 x 20 mg Bisacodyl</td>
<td>1 x 10 mg Bisacodyl</td>
<td></td>
</tr>
</tbody>
</table>

2 days before CTC 1 day before CTC day of CTC

*no fibrous vegetables and fruit, no whole-wheat cereal products, no nuts.*
Limited bowel preparation for CT colonography

Participants were prepared with a low-fibre diet two days before CT colonography. A combination of 80 ml barium sulphate suspension (Tagitol V, E-Z-EM Inc., Westbury, USA) and 180 ml diatrizoate meglumine (200mg/ml hospital pharmacy) was prescribed for faecal tagging. Bisacodyl (hospital pharmacy AMC) was given the day before and on the day of the examination to reduce the amount of faeces in the colon (Fig. 1).

Table 1. Participant characteristics

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CT colonography procedure

CT colonography was performed 1 to 4 weeks (mean 25 days) prior to optical colonoscopy. Participants were scanned in the Academic Medical Center by a dedicated CT colonography technician or research fellow [S.J.]. Through a thin flexible rectal tube the colon was distended with carbon dioxide (CO₂) by using an automatic insufflator (ProtocO₂l, E-Z-EM, Westbury-NY, USA). Butyl scopolamine
bromide (20 mg, Buscopan; Boehringer Ingelheim, Ingelheim, Germany) or, if contraindicated, Glucagon Hydrochloride (1 mg, Glucagon; Novo Nordisk A/S, Bagsvaerd, Denmark) was given intravenously immediately prior to the scan. Examinations were performed within a 22-seconds breath hold on a Philips Mx8000 CT scanner in supine and prone positions. The time that patients spent in the CT-room and the amount of insufflated CO₂ was recorded by a research nurse [A.H.].

Cathartic bowel preparation for optical colonoscopy

Bowel preparation for optical colonoscopy consisted of 4 litres poly-ethylene glycol electrolyte solution (Klean Prep, Helsinn Birex Pharmaceuticals, Dublin, Ireland) ingested the day before the examination or, if the examination was in the afternoon, 2 litres the day before and 2 litres on the day of the examination. After starting the catharsis participants were not allowed to eat.

Optical colonoscopy procedure

An experienced staff member (gastroenterologist or a gastro-intestinal surgeon with an average experience of 11 years, range 1-26 years) or a gastroenterology fellow under direct supervision of a experienced staff member performed the optical colonoscopy in the Academic Medical Center or the Onze Lieve Vrouwe Gasthuis. Participants received a standard dose of sedatives (5 mg of midazolam; Dormicum, Roche, Basel, Switzerland), or analgesics (0.05 mg Fentanyl-Janssen, Janssen Pharmaceuticals, Beerse, Belgium or 0.5 mg of Rapifen; hospital pharmacy) on request. The endoscopist increased the dose until sedation or pain control was sufficient. Butyl scopolamine bromide (20 mg, Buscopan; Boehringer Ingelheim, Ingelheim, Germany) was administered intravenously. During the examination a research nurse [A.H.] recorded whether participants received sedatives or analgesics.

<table>
<thead>
<tr>
<th>Symptoms reported</th>
<th>Abdominal pain</th>
<th>Diarrhoea</th>
<th>Flatulence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>n=78</td>
<td>4/78 (5)</td>
<td>15/158 (10)</td>
</tr>
<tr>
<td>No</td>
<td>n=93</td>
<td>31/78 (40)</td>
<td>52/158 (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25/78 (32)</td>
<td>45/158 (29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/78 (12)</td>
<td>26/158 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/78 (12)</td>
<td>20/158 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/78 (12)</td>
<td>20/158 (13)</td>
</tr>
</tbody>
</table>

Participants indicated whether they experienced side-effects of the bowel preparation for CT colonography. If side-effects were present, the burden of the side-effect was rated using a five-point scale. Values in parenthesis are percentages.

<table>
<thead>
<tr>
<th>Symptoms reported</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=158</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=98</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The time to complete the optical colonoscopy (insertion and inspection) was captured with a stopwatch. After the examination participants were admitted to the recovery ward for two hours, upon which they could go home.

**Figure 2. Flow-chart shows participation of the study population**

468 eligible participants → 85 not requested
- organizational, 25
- could not be reached, 60

→ 203 participants refused

180 participants included

→ 7 individuals excluded
- no participation; second thoughts, 3
- no participation; reported allergic reaction, 2
- no participation; claustrophobia, 1
- no colonoscopy; diagnosed with lung cancer after CTC, 1

→ 173 study participants

**Statistical Analysis**

Data from participants who completed both examinations (CT colonography and optical colonoscopy) were included for analysis. Pre-test appraisal differences between CT colonography and optical colonoscopy and post-test experience differences between both examinations were tested for statistical significance using the Wilcoxon signed rank test. Differences in preference were tested for significance with Chi-square test after dichotomization (preference for CT colonography versus preference for optical colonoscopy); participants that were indifferent were not included in the analysis.
Chapter 4

The Chi-square test was also used to test for significant differences in preference between the first and the second measurement (immediately post-test versus 5-weeks post-test). P <0.05 was considered to indicate a statistically significant difference.

Univariate logistic regression analysis was used to investigate associations between participants’ preferences for CT colonography or optical colonoscopy (for two time points: immediately post-test and 5-weeks post-test) and patient-related factors: age ≥ 65 years, sex, completion of academic or higher vocational education, income with respect to 27000 Euros (mean net Dutch annual income per household) or greater, recent symptoms of colorectal cancer, indication for surveillance (personal or familial history of colorectal carcinoma or polyps), difficult or painful defecation habits in daily life, use of sedatives or analgesics during optical colonoscopy, above average duration of the optical colonoscopy examination, presence of polyps at optical colonoscopy, above average duration of the CT colonography examination, above average amount of CO₂ used for colonic distension at CT colonography, and experience parameters on the day of the examination (burdensome bowel preparation for CT colonography or for optical colonoscopy; and pain, embarrassment or discomfort during CT colonography or optical colonoscopy [no, mild and moderate versus severe and extreme burden]). Subsequently, covariates with a P value of .10 or lower were included in the multivariate logistic regression model. A stepwise
backward selection strategy was used. Odds ratios are provided: an odds ratio less than 1 indicates a positive association with a preference for CT colonography; an odds ratio greater than 1 indicates a positive association with a preference for optical.

**Results**

**Study population**

Of 468 eligible individuals that were scheduled to undergo an optical colonoscopy during the inclusion period, 173 participants were included for analysis (Figure 2, Table 1) (17).

**Bowel preparation, CT colonography and optical colonoscopy procedures**

For CT colonography, all participants used the prescribed preparation. Participants rated the use of bisacodyl the most burdensome factor of the CT colonography preparation (Figure 3). Side-effects as abdominal pain, diarrhoea and flatulence were reported by respectively 46% (78/171), 94% (158/168) and 42% (72/170) of participants and were perceived as severely or extremely burdensome by respectively 23% (18/78), 29% (46/158) and 18% (13/72) (table 2). Diarrhoea was more burdensome compared to abdominal pain (p=0.015) and flatulence (p<0.001), while abdominal pain was more burdensome than flatulence (p=0.049).

The average time that participants spent in the CT examination room was 21 minutes (range 13-48). Buscopan was administered to 84% (143/170) of participants and glucagon to 13% (22/170) of participants. The average amount of insufflated CO₂ to distend the colon was 3.9 litres (range 2-8). The majority of participants (56%; 89/159) found CO₂ insufflation of the colon the most burdensome aspect of the CT colonography procedure, followed by the breath hold (25%; 39/159).

For optical colonoscopy, an average of 4 litres polyethylene glycol electrolyte solution (PEG) was used (range 2.5-6). The average duration of the optical colonoscopy examination was 40 minutes (range 12-90). Sedation and/or analgesics were administered to 82% (139/169) of participants. In 73% (127/173) of participants a polyp was detected at optical colonoscopy (17). The movement of the scope was considered the most burdensome aspect of optical colonoscopy (50%; 81/162) followed by the CO₂ insufflation (30%; 48/162).
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Experience of bowel preparation and procedure (CT colonography versus optical colonoscopy)

The total burden of the CT colonography preparation was significantly lower compared to the optical colonoscopy preparation (p<0.001); the CT colonography preparation was considered severe or extreme by 9% (15/171) of participants versus 59% (97/165) for optical colonoscopy (Figure 4a).

The total burden of the CT colonography procedure was also significantly lower in comparison to the optical colonoscopy procedure (p<0.001); 2% (4/173) rated CT colonography as severe (no participant considered CT colonography extremely burdensome) versus 23% (38/166) who rated optical colonoscopy severe or extreme burdensome (Figure 4b). Participants experienced significantly more pain (p<0.001) and discomfort (p<0.001) during the optical colonoscopy procedure than during the CT colonography procedure (Figure 5). Embarrassment was rated as none or mild by 97% (166/172) for CT-colonography and 93% (154/166) for optical colonoscopy; no statistical significant difference (p=0.19).

Table 3. Listed reasons why participants preferred either CT colonography or optical colonoscopy (5 weeks post-test)

<table>
<thead>
<tr>
<th>Preference for CT colonography (n=115)</th>
<th>Preference for optical colonoscopy (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 litres PEG was burdensome</td>
<td>OC is therapeutic</td>
</tr>
<tr>
<td>43 (37%)</td>
<td>20 (54%)</td>
</tr>
<tr>
<td>Complete CTC examination (preparation and procedure) less burdensome</td>
<td>CTC preparation was burdensome</td>
</tr>
<tr>
<td>17 (15%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>CTC preparation less burdensome</td>
<td>In case of a positive CTC then follow-up with OC (2 examinations)</td>
</tr>
<tr>
<td>16 (15%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>No sedation for CTC</td>
<td>OC is more accurate</td>
</tr>
<tr>
<td>7 (6%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>No pain during CTC</td>
<td>Discomfort during CTC examination</td>
</tr>
<tr>
<td>6 (5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Less burden during CTC</td>
<td>Sedatives at OC</td>
</tr>
<tr>
<td>5 (4%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pain during OC</td>
<td>Ability to watch screen during OC</td>
</tr>
<tr>
<td>4 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>If not necessary no (therapeutic) OC</td>
<td>No particular reason</td>
</tr>
<tr>
<td>3 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Simpler preparation for OC</td>
<td></td>
</tr>
<tr>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Evaluation of extracolonic pathology</td>
<td></td>
</tr>
<tr>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>No particular reason</td>
<td></td>
</tr>
<tr>
<td>10 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Participants wrote down on the questionnaire why they preferred CT colonography or optical colonoscopy as future examination. No list of possible reasons was provided.
**Pre- and post-test appraisal of bowel preparation and procedure**

In the pre- (2 weeks prior at home) and post-test (5 weeks after the examinations at home) appraisal; respectively 94% (152/162) and 87% (144/165) of participants indicated that the optical colonoscopy preparation would be or was more burdensome to undergo than the CT colonography preparation. With regard to the examination, respectively 94% (149/159) and 87% (142/164) of participants indicated pre- and post-test that optical colonoscopy was more burdensome than CT colonography. The small shift in the post-test appraisal in favour of optical colonoscopy preparation and procedure was significant (respectively p=0.003 and p=0.005). This is in line with the fact that 18% (30/165) of participants indicated that CT colonography was more burdensome than they had anticipated.

**Figure 4a-b. Total burden of the bowel preparation and procedure**

Figure 4a shows that the bowel preparation for optical colonoscopy was considered more burdensome compared to the bowel preparation for CT colonography (p< 0.001). Figure 5b demonstrates that the optical colonoscopy procedure was more burdensome to undergo than the CTC procedure (p< 0.001).

**Figure 5. Pain and discomfort associated with the examination**

Participants experienced more pain and discomfort during the optical colonoscopy examination compared to the CT colonography examination (p-values <0.001).
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Pre-test, 57% (90/159) of participants was most reluctant to undergo the optical colonoscopy procedure compared to the preparation for optical colonoscopy; post-test, 67% (111/165) actually considered the optical colonoscopy preparation more burdensome than optical colonoscopy itself (p<0.001). The bowel preparation for optical colonoscopy was considered the most burdensome event, as indicated immediately post-test and 5-weeks later at home (Figure 6).

Participants’ preference and determinants of preference

In the recovery room after optical colonoscopy as well as 5 weeks later at home most participants indicated a preference for CT colonography as their next examination (p-values <0.001); respectively 76% (124/164) and 69% (115/166) of participants preferred CT colonography versus 16% (27/164) and 22% (37/166) of participants who preferred optical colonoscopy (Figure 7). The small shift after 5 weeks towards optical colonoscopy was significant (p=0.03). Table 3 displays the different reasons of participants for their choice of preference.

![Figure 6. Most burdensome event](image)

Figure shows participants’ responses of what was considered the most burdensome event of both examinations combined (optical colonoscopy preparation or optical colonoscopy procedure or CT colonography preparation or CT colonography procedure) directly post-test (n=147) and 5-weeks later at home (n=157).

With regard to associations between preference and patient-related factors, recent symptoms of colorectal cancer was a positive determinant of a preference for optical colonoscopy directly after optical colonoscopy (odds ratio 1.70; p=0.03) but 5 weeks later at home this association was no longer present (Appendix B1). With regard to participants’ experience parameters, a burdensome bowel preparation for CT colonography (odds ratio 6.06; p=0.01) and a painful CT colonography procedure (odds ratio 6.34; p=0.03) were independent determinants for optical colonoscopy preference. Likewise, a burdensome optical colonoscopy preparation (odds ratio 0.40; p=0.05) and pain at optical colonoscopy (odds ratio 0.10; p=0.01) were
associated with a preference for CT colonography. After 5 weeks, the same determinants of experience were still associated (all p-values ≤ 0.04) with the same preference outcome (appendix B2).

**Discussion**

In our 5-weeks follow-up study, the majority of participants (69%; 115/166) indicated a preference for CT colonography as their next examination. This preference was apparent despite the fact that participants were informed that in 20% of CT colonography examinations a referral for optical colonoscopy would still be required for removal of polyps. The cathartic bowel preparation and pain and discomfort experienced during optical colonoscopy were such that optical colonoscopy was considered a more burdensome test than limited prepared CT colonography. In accordance with previous studies, we found a better patient tolerance for the limited preparation versus the cathartic preparation (13-16). However in our study, almost all participants (158/168) experienced diarrhoea during the CT colonography preparation and this side-effect was considered very burdensome. Although Taylor et al. indicated an increased defecation frequency in their study (15), the occurrence of diarrhoea was not reported or remarkably only a few patients experienced diarrhoea in these earlier studies (13, 14, 16). For example, Iannaccone et al reported that diarrhoea occurred in just 6% (13/203) of participants (16). This is worth mentioning, because the use of iodinated contrast agents and/or added laxatives is generally associated with diarrhoea (19). In that study a higher dose of diatrizoate meglumine (200 mL with a concentration of 370 mg/mL) was used than in our study.
(180 mL with a concentration of 200 mg/mL) but no bisacodyl was added (16). At present, we do not add any laxatives anymore to the preparation and we have reduced the dose of iodinated contrast. Patients still experience diarrhoea with this new protocol but the burden of diarrhoea is significantly improved and image quality has not been impaired (20). Despite the occurrence of side-effects in our study, the preparation for CT colonography was well tolerated by participants and considered significantly less burdensome than the preparation for optical colonoscopy (9% of participants rated the CT colonography preparation as severely or extremely burdensome compared to 59% for optical colonoscopy; P<0.001).

With regard to the CT colonography examination, 56% (89/159) of participants indicated that the insufflation of the colon with CO₂ was the most burdensome part. This is in line with a previous study that showed that insufflation of air and the insertion of the inflexible rectal tube were considered the most burdensome aspects (13). Insertion of a rectal tube was in our study not considered burdensome because we used a thin flexible catheter. Although in our study several aspects of the CTC examination were rated severely or extremely burdensome by some participants, the complete procedure was considered severely burdensome by only 2% (4/173) and no participant considered the examination extremely burdensome. In comparison, significantly more participants; 23% (38/166) perceived the optical colonoscopy examination as severe or extreme burdensome (p<0.001).

Five weeks after completing both tests, 69% of participants preferred CT colonography and 22% preferred optical colonoscopy. In an earlier acceptance study comparing cathartic CT colonography to optical colonoscopy, 61% of participants preferred CT colonography (6). It is reasonable to assume that the present 8% increase in CT colonography preference can be attributed to the limited preparation as other factors were the same (except for the use of a flexible catheter). The observed increase was not as large as we anticipated probably because most participants had diarrhoea as side-effect. This is underlined by the fact that a burdensome CT colonography preparation was associated with an optical colonoscopy preference (p=0.01). However, the decisive factor for most participants to prefer optical colonoscopy was the therapeutic aspect. As this is an important benefit of optical colonoscopy, it is a detriment of limited CT colonography (in comparison to cathartic CT colonography) because same day referral for therapeutic optical colonoscopy is not possible.

Some limitations of our study should be discussed. First, the bowel preparation for optical colonoscopy comprised standard 4 litres of polyethylene-glycol solution (PEG)
(KleanPrep; Norgine Ltd; Harfield, UK) [21, 22]. However, 2 litres of PEG (Moviprep; Norgine Ltd; Harfield, UK) or sodium phosphate can prepare the colon as effectively [23, 24, 25], although the latter cannot be used in patients with heart and kidney failure [26, 27]. Preference outcome might have shifted towards optical colonoscopy if a milder preparation had been used for optical colonoscopy. A second potential limitation is that participants were told that the accuracy of CT colonography and optical colonoscopy with limited preparation were comparable [16]. It is likely that better accuracy for optical colonoscopy might move the preference pattern towards optical colonoscopy [28]. Third, the fact that only participants were included who were willing to undergo CT colonography in addition to their scheduled optical colonoscopy might have influenced our results in favour of CT colonography. Fourth, a surveillance population of individuals at increased risk was investigated and therefore we cannot be certain if our data are applicable to a screening population at average risk. However, as the referral rate for optical colonoscopy in a screening setting would probably be lower than the indicated 20% in our study, we believe that the reported preference for CT colonography could be an underestimation. Finally, no randomised comparison was made between non-cathartic and cathartic CT colonography. However, as the PEG preparation for optical colonoscopy is also widely used for cathartic CT colonography, we believe that a limited preparation will be preferred above a PEG preparation for CT colonography.

In conclusion, this prospective study investigated individual experience and preference of CT colonography with a limited preparation more stringent than prior studies. Our results demonstrated that the occurrence of diarrhoea was frequent and considered a burdensome side-effect of the CT colonography preparation. To optimize patient acceptance, further efforts should be made to reduce this side-effect. CT colonography however was better tolerated by participants than optical colonoscopy with regard to both preparation and procedure. As such, an apparent preference for CT colonography was observed in this population at increased-risk for colorectal cancer. Therefore, we believe that CT colonography with a limited bowel preparation can be of value to increase participation rates in screening programs for colorectal cancer.

**Acknowledgments**

We would like to thank Marjolein Liedenbaum and Christina Lavini for their critical review of this manuscript.
### Appendix A. Content of Questionnaires and Number of Responses per Question

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Q 1</th>
<th>Q 2</th>
<th>Q 3</th>
<th>Q 4</th>
<th>Q 5</th>
<th>Q 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where and when completed?</td>
<td>By mail 2 weeks before CTC</td>
<td>In waiting room before CTC</td>
<td>In waiting room after CTC</td>
<td>In waiting room before OC</td>
<td>In recovery room after OC</td>
<td>At home by mail 5 weeks after OC</td>
</tr>
<tr>
<td>Number of returned questionnaires</td>
<td>173/173 (100)</td>
<td>173/173 (100)</td>
<td>173/173 (100)</td>
<td>169/173 (98)</td>
<td>167/173 (97)</td>
<td>166/173 (96)</td>
</tr>
<tr>
<td>Baseline characteristics ±</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Most reluctant factor of the examination</td>
<td>173/173 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>161/173 (93)</td>
<td>-</td>
</tr>
<tr>
<td>How burdensome was low-fibre diet</td>
<td>-</td>
<td>173/173 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>How burdensome was Bisacodyl</td>
<td>-</td>
<td>169/173 (98)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>How burdensome were contrast agents</td>
<td>-</td>
<td>173/173 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Side-effects of the CTC bowel preparation</td>
<td>-</td>
<td>168/173 (97)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total burden of entire bowel preparation</td>
<td>-</td>
<td>171/173 (99)</td>
<td>-</td>
<td>165/171 (95)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>How painful was procedure</td>
<td>-</td>
<td>-</td>
<td>171/173 (99)</td>
<td>-</td>
<td>167/173 (97)</td>
<td>-</td>
</tr>
<tr>
<td>How embarrassing was procedure</td>
<td>-</td>
<td>-</td>
<td>172/173 (99)</td>
<td>-</td>
<td>166/173 (96)</td>
<td>-</td>
</tr>
<tr>
<td>How much discomfort was procedure</td>
<td>-</td>
<td>-</td>
<td>173/173 (100)</td>
<td>-</td>
<td>164/173 (95)</td>
<td>-</td>
</tr>
<tr>
<td>Total burden of entire procedure</td>
<td>-</td>
<td>-</td>
<td>173/173 (100)</td>
<td>-</td>
<td>167/173 (97)</td>
<td>-</td>
</tr>
<tr>
<td>Most burdensome aspect of procedure</td>
<td>-</td>
<td>-</td>
<td>159/173 (92)</td>
<td>-</td>
<td>162/173 (94)</td>
<td>-</td>
</tr>
<tr>
<td>Most burdensome preparation; CTC or OC</td>
<td>162/173 (94) §</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>160/173 (92)</td>
<td>165/173 (95)</td>
</tr>
<tr>
<td>Most burdensome procedure; CTC or OC</td>
<td>159/173 (92) §</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>159/173 (92)</td>
<td>164/173 (95)</td>
</tr>
<tr>
<td>Preference for examination; CTC or OC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>164/173 (95)</td>
<td>166/173 (96)</td>
<td>-</td>
</tr>
</tbody>
</table>

*With burdensome is meant the extent of burden (e.g. the degree of unpleasantness) that was associated with a particular aspect and rated on a five-point scale; 1. not burdensome, 2. mildly burdensome, 3. moderately burdensome, 4. severely burdensome or 5. extremely burdensome. Participants were asked to rate both the individual aspects of the preparation and procedure as well as the entire preparation and procedure as a whole (i.e. = total burden).*
### Appendix B1. Patient-related Determinants of Participants’ Preference for CT Colonography or Optical Colonoscopy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direct post-test</th>
<th>5-weeks post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>0.13 (0.02-0.97) p=0.05</td>
<td>0.14 (0.02-1.18) p=0.07</td>
</tr>
<tr>
<td>Female</td>
<td>0.93 (0.39-2.20) p=0.87</td>
<td>NA</td>
</tr>
<tr>
<td>High level of education</td>
<td>2.34 (1.00-5.49) p=0.05</td>
<td>1.92 (0.75-4.90) p=0.17</td>
</tr>
<tr>
<td>Income ≥ 27000 euro</td>
<td>1.02 (0.37-2.80) p=0.97</td>
<td>NA</td>
</tr>
<tr>
<td>Symptoms of colorectal cancer at present</td>
<td>1.70 (0.70-4.10) p=0.03</td>
<td>1.02 (1.00-1.04) p=0.03</td>
</tr>
<tr>
<td>Personal history of colorectal polyps</td>
<td>0.51 (0.22-1.21) p=0.13</td>
<td>NA</td>
</tr>
<tr>
<td>Personal history of colorectal cancer</td>
<td>0.89 (0.30-2.59) p=0.82</td>
<td>NA</td>
</tr>
<tr>
<td>Family history of colorectal polyps or cancer</td>
<td>2.52 (0.80-7.92) p=0.11</td>
<td>NA</td>
</tr>
<tr>
<td>Difficult or painful defecation in daily life</td>
<td>0.27 (0.61-1.23) p=0.09</td>
<td>0.30 (0.07-1.41) p=0.13</td>
</tr>
<tr>
<td>Use of sedatives or analgesics at optical colonoscopy</td>
<td>1.20 (0.37-3.82) p=0.76</td>
<td>NA</td>
</tr>
<tr>
<td>Duration optical colonoscopy &gt; 40 min</td>
<td>1.02 (0.99-1.05) p=0.26</td>
<td>NA</td>
</tr>
<tr>
<td>Depiction of polyps at optical colonoscopy</td>
<td>1.27 (0.47-3.42) p=0.64</td>
<td>NA</td>
</tr>
<tr>
<td>Duration CT colonography &gt; 20 min</td>
<td>1.56 (0.66-3.66) p=0.31</td>
<td>NA</td>
</tr>
<tr>
<td>Insufflation of CO₂ at CT colonography (&gt; 4 litres)</td>
<td>1.08 (0.46-2.57) p=0.86</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Appendix B2. Experience determinants of participants’ preference for CTC or OC

<table>
<thead>
<tr>
<th></th>
<th>Direct post-test</th>
<th>5-weeks post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burdensome bowel preparation for CT colonography</strong></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>3.59 (1.16-11.14)</td>
<td>6.06 (1.61-22.87)</td>
</tr>
<tr>
<td></td>
<td>p=0.03</td>
<td>p=0.01</td>
</tr>
<tr>
<td><strong>Painful CT colonography examination</strong></td>
<td>5.13 (1.20-22.01)</td>
<td>6.34 (1.23-32.60)</td>
</tr>
<tr>
<td></td>
<td>p=0.03</td>
<td>p=0.03</td>
</tr>
<tr>
<td><strong>Embarrassment experienced during CT colonography</strong></td>
<td>0.00 (0.00-)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>p=1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Discomfort experienced during CT colonography</strong></td>
<td>0.94 (0.92-8.17)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>p=0.94</td>
<td></td>
</tr>
<tr>
<td><strong>Burdensome bowel preparation for optical colonoscopy</strong></td>
<td>0.42 (0.18-0.98)</td>
<td>0.40 (0.16-1.02)</td>
</tr>
<tr>
<td></td>
<td>p=0.05</td>
<td>p=0.05</td>
</tr>
<tr>
<td><strong>Painful optical colonoscopy examination</strong></td>
<td>0.17 (0.04-0.74)</td>
<td>0.10 (0.02-0.58)</td>
</tr>
<tr>
<td></td>
<td>p=0.02</td>
<td>p=0.01</td>
</tr>
<tr>
<td><strong>Embarrassment experienced during optical colonoscopy</strong></td>
<td>0.00 (0.00-)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>p=1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Discomfort experienced during CT optical colonoscopy</strong></td>
<td>0.18 (0.24-1.43)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>p=0.11</td>
<td></td>
</tr>
</tbody>
</table>

- An odds ratio less than one indicates a positive association with a preference for CT colonography.
- An odds ratio greater than one indicates a positive association with a preference for optical colonoscopy.
Patient acceptance of limited prepped CT colonography

References

4. Nelson N, Virtual Colonoscopy Accepted As Primary Colon Cancer Screening Test. JNCI 2008; 100;1492-1494
20. Liedenbaum MH, Gouw CIBF, de Vries AH, Bipat et al. Two different doses of iodinated fecal tagging agent for CT colonography: evaluation of tagging quality, homogeneity, patient acceptance and diagnostic accuracy. Accepted by European Radiology
Chapter 5

Performance of Radiographers in the evaluation of CT Colonographic Images

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Jasper Florie
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Shandra Bipat
C. Yung Nio
Jaap Stoker

American Journal of Roentgenology 2007;188:249–255
Chapter 5

Abstract

Purpose: The purpose of this study was to compare the accuracy of radiographers with that of radiologists in the interpretation of CT colonographic images.

Methods: Four observers (a radiologist, a radiologist in training, and two radiographers) evaluated 145 data sets using a primary 3D approach. The radiographers were part of our CT colonography work group and underwent training that consisted of 20 cases. The reference standard was optical colonoscopy with second-look colonoscopy for discrepant lesions ≥ 10 mm in diameter. Mean sensitivities per patient and per polyp stratified for size (any size, ≥ 6 mm, and ≥ 10 mm) was determined for the radiologists and radiographers. Specificity was determined on a per-patient basis.

Results: At colonoscopy in 86 of 145 patients, a total of 317 polyps were found (60 polyps ≥ 6 mm in 26 patients and 31 polyps ≥ 10 mm in 18 patients). No statistically significant differences were found in detection rates between radiologists and radiographers. Sensitivities for patients with a lesion of any size (66% for radiologists vs 65% for radiographers), ≥ 6 mm (81% vs 87%), and ≥ 10 mm (both 78%) were similar for all observers. On a per-polyp basis, detection rates were equivalent regardless of polyp size (47% vs 40%), for lesions ≥ 6 mm (71% vs 65%), and for lesions ≥ 10 mm (69% vs 66%). Mean specificities were similar among patients without lesions (31% vs 30%), patients without lesions ≥ 6 mm (71% vs 67%), and patients without lesions ≥ 10 mm (93% vs 93%).

Conclusion: Radiographers with training in CT colonographic evaluation achieved sensitivity and specificity in polyp detection comparable with that of radiologists. Radiographers can be considered reviewers in the evaluation of CT colonographic images.
Introduction

CT colonography (CTC) is considered a possible screening tool in the detection of colorectal adenoma. Although several studies [1–5] have shown CTC has excellent accuracy in the detection of medium (6–9 mm) and large (≥ 10 mm) polyps, the detection rates cannot be consistently reproduced [6–8]. A possible explanation is the wide range of reviewer performance. The origins of interobserver variability are not completely understood, but high volumes of data and low disease prevalence, which lead to reviewer fatigue, may play a role. These problems are of particular concern in screening, in which large numbers of patients without symptoms are examined.

A double-interpretation strategy similar to that used for mammographic screening may be feasible for limiting wide interobserver variability. Johnson et al. [7] found a 19–29% increase in overall sensitivity of CTC when a second reviewer was used. Double interpretation is time-consuming, increases costs, and may therefore not be feasible in every radiology department. Computer-aided diagnosis is a promising tool in development that may be used as a possible second reviewer [9–11].

Another alternative may be to deploy trained paramedical personnel as second reviewers [12, 13]. The aim of the study was to investigate the reviewer performance of two trained radiographers in comparison with that of two radiologists in the evaluation of CTC examinations of 150 patients by comparing the sensitivity and specificity of CTC in polyp detection with those of the reference standard, optical colonoscopy.

Materials and Methods

Patients and Setting

We selected the first 150 consecutively enrolled patients from a series of 249 patients at increased risk who had participated in a study on the accuracy of CTC [5]. These patients underwent technically successful CTC examinations. Five patients were excluded because of unavailability of the case record form or archived CTC images of the lesions. Table 1 shows the baseline characteristics.

All patients were at increased risk of development of colorectal cancer because of a personal or family history of colorectal polyps or cancer and were scheduled to undergo colonoscopy. Exclusion criteria were age less than 18 years, diagnosis of colorectal polyp or cancer during recent colon examination, and colostomy after
colorectal surgery. Patients were first seen at the endoscopy departments of the
Academic Medical Center, University of Amsterdam, and Slotervaart Hospital,
Amsterdam, and were included between October 29, 2000, and September 25, 2002.
Eligible patients were invited to the study and asked for written informed consent.
The medical ethics committee of the Academic Medical Center approved the
aforementioned accuracy study and indicated that no additional approval and no
additional informed consent from patients were required for this study.

Diagnostic Procedures

Bowel preparation — Patients underwent preparation with a full bowel cleansing
consisting of 4–6 L of polyethylene glycol electrolyte solution (Klean-Prep, Helsinn
Birex Pharmaceuticals) on the day before and/or the day of the examination.

CTC Procedure — CTC was performed 1 hour before colonoscopy. A bowel relaxant
(20 mg of butylscopolamine bromide, Buscopan, Boehringer-Ingelheim, or 1 mg of
glucagon hydrochloride, Glucagen, Novo Nordisk) was administered IV. Distention of
the colon was achieved by manual insufflation of approximately 2 L of air containing
13.4% carbon dioxide. CT scans were obtained in the supine and prone positions.
Each examination was performed with a 22-second breathhold. The scans were

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the study population (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
</tr>
<tr>
<td>Age in years: mean ± sd (range)</td>
</tr>
<tr>
<td>Hospital:</td>
</tr>
<tr>
<td>Academic Medical Center / Slotervaart hospital</td>
</tr>
<tr>
<td>Patients:</td>
</tr>
<tr>
<td>Without polyps</td>
</tr>
<tr>
<td>With polyps (all sizes)</td>
</tr>
<tr>
<td>With at least 1 large polyp</td>
</tr>
<tr>
<td>Indications:</td>
</tr>
<tr>
<td>Personal history of colorectal polyp or cancer</td>
</tr>
<tr>
<td>Family history of colorectal polyp or cancer</td>
</tr>
<tr>
<td>Coexistent symptoms:</td>
</tr>
<tr>
<td>No symptoms</td>
</tr>
<tr>
<td>Hematochezia</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Altered bowel habits</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
</tbody>
</table>
Radiographers in CT colonography

obtained with a 4-MDCT scanner (Mx8000, Philips Medical Systems) with the following parameters: 120 kV; collimation, 4 × 2.5 mm; rotation time, 0.75 second; pitch, 1.25 (table feed per rotation / total collimation); slice thickness, 3.2 mm; reconstruction interval, 1.6 mm; standard medium-sharp reconstruction filter.

At the beginning of the study, scanning was performed with an effective tube current of 100 mAs. In the course of the study, however, it became clear that substantial radiation dose reduction did not impair sensitivity or specificity [14, 15], and we reduced the effective tube current according to the abdominal circumference of the patient. Slender (≤ 87.5 cm) patients were scanned at 25 mAs, medium-sized (87.5–102.5 cm) patients at 40 mAs, and larger (> 102.5 cm) patients at 70 mAs. The estimated effective dose for a complete examination (supine and prone) was 5 mSv for an average-sized patient.

Colonoscopy — Colonoscopy was performed by an experienced staff member (gastroenterologist or gastrointestinal surgeon) or by a gastroenterology fellow under direct supervision of the attending experienced staff member of the endoscopy departments of the Academic Medical Center and the Slotervaart Hospital. While performing colonoscopy, the endoscopist did not know the CTC findings. Patients received 2.5–7.5 mg of midazolam (Dormicum, Roche) and 0.05–0.1 mg of fentanyl (Fentanyl-Janssen, Janssen Pharmaceuticals) on request. The examination was attended by the research fellow and recorded on videotape. The size, morphologic features, and segmental location of polyps were documented on a case record form by the endoscopist who performed the examination and by the attending research fellow. Polyp size was estimated before removal on the basis of comparison with an open biopsy forceps of known size (8 mm). A polyp was considered flat if its height was less than one half the diameter of the lesion.

Determination of Lesion Status

Two research fellows not involved in interpreting the findings matched CT colonographic and colonoscopic (reference standard) findings. Face-to-face comparison was made of the CTC and colonoscopic images. A polyp detected on CTC was labeled a true-positive finding on the basis of three criteria. First, the segmental location of the CTC finding had to correspond with the segmental location indicated on the case record form or with the adjacent segment. Second, the polyp size estimated by the endoscopist had to correspond with the CTC measurement. Third, the appearance of the lesions had to closely resemble that of the corresponding polyp.
at the videotaped colonoscopic examination. Because polyp size estimation at colonoscopy is prone to error, we accepted a margin of error of 3 mm for polyps < 6 mm and of 5 mm for polyps ≥ 6 mm.

If unexplained false-positive findings ≥ 10 mm were found, second-look colonoscopy was performed to verify whether these lesions were indeed false-positive findings. In the case of second-look colonoscopy, the endoscopist was informed of the location, morphologic features, and measured size of the lesion on CTC. This step was taken only in the initial study for lesions detected by the radiologists.

CTC Data Evaluation

Reviewers — Four observers with different levels of experience reviewed all data. Reviewer 1 was a radiologist with 9 years of experience in abdominal radiology. This abdominal radiologist had interpreted more than 9,000 abdominal CT examinations. Reviewer 2 was a radiologist in training who had been involved in research on CT and MR colonography and had attended approximately 50 colonoscopic examinations. As part of a research project, reviewer 2 had compared 50 CTC cases with videotaped colonoscopic examinations in a face-to-face manner. Reviewers 1 and 2 had evaluated the 150 data sets presented as part of a larger accuracy study [5] on CTC and had both evaluated more than 50 CTC cases before this study. Reviewers 3 and 4 were radiographers with more than 5 years of experience in CT examinations. They were part of the CTC work group at our institution, and each had performed approximately 50 CTC examinations. Reviewers 3 and 4 had no experience in the evaluation of CT or CTC examinations.

Training in review of CTC images — The radiographers trained by evaluating 20 complete (supine and prone) CTC data sets. The results of the evaluations were checked, and feedback was provided by the research fellow with use of the videotaped colonoscopic examinations. All reviewers received the same instructions for data review.

Review method — The observers were blinded to all clinical findings and the colonoscopic results. The examinations were evaluated on a workstation with a primary 3D unfolded cube review technique with axial 2D and multiplanar reconstruction images for problem solving (EasyVision, Philips Medical Systems) [16]. All reviewers were scheduled free from clinical work to interpret the examination findings. No more than 10 cases were interpreted per session. The reviewers scored the presence, morphologic features, size, and location of polyps or colorectal cancer.
Observers were asked to provide a degree of confidence regarding polyp presence (0%, no polyp; 25%, probably no polyp; 50%, possibly a polyp; 75%, probably a polyp; 100%, certainly a polyp). Only lesions on CTC scans that were scored with a certainty of 50% or more were considered for analysis. Review time was recorded with a stopwatch.

Outcome parameters
Because of the potential future role of CTC in screening for colorectal adenoma and carcinoma, we used per-patient sensitivity and specificity as the main outcome parameters. We also calculated per-polyp sensitivity and the false-positive rate. All results were stratified according to cut-off values of 6, 7, 8, 9, and 10 mm.

*Per patient* — Per-patient sensitivity was defined as the number of patients with at least one lesion detected with CTC relative to the number of patients with polyps identified during colonoscopy. In the size-stratified analysis, a patient in whom polyps were detected with CTC was considered to be a true-positive patient if at least one polyp in the respective size range was seen with colonoscopy. A patient was considered a false-positive patient when no polyps or only those in a smaller size category were detected during colonoscopy.

Per-patient specificity was defined as the number of patients with no polyps detected during colonoscopy relative to the number of patients without polyps at colonoscopy. In the size-stratified analysis, a patient in whom no polyps had been detected with CTC was considered a true-negative patient if no polyps in that respective size range or larger were seen with colonoscopy. A patient was considered a false-negative patient if polyps of that size or larger were detected during colonoscopy.

*Per polyp* — Per-polyp sensitivity was defined as the number of polyps detected with CTC relative to the number of polyps identified during colonoscopy. False-positive findings were CTC findings that did not match endoscopic findings as documented on the case record form and the colonoscopic videotape.

*Interobserver agreement* — Interobserver agreement was determined by calculating the agreement in percentages on a per-polyp basis for colonoscopically confirmed lesions. Agreements were calculated for all polyps and according to cutoff values of 6, 7, 8, 9, and 10 mm.
Reviewers were in agreement if both recorded the same lesion or if both recorded no findings.

_Predictive values_ — Predictive values were determined for the aforementioned size categories. Positive predictive value was defined as the proportion of patients with a true-positive finding among all patients with positive findings on CTC. Negative predictive value was defined as the proportion of patients with a true-negative finding among all patients without findings on CTC.

_Predictive values_ — Predictive values were determined for the aforementioned size categories. Positive predictive value was defined as the proportion of patients with a true-positive finding among all patients with positive findings on CTC. Negative predictive value was defined as the proportion of patients with a true-negative finding among all patients without findings on CTC.

*Combined sensitivity per patient* — For screening purposes, a double interpretation strategy can be applied. We calculated sensitivity after combining the results of different reviewers. For this purpose, true-positive lesions identified at CTC by two observers were summarized for calculation of combined sensitivity. This calculation was performed for each set of two observers: observer 1 plus observer 2, observer 1 plus observer 3, and so on. Subtracting the sensitivity of the observer with the highest value from the combined sensitivity made it possible to determine an increase in sensitivity.

**Statistical Analysis**
Differences in sensitivity and specificity between observers were tested for significance using the McNemar statistic. In addition, sensitivity and specificity for the radiologists (reviewers 1 and 2) and radiographers (reviewers 3 and 4) as groups were compared by use of the McNemar test. Statistical significance was considered $p < 0.05$.

**Results**

*Colonoscopic findings*
A total of 317 polyps were detected, of which 31 were large ($\geq 10$ mm), 29 medium (6–9 mm), and 257 small (< 6 mm). These polyps were found in 86 (59%) of 145 patients. In 18 (12%) of the patients, the largest polyp was $\geq 10$ mm; in 26 (18%) of the patients, a polyp measuring at least 6 mm was found. No histologic findings were retrieved on 87 polyps. Eighty eight (28%) of the 317 polyps were adenomas. Two colorectal carcinomas were found and were categorized among lesions $\geq 10$ mm. Among the 317 polyps, 232 had a sessile morphology, 25 pedunculated, and 60
flat. Colonoscopy initially revealed that 16 (89%) of 18 patients had large polyps. Two second-look endoscopic examinations were performed because two lesions ≥ 10 mm detected with CTC but not with colonoscopy could not be explained on the colonoscopic videotape. These lesions proved to be polyps initially missed at conventional colonoscopy.

**CTC**

The median review time for a complete supine and prone CTC examination was 16 minutes (range, 7–37 minutes) for reviewer 1, 13 minutes (range, 7–48 minutes) for reviewer 2, 16 minutes (range, 8–80 minutes) for reviewer 3, and 20 minutes (range, 8–74 minutes) for reviewer 4.

<table>
<thead>
<tr>
<th>Table 2. Performance characteristics of CT colonography (sensitivity and specificity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per patient</strong></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>All sizes</td>
</tr>
<tr>
<td>Radiologist (R1)</td>
</tr>
<tr>
<td>n=86</td>
</tr>
<tr>
<td>Radiologist in training (R2)</td>
</tr>
<tr>
<td>n=26</td>
</tr>
<tr>
<td>Radiographer (R3)</td>
</tr>
<tr>
<td>n=24</td>
</tr>
<tr>
<td>Radiographer (R4)</td>
</tr>
<tr>
<td>n=22</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
</tr>
<tr>
<td>All sizes</td>
</tr>
<tr>
<td>Radiologist (R1)</td>
</tr>
<tr>
<td>n=59</td>
</tr>
<tr>
<td>Radiologist in training (R2)</td>
</tr>
<tr>
<td>n=119</td>
</tr>
<tr>
<td>Radiographer (R3)</td>
</tr>
<tr>
<td>n=121</td>
</tr>
<tr>
<td>Radiographer (R4)</td>
</tr>
<tr>
<td>n=123</td>
</tr>
<tr>
<td><strong>Per polyp</strong></td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
</tr>
<tr>
<td>All sizes</td>
</tr>
<tr>
<td>Radiologist (R1)</td>
</tr>
<tr>
<td>n=317</td>
</tr>
<tr>
<td>Radiologist in training (R2)</td>
</tr>
<tr>
<td>n=60</td>
</tr>
<tr>
<td>Radiographer (R3)</td>
</tr>
<tr>
<td>n=49</td>
</tr>
<tr>
<td>Radiographer (R4)</td>
</tr>
<tr>
<td>n=42</td>
</tr>
</tbody>
</table>

(R1; reviewer 1, R2; reviewer 2, etc).
1: reviewer 2 and 4 observed significantly more false positive patients (all p-values <0.05).
2: a significant lower sensitivity was observed for reviewer 4.
3: significant difference in sensitivity between radiologists and radiographers.
Per Patient

Sensitivity and specificity — Table 2 shows the performance characteristics of all observers for CTC according to polyp size per patient and per polyp. All reviewers correctly identified 14 (78%) of the 18 patients with at least one large polyp (≥ 10 mm).

The same four patients with large polyps were missed by all observers. Three of four missed cases were flat adenoma. One patient had a pedunculated adenoma. After unblinding of the colonoscopic results, we could only positively identify one patient in retrospect on the CTC examination (Fig. 1).

Per patient, no significant differences in sensitivity stratified for polyp size were observed between reviewers or between groups (radiologists vs radiographers). Specificity among patients without large polyps ranged between 91% and 94% for the observers. Specificity values were comparable except for lesions ≥ 6 mm; reviewers 2 and 4 had significantly more false-positive findings (p < 0.05). For all other thresholds, no statistically significant differences were found between observers or between groups.
Predictive values — Table 3 shows the predictive values for the reviewers. Because the number of false-positive findings among patients with large lesions was relatively small, mean negative predictive values for patients without polyps $\geq 10$ mm were high (97%). The positive predictive values for identification of patients with large polyps were 64% for reviewer 1, 56% for reviewer 2, 61% for reviewer 3, and 58% for reviewer 4.

Per Polyp

Sensitivity — In Table 2 the performance characteristics are displayed on a per-polyp basis stratified for size. Reviewers 2 and 3 correctly identified 22 (71%) of 31 large polyps; reviewers 1 and 4 detected 21 (68%) and 19 (61%) large polyps. Reviewer 4 had higher false-negative rates for all categories; however, only the false-negative rate for polyps of all sizes was significantly higher than that of the other reviewers ($p < 0.05$). Consequently, a significant difference in sensitivity between radiologists and radiographers as groups was also found for polyps of all sizes but not in the other categories.

<table>
<thead>
<tr>
<th>Table 3. Negative and positive predictive values of CT colonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient NPV</td>
</tr>
<tr>
<td>Radiologist (R1)</td>
</tr>
<tr>
<td>Radiologist in training (R2)</td>
</tr>
<tr>
<td>Radiographer (R3)</td>
</tr>
<tr>
<td>Radiographer (R4)</td>
</tr>
<tr>
<td>Per patient PPV</td>
</tr>
<tr>
<td>Radiologist (R1)</td>
</tr>
<tr>
<td>Radiologist in training (R2)</td>
</tr>
<tr>
<td>Radiographer (R3)</td>
</tr>
<tr>
<td>Radiographer (R4)</td>
</tr>
</tbody>
</table>

R1; reviewer 1, R2; reviewer 2, etc.

False-positive findings — Table 4 shows the false-positive findings stratified according to lesion size. For every size category, the radiographers as a group had more false-positive findings than did the radiologists. This difference was not statistically
significant. False-positive lesions ≥ 10 mm found by the radiographers were checked by the research fellow. Follow-up colonoscopic examinations performed as part of the patient surveillance program also were evaluated for new lesions. None of the large false-positive lesions had to be reassigned true-positive status. The false-positive lesions ≥ 10 mm found by the radiologists are described earlier (Determination of Lesion Status).

Interobserver Analysis
Most reviewers detected and missed the same lesions. This phenomenon was most apparent for reviewers 1 and 2, with interobserver agreement ranging from good to excellent (81% for all lesions, 88% for lesions ≥ 6 mm, and 97% for lesions ≥ 10 mm). The other reviewers had good interobserver agreement, which ranged from 71% to 91% (Table 5).

| Table 4. False positive findings of CT colonography |
|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| FP findings |
| All sizes | ≥ 6 mm | ≥ 7 mm | ≥ 8 mm | ≥ 9 mm | ≥10 mm |
| Radiologist (R1) | 350 | 84 | 62 | 37 | 20 | 16 |
| Radiologist in training (R2) | 318 | 68 | 37 | 19 | 13 | 9 |
| Radiographer (R3) | 411 | 73 | 43 | 26 | 18 | 11 |
| Radiographer (R4) | 396 | 126 | 93 | 52 | 35 | 23 |

(R1; reviewer 1, R2; reviewer 2, etc).

Combined Sensitivity per Patient
Because every observer detected and missed the presence of lesions ≥ 9 mm and ≥ 10 mm in the same patients, no increase in sensitivity (79% and 78%, respectively) was found when results were combined. The combined sensitivity for lesions ≥ 8 mm for any set of two observers was 82% (18/22); the sensitivity increased 5% (one patient), from 77% to 82%, when the results for reviewers 1 and 3 were combined. For all other combinations, no increase was observed. For lesions ≥ 7 mm, the combined sensitivity was 83% (20/24), an increase of 5% (one patient) if reviewer 1 was combined with reviewer 3. For all other combinations, no increase was observed. For lesions ≥ 6 mm, no increase in sensitivity was found when the results of any of the observers were combined.
We investigated the performance characteristics of CTC by radiographers in 145 consecutive patients at increased risk of colorectal carcinoma. We found detection rates for colorectal polyps similar to those of radiologists. The sensitivity for large polyps was 78% for all reviewers at a specificity of 91–94%. All observers detected and missed the presence of large polyps in the same patients.

In the literature, similar rates of polyp detection on CTC have been reported for radiologists and radiographers. Bodily et al. [12] found that in a selected data set of 50 cases, non-radiologists correctly identified polyps in 78% of patients with large lesions; the rate was 81% for radiologists. In 2006, in a European multicenter study [17] in which the performance of CTC experienced radiologists was compared with that of recently trained radiologists and radiographers, the results were similar for the two groups. Although experienced reviewers found more lesions, detection rates were comparable among the newly trained radiologists and radiographers. Newly trained radiologists detected 71% of all cancers and 46% of large polyps versus 73% and 39% for the radiographers.

### Table 5. Agreement between reviewers for colonoscopic proved lesions

<table>
<thead>
<tr>
<th>Polyp Size</th>
<th>Radiologist (R1) vs Radiologist in training (R2)</th>
<th>Radiologist (R1) vs Radiographer (R3)</th>
<th>Radiologist (R1) vs Radiographer (R4)</th>
<th>Radiologist in training (R2) vs Radiographer (R3)</th>
<th>Radiologist in training (R2) vs Radiographer (R4)</th>
<th>Radiographer (R3) vs Radiographer (R4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 mm</td>
<td>y:39, n:14 (88%)</td>
<td>y:37, n:14 (85%)</td>
<td>y:40, n:12 (87%)</td>
<td>y:32, n:12 (73%)</td>
<td>y:32, n:12 (77%)</td>
<td>y:32, n:14 (77%)</td>
</tr>
<tr>
<td>(n=60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 7 mm</td>
<td>y:32, n:13 (92%)</td>
<td>y:29, n:12 (84%)</td>
<td>y:32, n:11 (88%)</td>
<td>y:26, n:10 (73%)</td>
<td>y:26, n:10 (78%)</td>
<td>y:26, n:12 (78%)</td>
</tr>
<tr>
<td>(n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 8 mm</td>
<td>y:29, n:12 (98%)</td>
<td>y:26, n:11 (88%)</td>
<td>y:26, n:10 (86%)</td>
<td>y:22, n:9 (76%)</td>
<td>y:22, n:9 (74%)</td>
<td>y:22, n:9 (74%)</td>
</tr>
<tr>
<td>(n=42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 9 mm</td>
<td>y:22, n:9 (97%)</td>
<td>y:21, n:8 (91%)</td>
<td>y:21, n:7 (88%)</td>
<td>y:17, n:7 (75%)</td>
<td>y:17, n:6 (72%)</td>
<td>y:17, n:6 (72%)</td>
</tr>
<tr>
<td>(n=32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>y:21, n:9 (97%)</td>
<td>y:20, n:8 (90%)</td>
<td>y:20, n:7 (87%)</td>
<td>y:16, n:7 (75%)</td>
<td>y:16, n:6 (71%)</td>
<td>y:16, n:6 (71%)</td>
</tr>
<tr>
<td>(n=31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Y: number of polyps detected by both reviewers.
N: number of polyps not detected by both reviewers.
(R1; reviewer 1, R2; reviewer 2, etc.)
Our findings differ from those in the earlier studies because a different review method was used to evaluate the CTC examinations. We used a primary 3D evaluation approach [3, 5]. This more intuitive evaluation technique has greater conspicuity and exposure times to polyps than a primary 2D method. A primary 3D method therefore may be preferable for radiographers who have no experience in evaluating abdominal CT scans. Although whether radiographers would perform in a similar manner with a primary 2D approach cannot be distilled from our findings, findings in the earlier studies [12, 17] suggest as much.

Median review times in this study were higher for radiographers than for radiologists as a group (18 vs 14 minutes). This finding is in line with those in a study by Burling et al. [18] in which (experienced) radiologists using 2D technique interpreted images faster than did radiographic technicians, especially in cases in which there were pathologic findings. In that study, radiographers performed significantly better with longer review times, although large variation existed among newly trained reviewers. In our study, more time was needed for radiographers as a group to perform similarly, but individual review times differed considerably between the two radiographers. Reviewer 3 (a radiographer) needed the same median time to review an examination as the experienced abdominal radiologist. The enhanced 3D viewing method used in this study allowed single (one-way) navigation through the colon, considerably reducing viewing time [16]. The review times in this study were therefore comparable with those reported in studies with a primary 2D approach [7, 8, 19]. It is important to understand, however, that all reviewers were scheduled free from clinical work, and no time limit was imposed. These data therefore cannot be extrapolated to a production environment, and we do not know whether radiographers can perform as well in daily routine.

The radiographers who participated in this study were highly motivated and had great interest in CTC. They not only had performed many CTC examinations themselves but also had taken part in postprocessing of CTC images, such as segmentation and creating a centerline. The dedication of the radiographers was probably an essential element in their good performance in this study. We believe that because the radiographers were familiar with the software of the unfolded cube technique, an approach not widely used, it was also easier for them to interpret the images than if they had been unfamiliar with this technique.

Our study has several limitations. A short learning curve of only 20 cases for the radiographers was used to train the observers. Burling et al. (Burling D et al., presented at the 2005 annual meeting of the European Society of Gastrointestinal
Radiographers in CT colonography

and Abdominal Radiology) reported that training of reviewers with 50 cases probably is not enough to achieve competence and that a learning curve was observed even after 350 cases. In addition, the reviewer experience was not the same for every observer because the radiologists had evaluated the patients as part of a larger accuracy study [5]. Review experience was especially distorted at the end of the study, the radiologists having almost twice as much reviewer experience as the radiographers. Although no feedback was provided during the course of the study, this disadvantage might have been present among the radiographers. Detection rates, however, were comparable, and this finding affirms the capabilities of radiographers in the evaluation of CTC images. For calculation of interobserver variability, kappa value is the accepted statistic. Because this measure strongly depends on disease prevalence, we did not calculate kappa values on a per-patient basis but calculated indexes of positive and negative categories for colonoscopically proven lesions. With this method, false-positive findings are ignored in the calculation of agreement measures.

Some of the CT examinations evaluated by the radiographers were also performed by those radiographers. The radiographers, however, had no knowledge of previous findings, and because there was considerable time between the examination and the evaluation, we do not believe this factor influenced their results.

In this study, a balloon-tipped tube was inserted to insufflate the colon. The balloon was inflated with water and obscured the distal rectum. As a consequence, one large polyp in the rectum was missed, and most likely the use of air for balloon insufflation would have prevented this problem. Because adequate distention has been reported with only a thin rectal tube without a balloon [20], we no longer use balloon-tipped catheters. We use only a thin rectal tube with a small balloon that is deflated with the patient in the prone position.

Our patients received full bowel preparation, but such preparation may not be desirable for screening [2, 21–24]. Bowel preparation did not include tagging of the residual fluid with a contrast agent, which is currently considered standard practice. The lack of an oral contrast agent might have influenced our results negatively, because differentiation of polyps from feces is more difficult without contrast material, and polyps can be obscured in residual fluid. The challenge of discriminating tagged feces and polyps in a (reduced) bowel preparation has not been put to the test in this study.

Although this study showed no or only a slight increase in sensitivity for combined interpretation, a double-interpretation strategy, as in mammographic screening, may
be a good review method for optimizing accuracy [7, 12]. In screening, however, the sheer number of patients markedly increases the workload of radiologists, and double interpretation by radiologists is probably not cost-effective in that situation. This problem may hamper implementation of CTC as a screening technique for colorectal adenoma and carcinoma. Computer-aided detection is an instrument under development that has had good initial results [9–11] and has recently gained regulatory approval. This promising tool may have an important role as a second review in CTC. Another good alternative may be to deploy a radiographer instead of a radiologist as a second reviewer. In that way the radiographer would alleviate some of the workload for radiologists, and costs would not be as high as with employment of two radiologists.

In conclusion, the results of this study suggest that dedicated radiographers trained in interpretation of CTC examinations can achieve accuracy comparable with that of radiologists in the evaluation of CTC. The results imply that deployment of a radiographer as a reviewer in CTC is acceptable. This finding is of particular interest in double-interpretation screening.

**Acknowledgment**

We thank Henk W. Venema for critical review of the manuscript.
Reference List

Chapter 5


Does a Computer-Aided Detection Algorithm in a Second Read Paradigm enhance the Performance of Experienced Computed Tomography Colonography Readers in a Population of Increased Risk?

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Jasper Florie
Chung Y. Nio
Roel Truyen
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European Radiology 2009 19:941-950
Abstract

**Purpose:** We prospectively determined whether computer-aided detection (CAD) could improve the performance characteristics of computed tomography colonography (CTC) in a population of increased risk for colorectal cancer. Therefore, we included 170 consecutive patients that underwent both CTC and colonoscopy.

**Methods:** All findings ≥6 mm were evaluated at colonoscopy by segmental unblinding. We determined per patient sensitivity and specificity for polyps ≥6 mm and ≥10 mm without and with computer-aided detection (CAD). The McNemar test was used for comparison the results without and with CAD.

**Results:** Unblinded colonoscopy detected 50 patients with lesions ≥6 mm and 25 patients with lesions ≥10 mm. Sensitivity of CTC without CAD for these size categories was 80% (40/50, 95% CI: 69–81%) and 64% (16/25, 95% CI: 45–83%), respectively. CTC with CAD detected one additional patient with a lesion ≥6 mm and two with a lesion ≥10 mm, resulting in a sensitivity of 82% (41/50, 95% CI: 71–93%) (p=0.50) and 72% (18/25, 95% CI: 54–90%) (p=1.0), respectively. Specificity without CAD for polyps ≥6 mm and ≥10 mm was 84% (101/120, 95% CI: 78–91%) and 94% (136/145, 95% CI: 90–98%), respectively. With CAD, the specificity remained (nearly) unchanged: 83% (99/120, 95% CI: 76–89%) and 94% (136/145, 95% CI: 90–98%), respectively.

**Conclusion:** Thus, although CTC with CAD detected a few more patients than CTC without CAD, it had no statistically significant positive influence on CTC performance.


Introduction

Computed tomography colonography (CTC) has consistently shown to have a high accuracy for colorectal neoplasia, and has recently been included in the official guidelines for colorectal cancer screening [1]. In the past years, efforts have been made to increase its accuracy, e.g., labeling fecal material with a contrast agent (fecal tagging), automatic insufflation and improvement of workstations. Despite these efforts, visible lesions are still missed, even by well-trained radiologists.

Computer-aided detection (CAD) is a promising technique [2–5] that could be helpful in reducing these false negative findings [6,7]. However, even if the CAD performance would be excellent, it does not automatically translate into equivalent reader performance [8, 9], i.e., CAD hits can be disregarded by the observer. This stresses the complex interaction between CAD and the observers.

Recent studies concluded that in a selected population CAD significantly improved per-polyp sensitivity for less experienced observers [10–13]. Though experienced observers benefited proportionally less from CAD [14, 15]. Therefore, the potential increase by CAD in accuracy for experienced observers is still controversial.

The additional value of CAD was tested in a selected and polyp-enriched population only. This may have a positive effect on the observer performance since observers may be more easily triggered to detect polyps. Secondly, the a priori chance that a finding is indeed a polyp has increased. Therefore, the additional value of CAD (that will have a similar detection pattern irrespective of the population) may be larger.

To our knowledge, the effect of CAD on the performance of observers has not been prospectively evaluated in an unselected patient population of increased risk for colorectal cancer. Therefore, the purpose of this study was to determine whether CAD in a second read paradigm could improve the performance characteristics in a practical setting. Based on indirect comparison of two experienced observers and CAD [16], we hypothesized that CAD could still improve experienced observer performance.

Materials and methods

The institutional review board of both hospitals approved the study. All patients gave written informed consent.
Table 1. The table displays the baseline patient characteristics and procedural details of CT-colonography (n=170)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>98 / 72</td>
</tr>
<tr>
<td>Age in years: mean ± SD</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>Symptomatic (according to referring physician)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>45</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
</tr>
<tr>
<td>Changed bowel habits</td>
<td>25</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>16</td>
</tr>
<tr>
<td>Hospital:</td>
<td></td>
</tr>
<tr>
<td>Academic Medical Center</td>
<td>137</td>
</tr>
<tr>
<td>Onze Lieve Vrouwe Gasthuis</td>
<td>33</td>
</tr>
<tr>
<td>History of colonoscopy or sigmoidoscopy</td>
<td></td>
</tr>
<tr>
<td>10 years prior to CTC</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107</td>
</tr>
<tr>
<td>No</td>
<td>53</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
</tr>
<tr>
<td>Patients:</td>
<td></td>
</tr>
<tr>
<td>Without polyps ≥6mm</td>
<td>120</td>
</tr>
<tr>
<td>With polyps ≥6mm</td>
<td>50</td>
</tr>
<tr>
<td>With a polyp ≥10mm</td>
<td>25</td>
</tr>
<tr>
<td>Bowel preparation</td>
<td></td>
</tr>
<tr>
<td>PEG</td>
<td>167</td>
</tr>
<tr>
<td>Sodium phosphate</td>
<td>1</td>
</tr>
<tr>
<td>CT-system used</td>
<td></td>
</tr>
<tr>
<td>4-slice(^1)</td>
<td>7</td>
</tr>
<tr>
<td>64-slice(^2)</td>
<td>163</td>
</tr>
<tr>
<td>Spasmolytics</td>
<td></td>
</tr>
<tr>
<td>20 mg Butyl scopolamine bromide(^3)</td>
<td>136</td>
</tr>
<tr>
<td>1 mg Glucagon(^4)</td>
<td>28</td>
</tr>
<tr>
<td>No spasmolytics</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td></td>
</tr>
<tr>
<td>&lt;103cm</td>
<td>82</td>
</tr>
<tr>
<td>≥103cm</td>
<td>88</td>
</tr>
<tr>
<td>Mean volume of insufflated CO(_2)(^5)</td>
<td>4.5 l (2.2-7.6)</td>
</tr>
<tr>
<td>Mean scanner room examination time</td>
<td>21 minute (12-35)</td>
</tr>
<tr>
<td>Number of complications</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\) Mx 8000, Philips Medical Systems, Best, the Netherlands.
\(^2\) Brilliance 64, Philips Medical Systems, Best, the Netherlands.
\(^3\) Boehringer Ingelheim, Ingelheim, Germany.
\(^4\) Glucagon; Novo Nordisk A/S, Bagsvaerd, Denmark.
\(^5\) ProtoCO2I, E-Z-EM, Lake Success, NY, USA.
Study population
Consecutive patients with a personal or family history of colorectal polyps or cancer were invited to participate from February 2006 until July 2007. All patients were scheduled to undergo a routine colonoscopy at one or other of the two participating hospitals. Exclusion criteria were: age under 18 years, pregnancy, personal history of inflammatory bowel disease, familial adenomatous polyposis, Peutz-Jeghers syndrome, hereditary non-polyposis colorectal cancer, prior allergic reaction to iodine contrast, untreated hyperthyroidism, known colorectal polyps that were not removed at an earlier endoscopy.

Patients ingested 4 l polyethylene glycol electrolyte solution (KleanPrep; Helsinn Birex Pharmaceuticals, Dublin, Ireland) on the day before and the day of the examinations. If contraindicated, other regimes were used. Patients ingested 50 ml oral iodine contrast (ioxithalamate, 300 mg ml⁻¹) (Telebrix, Guerbet, Roissy, France) with each liter of polyethylene glycol electrolyte solution.

All CT-examinations were performed on two different CT systems. The CT parameters for the four-slice CT were 120 kV, 50 mAs (abdominal circumference ≤ 103 cm) or 70 mAs (>103 cm), effective slice thickness 3.2 mm, pitch 1.25 and reconstruction interval 1.6 mm. The CT parameters for the 64-slice CT were 120 kV, 58 mAs (abdominal circumference ≤ 103 cm) or 82 mAs (>103 cm), effective slice thickness 0.9 mm, pitch 0.984 and reconstruction interval 0.7 mm. Procedural details and baseline characteristics are listed in Table 1.

Observers
The CTC examinations were evaluated by one observer of a group of five observers; one board certified abdominal radiologist, two radiology residents (2nd and 4th year) and two radiology research fellows. The observers read the CTC examinations in a quiet environment not pressured to provide rapid reports, although they knew that the colonoscopy would be performed within 3 h. They were blinded to clinical data. Although their experience varied, all had seen at least 100 CTC examinations verified by colonoscopy, often combined with additional examinations without direct feedback (Table 2).

Just prior to the study, all had passed a test of 25 selected CTC examinations [17] by scoring above a predefined per polyp sensitivity threshold of 90%. In 12 of these 25 patients, 19 polyps ≥6 mm (one flat lesion) and 10 polyps larger than 10 mm could be detected.
The observers were blinded to the CAD results during the initial reading. All patients were evaluated with a primary three-dimensional (3D) method (Endo 3D Unfolded, ViewForum, Philips Medical Systems, Best, The Netherlands). This validated method [18] was used to increase surface visibility and reduce reading time. Additional two-dimensional (2D) displays with instant on-screen correlation were used for problem solving. Stool subtraction software was not used. The observers digitally recorded size (mm), morphology (pedunculated, sessile, flat) and colon segment (cecum, ascending colon, transverse colon, descending colon, sigmoid colon or rectum).

After their unassisted reading they were able to access the CAD results. Readers were permitted to discard unassisted findings after CAD application. The incorporated commercially available CAD algorithm (ColonCAD, Philips Medical Systems, Best, The Netherlands) had a fixed sensitivity threshold that was not changed during the study. The CAD algorithm was trained on annotated polyp data from 13 patients from a comparative study of 249 patients [19]. These datasets had been verified by colonoscopy and contained a total of 80 polyps ≥5 mm. In this study, by mouse-clicking a listed candidate, corresponding 3D, 2D axial and 2D MPR views were shown with a mark on the polyp candidate (Fig. 1).

If the observers identified CAD lesions that were not detected in the unassisted evaluation, these could be added to the initial list of findings.

### Table 2

Table lists the number of read CTC cases per observer and observer experience with and without colonoscopic verification

<table>
<thead>
<tr>
<th>Observer</th>
<th>Number of read cases</th>
<th>Number of endoscopic examinations with colonoscopic verification</th>
<th>Number of endoscopic examinations without colonoscopic verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 2</td>
<td>36/170</td>
<td>300 CTC and 300 MRC</td>
<td>225 CTC</td>
</tr>
<tr>
<td>Observer 3</td>
<td>29/170</td>
<td>300 CTC</td>
<td>75 CTC</td>
</tr>
<tr>
<td>Observer 4</td>
<td>36/170</td>
<td>230 CTC and 30 MRC</td>
<td>100 CTC &amp; 240 MRC</td>
</tr>
<tr>
<td>Observer 5</td>
<td>51/170</td>
<td>100 CTC</td>
<td>25</td>
</tr>
</tbody>
</table>

*a* Including: Matching polyps in 200 CTC studies of patients of increased risk.

*b* Including: 25 test patients.

**CTC image analysis**

The observers were blinded to the CAD results during the initial reading. All patients were evaluated with a primary three-dimensional (3D) method (Endo 3D Unfolded, ViewForum, Philips Medical Systems, Best, The Netherlands). This validated method [18] was used to increase surface visibility and reduce reading time. Additional two-dimensional (2D) displays with instant on-screen correlation were used for problem solving. Stool subtraction software was not used. The observers digitally recorded size (mm), morphology (pedunculated, sessile, flat) and colon segment (cecum, ascending colon, transverse colon, descending colon, sigmoid colon or rectum).

After their unassisted reading they were able to access the CAD results. Readers were permitted to discard unassisted findings after CAD application. The incorporated commercially available CAD algorithm (ColonCAD, Philips Medical Systems, Best, The Netherlands) had a fixed sensitivity threshold that was not changed during the study. The CAD algorithm was trained on annotated polyp data from 13 patients from a comparative study of 249 patients [19]. These datasets had been verified by colonoscopy and contained a total of 80 polyps ≥5 mm. In this study, by mouse-clicking a listed candidate, corresponding 3D, 2D axial and 2D MPR views were shown with a mark on the polyp candidate (Fig. 1).

If the observers identified CAD lesions that were not detected in the unassisted evaluation, these could be added to the initial list of findings.
**Interpretation time and image quality**

Interpretation times for the unassisted read and for the evaluation of CAD candidates were recorded with a stopwatch for both the prone and supine positions.

When the reading was completed, the observer assessed the degree of colonic distension and quality of the fecal tagging on a four-point Likert-scale (good, sufficient, moderate, poor). The overall quality of the examination was assessed as “diagnostic” or “non-diagnostic”. If the quality was assessed as “non-diagnostic” by the examining physician, the patient was excluded.

![Figure 1. Screenshot of both monitors of the workstation displaying the patient in supine (left) and prone position (right). The white arrows mark a 16 mm sessile polyp that was detected by both CAD and the observer](image)

**Colonoscopy**

All patients underwent colonoscopy within 3 h after CTC. A gastroenterologist (>200 colonoscopies), or fellow or nurse under direct supervision of a staff member performed the colonoscopy with a standard colonoscope (CF-140L; Olympus, Tokyo, Japan). Chromo-endoscopy or narrowband imaging to improve flat polyp detection was not performed. Patients received on request midazolam (Dormicum, Roche, Basel, Switzerland) and fentanyl (Hameln Pharmaceuticals, Hameln, Germany) or propofol (Fresenius Kabi, Uppsala, Sweden) and fentanyl. The examination was digitally recorded.

Polyp characteristics (size, morphology and segmental location) were documented on a case record form by an attending research nurse. Polyp size was measured with open biopsy forceps (8 mm). The determination of the morphology of polyps was
done by the gastroenterologist based on the endoscopic classification of superficial neoplastic lesions [20]. In this classification, flat polyps were defined as lesions with a maximum height of 2.5 mm (closed cups of biopsy forceps). Segmental unblinding was performed for CT lesions 6 mm or larger. Histology was obtained at colonoscopy, except in those cases in which polyp removal was technically impossible or when material was lost during the procedure.

**Determination of lesion status**

Observers were instructed that only hyperplastic, adenomatous (advanced and not-advanced) and potentially malignant lesions were considered true-positive lesions. This qualification was based on the histology report or—if histology was not acquired—based on the endoscopic report.

For CTC, a polyp was considered true-positive, if: (1) its appearance resembled the corresponding polyp at colonoscopy, (2) its segment or adjacent segment corresponded with the reference standard segment and (3) the polyp size as estimated by the endoscopist corresponded with size as measured on CTC, considering a margin of error of 50%. Since the colonoscopy measurement is subject to inaccuracy [21, 22] this criterion could be overruled by the first two criteria.

Polyps \( \geq 6 \) mm at colonoscopy that were not identified by the observer without or with CAD, were re-evaluated with knowledge of the colonoscopic findings by a research fellow with experience of more than 300 CTC examinations verified by colonoscopy. In this re-evaluation the nature of all detection errors \( \geq 6 \) mm (false-negative findings) was assessed and differentiated between perception errors (visible in retrospect) and non-perception errors (lesions not visible in retrospect).

Lesions not confirmed by colonoscopy \( \geq 6 \) mm (false positives) were assessed by consensus by two experienced research fellows (300 colonoscopy verified CTC). The consensus panel determined whether the finding was related to bowel preparation.

**Statistical analysis**

**Power calculation**

Based on a prior feasibility study [16], we expected a 15% increase in sensitivity. In order to determine a statistically significant increase of 15% for polyps \( \geq 6 \) mm, at least 39 lesions were required. For this approach, a McNemar test with continuity correction and a p value of 0.05 to indicate statistical significance was used. Based on prior studies in this patient population, we assumed that the prevalence of
patients with polyps $\geq 6 \text{ mm}$ would be 25% [23]. We therefore required a minimal number of $39/0.25 = 156$ patients. The total number of patients determined was 170.

**Outcome parameters per patient**

Sensitivity, specificity, positive- and negative-predictive values of CTC without and with CAD were calculated. Sensitivity and number of false-positive findings were calculated for CAD without interaction of the observers (stand alone). Furthermore, sensitivity was calculated for unblinded colonoscopy. The outcome parameters were determined for polyps $\geq 6 \text{ mm}$ and $\geq 10 \text{ mm}$.

A patient was considered true-positive if CTC detected at least one polyp seen at colonoscopy, based on the matching criteria described previously. A patient was categorized as false negative if CTC detected no polyps (although present at the reference standard) or only those of a lower size category in comparison to the reference standard.

We used the McNemar test to compare per-patient sensitivity and specificity values between CTC without and with CAD.

**Outcome parameters per polyp**

We calculated the per-polyp sensitivity for CTC without and with CAD, CAD (stand alone) and blinded colonoscopy for lesions $6-9 \text{ mm}$ and $\geq 10 \text{ mm}$. In this study, more than one polyp was detected in some patients. Therefore, generalized estimating equations (GEE) (SPSS, 15.0, Statistics, Chicago, USA) was used to revise the data clustering and dependency. In the GEE, the adjusted confidence intervals with regard to per-polyp sensitivity for CTC and blinded colonoscopy (i.e., before unblinding of CTC results) were assessed for CTC without and with CAD. In this same GEE method, regression analyses were done to compare the sensitivity values.

**Outcome time parameters**

The median interpretation time of the CTC reading without CAD and the median time to evaluate all CAD results were calculated.

**Prevalence of flat polyps stratified for endoscopic colon examination**

Because a relatively high number of flat polyps were detected in this population we retrospectively determined whether a colon examination 10 years or less prior to the CTC in the patient’s history could effect the prevalence of these polyps. The rationale for this retrospective study was an article published by MacCarty et al. [24] that
suggested a higher prevalence of polyps in patients who had undergone a previous endoscopic colon examination. We did not specify the type of colon examination in colonoscopy, sigmoidoscopy or proctoscopy because it was not always clear which part of the colon was examined. The arbitrary period of 10 years was chosen since we assumed this would be the period from a polyp to grow into a tumor and a colon examination executed earlier may have effect the prevalence of flat lesions at CTC. The prevalence of polyps in the group that had undergone a colon examination and the group that had not were compared with the McNemar test and stratified for size.

**Figure 2.** The figure shows the flowchart of this study

![Flowchart showing patient enrollment and examination process](image)

**Results**

Of 448 eligible patients that were scheduled to undergo optical colonoscopy during the inclusion period, 170 “diagnostic” examinations were included in this study (Fig. 2). The baseline characteristics and procedural details are listed in Table 1.
The degree of bowel distention was assessed as “good” or “average” in 161 patients (95%), “moderate” in eight patients (5%) and “poor” in one patient (1%). Fecal tagging was assessed as “good” or “average” in 144 patients (85%), “moderate” in 24 (14%) and “poor” in two patients (1%).

Reference standard
Unblinded colonoscopy revealed that 50 out of 170 patients (29%) harbored one or more polyps ≥6 mm and 25 of 170 patients (15%) one or more polyps ≥10 mm. Table 3 displays the histological and morphological characteristics. One colorectal carcinoma (50 mm) was found.

<table>
<thead>
<tr>
<th>Table 3. Table displays the histology and morphology of polyps at seen and removed during colonoscopy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-9 mm (n=58)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Non-adenomatous lesions</td>
</tr>
<tr>
<td>Adenomatous lesions classified as “advanced”</td>
</tr>
<tr>
<td>Adenomatous lesions classified as “not advanced”</td>
</tr>
<tr>
<td>Unknown histology</td>
</tr>
<tr>
<td>CRC</td>
</tr>
<tr>
<td>Sessile</td>
</tr>
<tr>
<td>Pedunculated</td>
</tr>
<tr>
<td>Flat</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
</tbody>
</table>

Per-patient analysis
The per-patient sensitivity and specificity is displayed in Table 4. CAD did not significantly alter per-patient sensitivity and specificity for lesions ≥6 mm and ≥10 mm. Assisted by CAD, the observers detected one additional patient with a lesion ≥6 mm and two additional patients with a lesions ≥10 mm, resulting in a sensitivity of 82% (p=1.0) and 72% (p=0.5), respectively. Two patients were erroneously classified as having a lesion ≥6 mm after accepting a CAD hit and no patients without a lesion ≥10 mm were wrongly added to the list. CAD on a stand-alone basis detected 74% (37/50) and 64% (16/25) of the patients with lesions ≥6 mm and ≥10 mm. There was no statistically significant difference between the observers and CAD in the respective size categories (p=0.375 and
p=1.0). CAD had a median number of nine hits per-patient (25–75% quartiles: 5–15). Blinded colonoscopy detected 96% (48/50) and 100% (25/25) of the patients in the respective size categories. As displayed in Table 4, both the positive- and negative predictive values of the observers with and without CAD were nearly unchanged.

<table>
<thead>
<tr>
<th>Table 4. Table displays results per patient and per polyp</th>
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<tbody>
<tr>
<td>PER PATIENT</td>
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<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>≥6mm</td>
</tr>
<tr>
<td>≥10mm</td>
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<tr>
<td>Specificity</td>
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<td>PER POLYP</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>6-9mm</td>
</tr>
<tr>
<td>≥10mm</td>
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<tr>
<td>Total number of false positive lesions</td>
</tr>
<tr>
<td>6-9mm</td>
</tr>
<tr>
<td>≥10mm</td>
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</tbody>
</table>

**Per-polyp analysis**

Per-polyp sensitivity for polyps of 6–9 mm and ≥10 mm are displayed in Table 4. CAD detected one lesion 6–9 mm and three polyps ≥10 mm initially missed by the observer, but it did not significantly increase sensitivity of the observer for the
respective size categories ($p=0.31$ and $p=0.08$). No true-positive CAD hits were erroneously dismissed by observers. Per-polyp sensitivity was better for polyps $6-9$ mm than for polyps $\geq 10$ mm, without CAD as well as with CAD.

To a large extent this can be explained by the difficulty of the observers and CAD in detecting the relative prevalent number of undetected flat lesions $\geq 10$ mm; 23% ($3/13$) of the flat lesions $\geq 10$ mm were detected without CAD and 31% ($4/13$) with CAD (Fig. 3). Figure 4 shows that the largest part (6/10) of the missed flat large lesions (either without or with CAD) were not visible in retrospect (non-perception errors). Since these polyps cannot be detected, it is difficult to assess exactly why these non-perception errors were missed.

![Figure 3](image)

The three polypoid perception errors $6-9$ mm (Fig. 4) were missed because they were situated on a fold ($n=1$), were clearly smaller than 6 mm when measured on CT ($n=1$) or could be defined as flat on CT ($n=1$). The two polypoid perception errors $\geq 10$ mm were missed because they were situated on a fold ($n=1$) or because of unclear reasons ($n=1$).
Of the 53 false positive lesions detected by the reader without CAD, 23 (43%) findings were according to consensus related to bowel preparation. None of the four false-positive findings suggested by CAD and incorporated in the final list by the observer were related to bowel preparation.

Although CAD did not significantly increase sensitivity, it did not significantly alter specificity either: three extra false-positive lesions 6–9 mm and one extra lesion ≥10 mm in 170 patients were added to the list of the observer (Table 4). CAD on a stand-alone basis detected 72% (42/58) of the polyps 6–9 mm and 60% (18/30) of the polyps ≥10 mm. Blinded colonoscopy detected 95% (55/58) of the polyps 6–9 mm and 100% (30/30) of the polyps ≥10 mm.

**Figure 4.** Figure shows the number of false-negative findings and distribution perceptive and non-perceptive errors among flat and non-flat lesions

![Number of missed CT lesions without CAD](chart1)

![Number of missed CT lesions with CAD](chart2)
**Interpretation time**

The observers had an a median interpretation time of 16 min 00 s (25–75% quartiles: 11 min 35 s-23 min 6 s) to complete the examination and a median time of 1 min 26 s (25–75% quartiles: 28 s-2 min 46 s) to evaluate all CAD results after the initial reading.

**Prevalence of flat polyps stratified for endoscopic colon examination**

Sixty-three percent (107/170) of the patients had undergone an endoscopic colon examination prior to CTC, 31% (53/170) had not. For ten patients, the history could not be retrieved. Of the polyps 6–9 mm, in patients with a history of endoscopy 27% (12/44) were flat, in contrast to 8% (1/12) of the polyps in patients without a history of endoscopy (p=0.259). Of the polyps ≥10 mm, in patients with a history of endoscopy 60% (9/15) were flat, in contrast to 33% (4/12) of polyps in patients without a history of endoscopy (p=0.168). Thus, the prevalence of flat polyps in both size categories was higher in the group that had undergone colon examination, though statistical significance was not reached.

**Discussion**

Although CAD in a second-read paradigm detected one additional patient with a lesion ≥6 mm and two patients with a lesion ≥10 mm, it did not significantly improve per-patient sensitivity in this increased risk patient population. Several CTC studies in which the additional value of CAD was evaluated (after the interaction with the observer) have reported good results in terms of polyp detection [12, 25–27]. All concluded that the observers detected statistically more polyps with CAD.

In contrast to these studies, we did not find a significant additional value for CAD. The study design of these studies differs from our study in a number of aspects: patient selection, inclusion and exclusion criteria and reference standard. However, we think that the most important difference between the aforementioned studies and our study is the fact that the observers in our study were more experienced, i.e., more than 100 CTC cases verified by colonoscopy. Since there is good evidence that experience in CTC results in less false-negative findings [28, 29], it is logical that it is more difficult to substantially increase the sensitivity of the observer with CAD. In studies that report data about the additional value of CAD on experienced observers [30, 31], experienced observers benefited proportionately less from CAD when
compared with the inexperienced readers. This finding is supported by the results of this study.

Although a CAD algorithm has the potential to decrease the number of perceptual errors by exposing the observer to candidate lesions, it cannot account for interpretative errors. In the above-mentioned papers, a significant increase of false positives have been reported. Though the specificity in this study was not significantly increased, there were only two patients erroneously classified as having a lesion. Both false-positive lesions measured 6–9 mm, none was larger than 10 mm. Even though the sensitivity of the observers was low (i.e., 72% for lesions ≥10 mm), CAD was not able to increase their performance. In our opinion, the reported sensitivity requires looking for causes in the population itself. All nine polyps ≥10 mm missed by the observer with CAD had a flat morphology (Fig. 4). These flat polyps are an important cause of false-negative findings [32, 33]. In this population, 13 of the 30 lesions ≥10 mm were flat and therefore an important explanation of the moderate sensitivity, not only for the observer but for CAD as well.

The unexpectedly high number of flat lesions may be related to the history of patients; MacCarty et al. [34] reported in a prospective study of 75 consecutive patients that more than 50% of the false negatives missed by experienced readers were not even visible in retrospect in a population that had been screened by colonoscopy 5 years prior to CTC. Nearly all these polyps were flat. In this study population, the prevalence of flat lesions was higher (although not statistically significant) in the group of patients that had undergone a colonoscopy or sigmoidoscopy prior to CTC as well (Table 1).

We concur with MacCarty and coworkers that previous screening could adversely affect CTC sensitivity in two ways: first, it is likely that many easy-to-see polyps would be detected and removed at the initial screening, and fewer hard-to-see polyps would be detected and removed; second, endoscopic polypectomy may have been incomplete. Remnants of polyps are flatter than the original intact lesions, and would, therefore, be more difficult to detect. So we think that the selection of patients has an important influence on the test characteristics.

The type of bowel preparation, i.e., extensive or reduced, with or without oral contrast (iodine and/or barium) may influence the performance in terms of polyp detection and number of false-positive findings of CAD; polyps can be covered by fecal material or fecal remains may simulate polyps. In this study, we used PEG as an extensive bowel preparation for colonoscopy, combined with Telebrix that has a laxative effect as well. Although we have not evaluated the nature of all CAD
candidates, the additional value of CAD did not seem to be impaired by this type of bowel preparation used in this study, since none of the false-positive lesions incorporated in the final list of the observers were prep-related and only two of 22 false negative findings were covered by fecal material (although we think this is not the reason why they were missed).

This study has limitations; due to the small time-frame between the CTC and colonoscopy, the patients could be read by only one observer out of a group of five different observers. Each observer had a different level of experience. Therefore, although no statistically significant difference in sensitivity was measured between the observers, and none of the observers had a significant improvement in performance after CAD (data not shown), the best performing observers could have leveled out the sensitivity of the least performing observers. Still, the situation as described in this paper is similar to the practical setting of many hospitals; each examination will not be read by five different radiologists but by only one of a pool of experts.

Secondly, the level of experience of the group of five readers was relatively high. It is likely that the additional value of CAD would be larger if the data were read by a relatively inexperienced reader group [35, 36]. Therefore, our conclusion may not apply to relatively untrained readers.

Thirdly, we evaluated CAD using a primary 3D reading paradigm. Although the discussion as to whether to read the data in 2D or 3D is still not settled, a (slight) superiority in terms of polyp detection with 3D is reported by some studies [37, 38]. Since the reported sensitivities of a primary 2D paradigm tend to be lower, CAD may have a larger additional value when used in a 2D reading protocol.

Fourthly, the relatively large number of flat polyps may limit the generalization of the results of this study. However, if we leave out all 26 flat polyps, and we only consider the remaining 62 polypoid lesions, we still cannot demonstrate a significant contribution of CAD to the sensitivity of the observer. This number was still more than the 39 polyps that were needed to demonstrate a 15% sensitivity difference according to our power analysis.

In conclusion, although CTC with CAD in a second read paradigm detected a few more lesions than CTC without CAD, CAD has no statistically significant positive influence on CTC performance in an increased-risk population when used by a relative experienced group of observers.
Chapter 6

Acknowledgements

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References


Chapter 7

Effective Radiation Doses in CT Colonography: Results of an Inventory among Research Institutions

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Chapter 7

Abstract

Purpose: The purpose of this study was to estimate the effective dose that is currently used in CT colonography using scan parameters that were collected for this purpose, and to investigate trends in time.

Methods: PubMed was systematically searched from 1996 until January 2004 for studies investigating CT colonography. Research institutions were contacted and asked for their current scan protocol.

Results: Thirty-six institutions published 74 studies. Twenty-eight of the 36 institutions provided their current protocol. The median effective dose in 2004 was 5.1 mSv (range 1.2–11.7 mSv) per position. Most institutions (93%) scan in both the supine and prone positions. The median mAs value was 67 mAs (range 20–200), median collimation was 2.5 mm (range 0.75–5). From 1996 until 2004 a significant decrease in mAs and collimation (P=0.006, P<0.0001, respectively) was observed, while institutions that used a multislice scanner increased (P<0.0001). The effective dose remained constant (P=0.76).

Conclusion: In 2004 the median effective dose for a complete CT colonography was 10.2 mSv. Despite the increasing use of multislice scanners, which are slightly less dose efficient, the median effective dose remained approximately constant between 1996 and 2004. This is mainly caused by the use of lower mAs settings.
**Introduction**

At present, computed tomography (CT) colonography is undergoing scrutiny for its potential role in colorectal cancer screening [1–7]. An important consideration at this stage is the cancer risk associated with the radiation exposure from large-scale screening with CT. Risks imposed by diagnostic imaging are generally very low, but scanning high numbers of patients, as in a screening setting, will inevitably increase the number of radiation-induced cancer deaths related to medical imaging. Worldwide, about 14% of the total radiation burden is caused by diagnostic procedures with ionizing radiation [8, 9]. The International Commission on Radiological Protection (ICRP) estimated in 1999 that CT examinations in the UK are probably responsible for 40% of the collective dose due to diagnostic radiation [10]. A study, performed in an American hospital in 2000, reported that CT examinations account for almost 70% of the total effective dose, although these examinations make up only about 10% of all diagnostic radiological procedures [11].

The increasing use of multidetector-row scanners speeds up the examination time considerably and produces thinner slices so that eventually images are obtained with nearly isotropic resolution, but these scanners are slightly less efficient with the use of ionizing radiation compared with single-slice scanners. The efficiency is reduced in multislice scanners, in particular in four-slice scanners, due to the penumbra effect. Typical increases of 10–30% in effective dose have been reported for four-slice scanners [12]. For scanners with more detector arrays this effect is of less importance [13]. Another source of dose inefficiency is the fact that in spiral CT an additional layer of tissue is irradiated adjacent to the volume to be depicted, because the reconstruction of the first and last slices requires data beyond the boundaries of this volume [14]. This effect of z overscanning is most pronounced for CT scanners with a large beam collimation, as is the case for instance in 64-slice CT scanners. Additionally, for thinner slices sometimes higher tube currents are used to keep the noise in the image low.

Because no recent data on the effective doses associated with CT colonography are available, the potential risks of its large-scale application in colorectal cancer screening cannot be estimated. In order to assess the risks associated with CT colonography, we determined the effective dose of current scan protocols at institutions that published studies on the accuracy of this examination. In addition, we examined trends over time for the effective dose and various scan parameters.
Materials and Methods

Literature
We used the internet database PubMed to systematically search the medical literature in all languages from 1 January 1996 until 1 January 2004. Eligible were papers designed to investigate the accuracy of CT colonography in humans. The following search terms were used: ‘virtual colonoscopy’, ‘colonography’, ‘colography’ and ‘pneumocolon’. One report for each research institution was included. If an institution had published more than one study, the study with the highest number of patients was included. The main reason to use one paper per institution was that the scan protocol and ensuing effective dose of every institution would have the same weight in this analysis.

Some studies reported different scanners or scan protocols. In such cases we included the scanner or protocol with which most patients were scanned, as most likely this represented the preferred scanner or protocol at that institution. If this was unclear, the one with the lowest estimated effective dose was included. When a different scan protocol was used in the supine and prone positions, we calculated the mean effective dose of both protocols to estimate the effective dose for a single position. In case of uncertainties in the reported scan protocols the corresponding authors were contacted.

Survey
Research institutions, identified through the literature search, were contacted and asked for their current research and daily practice protocol. Daily practice protocols were used in this analysis to represent the current standard; the current research protocols are not discussed in this communication. A questionnaire was sent by e-mail or fax with a request to fill out the relevant scan parameters of their current scan protocol to enable us to estimate the current effective dose. Institutions were reminded once in case of non-response. Some centres indicated that they use higher milliampere values for obese patients or lower for thin patients. In case more scan protocols were reported, we used the protocols for average-sized patients to determine the effective dose. If different scanners were reported, the most modern scanner was included because in our opinion this corresponds best with the current scan protocol. Uncertainties in the current daily practice protocols were solved by contacting the institutions.
Effective dose in CT colonography

Estimation of effective doses

The effective dose of a CT examination is a measure of the radiation risk associated with the examination. It depends in the first place on the amount of radiation used in the examination, which is directly related to the effective mAs level \( \frac{\text{[tube current (mA) \times rotation time (s)]/pitch}}{\text{tube voltage (kV)}} \) and the tube voltage (kV) chosen by the user. The slice collimation, number of slices and scanner type are also of influence. Estimates of effective dose were performed with the ImPACT Patient Dosimetry Calculator (version 0.99u) [15]. The effective doses from the scan protocols reported in the literature and from the obtained current scan protocols were estimated with this calculator. Other dose calculators are available as well; the advantage of the program, used in this study, is that it was applicable for all scanner types of our survey. The authors of the reports and questionnaires included in this study were informed on the effective dose that we estimated.

Statistical Analysis

Both for the effective dose and the various scan parameters, medians, minimum, and maximum values were determined. A subgroup analysis according to the number of simultaneously acquired slices was performed. Trends over time were analysed for scan parameters (effective mAs, collimation) and effective dose by linear regression analysis using calendar year (publication year) as the explanatory variable. Another factor that influences the amount of radiation is tube voltage, which was nearly always 120 kV in the present study, and was not taken into account in this study any further. The trend in the use of multislice scanners was analysed with the chi-squared test statistic for trend.

The estimated effective doses were reported to the originating institutions. The corresponding authors were asked to check the scan parameters that were used for estimation of the effective dose in February 2004. In the trend analysis, therefore, 2004 represents the current scan protocols. Additionally, we performed a similar trend analysis based on paired data from the subset of institutions for which we had both historical and current data.

Results

Literature

We identified 36 institutions that published a total of 74 studies between 01-01-1996 and 01-01-2004 on the diagnostic value of CT colonography. Because only one study
per institution was used in this survey, 36 papers were included. Thirty-three of these 36 (92%) papers provided sufficient data to estimate the effective dose and were therefore used in this analysis.

Questionnaires
A total of 28 out of 36 (78%) institutions responded to our questionnaire and provided us with their current daily practice protocol for CT colonography. After we calculated the effective dose and final verification of the scan parameters by the participating institutions had taken place, the data of these institutions were included in this study.

<table>
<thead>
<tr>
<th>Table 1. Effective doses for CT colonography and scan parameters in present daily practice protocols (2004)</th>
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<tbody>
<tr>
<td>Number of simultaneously acquired slices</td>
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<tr>
<td>Number of institutions</td>
</tr>
<tr>
<td>Effective dose (mSv)</td>
</tr>
<tr>
<td>Effective tube charge (mAs)</td>
</tr>
<tr>
<td>Collimation per slice (mm)</td>
</tr>
</tbody>
</table>

Data are expressed as medians with the range in brackets.

Current scan protocols and effective doses
Table 1 lists the median effective dose, collimation per slice and effective mAs values according to scanner technique as used in the current daily practice protocols. In 2004 the median dose that was used to scan patients in one position for CT colonography was 5.1 mSv (range 1.2 – 11.7 mSv). Most institutions (26; 93%) scan patients in the supine and prone positions. The median mAs value was 66.8 mAs (range 20–200). The median collimation per slice was 2.5 mm (range 0.75–5). Six institutions (11%) used routinely intravenous contrast. In these six institutions the median tube current was 72.5 mAs (range 20–100), collimation 1.87 mm (range 1.25–2.5) and median dose 5.5 mSv (range 1.2–8.0). Table 2 displays the various daily practice protocols per research institution.
### Table 2. Daily practice scan protocols for CT colonography for the different institutions that participated in this survey. Dated February 2004

<table>
<thead>
<tr>
<th>Institution</th>
<th>Scanner Manufacturer</th>
<th>Beam collimat.</th>
<th>Eff As</th>
<th>kV</th>
<th>Pitch</th>
<th>Rot. time (s)</th>
<th>Eff. dose (mSv)</th>
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<td>8.5</td>
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<tr>
<td>Wisconsin</td>
<td>GE LightSpeed</td>
<td>16 x 1.25</td>
<td>74</td>
<td>120</td>
<td>0.68</td>
<td>0.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Yale</td>
<td>GE LightSpeed</td>
<td>4 x 1.25</td>
<td>53</td>
<td>120</td>
<td>1.5</td>
<td>0.8</td>
<td>5.1</td>
</tr>
</tbody>
</table>

(*) Institutions use a different scan protocol per position (supine (s) and prone (p)).
(**) Institutions scan patients in only supine position.

Note: At some institutions different doses are used dependent on patient size. This table displays the scan protocols for average patient size.

Effective doses were estimated by using the ImPACT Patient Dosimetry Calculator (version 0.99u) and displayed per position.
Chapter 7

Trends over time

Table 3 shows the effective dose, tube current, slice collimation and percentage of multislice scanners per year, based on reports in the literature and the questionnaire information.

The effective dose remained approximately constant (P= 0.76) between 1998 and 2004, while both tube current and slice collimation decreased (P=0.006, P<0.0001, respectively). The use of multislice scanners increased (P<0.0001) (Fig. 1). From 1998 until 2004 there was a decline on the average of 9.3 mAs per year (P=0.006). The use of multislice scanners sharply rose over the years. In 1998 no multislice scanners were used, while 27 (96%) institutions used a multislice scanner (4-, 8- or 16-slice scanner) in 2004. Consequently, the median slice collimation was reduced from 5 mm in 1998 to 2.5 mm in the daily practice protocols of 2004.

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Effective Dose (mSv)</th>
<th>% Multislice Scanners</th>
<th>Effective Tube Current (mAs)</th>
<th>Collimation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>1</td>
<td>3.6 mSv</td>
<td>0 %</td>
<td>77 mAs</td>
<td>5.0 mm</td>
</tr>
<tr>
<td>1999</td>
<td>4</td>
<td>6.7 mSv (2.2-10.6)</td>
<td>17 %</td>
<td>144 mAs (60-200)</td>
<td>5.0 mm (3.0-5.0)</td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
<td>3.6 mSv (1.7-7.8)</td>
<td>20 %</td>
<td>95 mAs (47-160)</td>
<td>4.5 mm (2.5-5.0)</td>
</tr>
<tr>
<td>2001</td>
<td>5</td>
<td>5.1 mSv (1.8-9.6)</td>
<td>40 %</td>
<td>115 mAs (47-179)</td>
<td>5.0 mm (2.5-5.0)</td>
</tr>
<tr>
<td>2002</td>
<td>10</td>
<td>4.5 mSv (0.6-11.0)</td>
<td>75 %</td>
<td>85 mAs (10-200)</td>
<td>3.4 mm (1.0-5.0)</td>
</tr>
<tr>
<td>2003</td>
<td>7</td>
<td>4.1 mSv (2.0-7.3)</td>
<td>86 %</td>
<td>67 mAs (27-107)</td>
<td>2.5 mm (1.0-5.0)</td>
</tr>
<tr>
<td>2004</td>
<td>28</td>
<td>5.1 mSv (1.2-11.7)</td>
<td>96 %</td>
<td>67 mAs (20-200)</td>
<td>2.5 mm (0.8-5.0)</td>
</tr>
</tbody>
</table>

The paired analysis of data from the same institution (n=26) showed the same trend, but did not reach statistical significance. Statistical analysis of the data reported in the literature and the current daily practice protocols obviously demonstrated that the effective dose and tube current are significantly correlated (P<0.0001). No significant correlation between the effective dose and the number of slices (P=0.74) or the slice collimation (P=0.52) was found. Not surprisingly, thinner collimations were associated with the number of simultaneously acquired slices (P<0.0001).
**Discussion**

In 2004 the median effective dose for a CT colonography was 5.1 mSv per position. Despite the increasing use of multislice scanners, the median effective dose remained approximately constant between 1996 and 2004. This was mainly caused by the use of lower mAs settings. As sensitivity and specificity are known to improve significantly when patients are scanned in the supine and prone positions, the...
majority of institutions (93%) scan patients twice, and consequently the dose doubles to 10.2 mSv.

Some institutions will have purchased new scanners or adjusted their scan protocol during the writing of this paper. Therefore, it should be noted that actual scan protocols from institutions may differ from the ones that are listed in this paper at the time of publication. The effective dose in this study was estimated with the ImPACT Patient Dosimetry Calculator [15]. Estimates of the effective dose obtained with dose calculation programs have an accuracy in the order of 20%. Somewhat different values could have been obtained using one of the other programs. Moreover, the dose in individual patients may differ from the dose reported here, which was determined in a mathematical model.

Our data are the first to provide a complete overview of recent scan techniques as employed in institutions that perform CT colonography research. These data are important for several reasons. First, they enable the estimation of the risk associated with CT colonography. Second, they demonstrate a trend in time, which provides insight in developments in the use of modern CT scan technique. Third, they demonstrate a considerable variance in technique and radiation dose in the institutions participating in this questionnaire.

The risks of low-dose scanning are not uncontested [16, 17]. Estimates on radiation risks are mainly based on data from the exposure of the Japanese population to the atomic bombs in 1945 [18]. Strong evidence on the harmful effects of low dose of ionizing radiation is not available and some believe that small amounts of radiation are not harmful but may be even healthy or beneficial for an individual person, the so-called radiation hormesis theory [19–21]. However, there is no evidence suggesting a threshold below which radiation exposure does not cause cancer [22, 23]. Therefore, the International Commission on Radiological Protection (ICRP) states that there is no safe amount of radiation. Estimations of the risks to induce a radiation-related fatal cancer are based on this so-called linear nonthreshold (LNT) model. In concordance with this model, a complete CT colonography examination of 10.2 mSv applied to a population aged 50, may result in a risk in the order of one fatal cancer in 4,000 individuals. However, the development of a radiation-induced cancer may become manifest only after a long latent period, possibly tens of years [24, 25]. When individuals are to be examined more than once the risk will increase proportionally.
Effective dose in CT colonography

Our study demonstrated that the increased use of multislice scanners in this period is not accompanied by a change in median effective dose. This is noteworthy, since the transition from single- to multislice CT has been associated with an increase in effective dose [11]. The present finding can be explained by a concomitant decrease in tube current (of mAs value), which probably reflects the increasing awareness of the feasibility of low-dose scanning for CT colonography. The fact that tube currents are decreased implicates that radiologists are more tolerant to image noise and therefore probably also put less emphasis on extracolonic findings. Even in the six institutions that routinely used intravenous contrast in 2004 daily practice only a slightly higher median tube current of 72.5 mAs was applied compared with the overall 66.8 mAs. Research institutions use a thinner collimation in CT colonography with the increasing use of multislice scanners. From 1998 until 2004 the slice collimation was reduced from 5 mm to 2.5 mm, a decrease of 50%. This is in line with a report by Stuart Taylor and colleagues that detection of polyps (especially smaller polyps) is highly dependent on collimation and pitch, and to a lesser extent on tube current [26].

A striking finding of our study is the vast range of effective doses for CT colonography in daily practice in the different institutions. The lowest dose used at present is 1.2 mSv and the highest 11.7 mSv per position. A surprising lack of consistency in technique and radiation dose seems thus to exist amongst leading research institutions around the world. It is unclear whether institutions that scan with higher doses perform better in polyp detection. Although the reason for this great variability is outside the scope of this paper, it would be interesting to further study this phenomenon.

We want to emphasize that the scan parameters reported in this communication are generally used in clinical practice and most likely not for screening purposes. Therefore it is not justified to extrapolate the risks reported in this paper to the risks of screening programs. Our data demonstrate that in CT colonography rather high radiation doses are being used at present. Medical doctors and patients are generally poorly aware of the cancer risks involved with the use of ionizing radiation in medical imaging [27, 28]. Physicians, and in particular radiologists, should be alert of the potential hazards, especially when applied to large numbers of asymptomatic subjects in a screening setting. At present, scan manufacturers propagate the use of dose reduction and modern CT scanners enable a more efficient use of dose. A fairly new development is automatic tube current modulation; that is the automatic adjustment of tube current to the attenuation in the patient. In our questionnaire we
did not ask for the use of this technique, which has the potential for substantial dose reduction [29]. As none of the responders mentioned the use of tube current modulation, we think that in the present survey this possibility for dose reduction was hardly used, if at all. Finally, we note that there is mounting evidence that CT colonography can be performed with effective doses below 1 mSv for a complete examination [30–32]. A feasibility study by van Gelder et al. [33] demonstrated that the detection rate of polyps for CT colonography performed at very low doses of approximately 2% (0.2 mSv) of the medium dose (12 mSv) was not significantly impaired. In fact, at present low-dose protocols are being investigated in clinical patients by some research institutions. In 2004 Iannaccone et al. [3] reported excellent per polyp detection rates of 95% for polyps greater than 8 mm with an effective dose of approximately 0.9 mSv. Because a reduction of effective dose results in a proportional reduction of risk, the use of such low doses will substantially diminish the drawback of exposure to ionizing radiation in CT colonography.

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References

Chapter 8

Summary and Conclusions
Implications and Future Research
Summary

This thesis addresses different aspects of CT colonography that are important for the potential implementation of this technique for surveillance of patients at increased-risk for colorectal cancer. In the first part of the thesis (chapter 2 through 4) image quality, diagnostic value and patient acceptance of CT colonography with a limited bowel preparation was investigated. In the next chapters, the diagnostic performance of radiographers (chapter 5) and of a computer aided detection algorithm was evaluated (chapter 6). Finally, the last study (chapter 7) presents an overview of the radiation doses used for CT colonography.

In chapter 2 our objective was to determine the optimal dosage of laxatives for CT colonography with limited bowel preparation with regard to both image quality and patient acceptance. Therefore, we compared four regimens with increasing levels of mild catharsis, using bisacodyl and magnesium citrate as laxative agents in forty patients. Our results showed good to excellent image readability of CT colonography examinations (37/40) regardless of the preparation used. Increasing the amount of laxatives did not lead to a higher attenuation of tagging or to more homogeneous tagging, and subjective image quality did not show significant improvement. A higher dosage of laxatives was however associated with a higher burden of diarrhoea and a higher overall burden of the bowel preparation. Our results are important because a mild bowel preparation with low catharsis will probably increase patient willingness to participate in a surveillance or screening program.

Chapter 3 addressed the diagnostic accuracy of CT colonography with limited bowel preparation. For this purpose, sensitivity and specificity for the depiction of colonic polyps was prospectively evaluated in 168 consecutive increased-risk patients, using colonoscopy as the reference standard. Two readers (a radiologist and a research fellow) evaluated all cases. Consensus, e.g. a double-read strategy, was performed if the reviewers were not in agreement on a lesion. Segmental unblinding was applied during colonoscopy. This allowed a second-look when CT colonography and colonoscopy results were discrepant for a given segment. In this way, the reference standard was enhanced. We found a sensitivity for CT colonography with limited bowel preparation of 76% and 82% for the identification of patients with polyps ≥6 mm and those with polyps ≥10 mm, respectively. Specificity was respectively 79% and 97% for these size-thresholds. Double reading improved reader performance
slightly, but not significantly. Detection rates were higher for colonoscopy (91% for $\geq 6\text{mm}$ and 88% for $\geq 10\text{ mm}$), than those at CT colonography, but this difference was not statistically significant. Our results concur with other studies that flat lesions are relatively frequent in a surveillance population, in our study 24%. This explains the somewhat lower sensitivity for CT colonography because the observers missed 50% of the lesions with a flat morphology.

In chapter 4 patient experience and preference was assessed for CT colonography with limited bowel preparation in comparison to full-preparation colonoscopy. A five week follow-up study was conducted as adverse reactions to tests tend to temper in time and the attitude at that point will better reflect the attitude towards future screening. Participants were asked to fill out questionnaires with regard to experience of the preparation and procedure. Furthermore, participants preference for CT colonography or optical colonoscopy as future examination of choice was assessed. Preference was based on the presumption that 20% of CT colonography examinations would result in an optical colonoscopy referral for polyp removal. Possible associations between preference outcome and experience parameters were determined with logistic regression. With regard to the results, 94% of participants experienced diarrhoea during the CT colonography preparation. This side-effect was perceived as severely or extremely burdensome by 29% of participants. To optimize patient acceptance, further efforts should be made to reduce this side-effect. Nonetheless, the overall burden was significantly lower for the CT colonography preparation than for the colonoscopy preparation. Furthermore, participants experienced significantly more pain and discomfort during the colonoscopy procedure. After 5 weeks, the majority (69%) of participants preferred CT colonography as future examination. Determinants of preference were a burdensome preparation and pain during the procedure. The fact that CT colonography with a limited bowel preparation was significantly better tolerated suggests that this technique could be of value to increase participation rates in surveillance or screening programs for colorectal cancer.

A double-read strategy might improve sensitivity of CT colonography. This approach however is time-consuming and expensive, and may therefore not be feasible in every radiology department. The deployment of trained paramedical personnel as second readers might be an attractive alternative. Preliminary reports have showed promising results with regard to polyp detection for non-radiologists. Therefore in
Summary

Chapter 5, the performance characteristics of radiographers were studied in comparison to those of radiologists in 150 cathartic prepared patients. Furthermore, we hypothesized that combining detection rates would lead to a substantial increase in sensitivity. Our data showed that the detection rates for lesions 10 mm and larger were identical for radiographers and radiologists (sensitivity was 78% for both). Specificity was respectively 91% and 94% for this size-threshold. Combining detection rates for this size-threshold did not lead to an increased sensitivity because all observers detected and missed the presence of polyps in the same patients. Therefore, we conclude that radiographers can be considered as adequate reviewers in CT colonography. However, in this thesis no added value with regard to sensitivity for significant lesions could be determined if the detection rates of radiographers were combined with those of radiologists.

Another possible double-reading strategy is the use of a computer aided detection (CAD) algorithm. Promising results in reducing false-negative findings for less experienced observers have been published. However, the potential increase in accuracy for experienced observers is still controversial. Furthermore, to date performance of CAD was investigated in selected and polyp-enriched populations but not in a daily-practice clinical situation. Therefore, in chapter 6 we determined whether CAD in a second read paradigm could improve the performance characteristics of experienced readers. Sensitivity of CT colonography without CAD for patients with lesions ≥6 mm and ≥10 mm was respectively 80% and 64%. With CAD one additional patient with a lesion ≥6 mm and two with a lesion ≥10 mm were detected, resulting in a sensitivity of 82% and 72%, respectively. This small increase was not significant. Specificity with and without CAD remained (nearly) unchanged. Thus, although CT colonography with CAD detected a few more patients than CTC without CAD, it had no statistically significant positive influence on the performance of experienced readers in a population at increased-risk for colorectal cancer.

A drawback of CT colonography is the fact that patients are exposed to ionizing radiation. Because no stringent data on the effective doses associated with CT colonography was available, the potential radiation risks could not be estimated. In chapter 7 an inventory of scan protocols for CT colonography among research institutions (survey) was performed and effective doses were estimated. In addition, we investigated trends over time for the effective dose and various scan parameters. Twenty-eight of 36 contacted institutions provided their scan protocol. We estimated
Chapter 8

A median effective dose for CT colonography of 10.2 mSv in 2004. If this dose is applied to a population aged 50, this may result in one fatal cancer in 4,000 individuals. A considerable variance in technique and radiation dose between institutions was observed. The use of multislice scanners increased between 1996 and 2004 but the median effective dose remained approximately constant in this time-period. This was mainly caused by the use of lower tube current (mAs) settings. Further studies on reducing the effective dose for CT colonography are warranted because a reduction of dose will result in a proportional reduction of risk.

Conclusions

Chapter 2. CT colonography with barium and an iodinated contrast medium as tagging agents, requires minimal amounts of laxatives.

Chapter 3. CT colonography with limited bowel preparation has comparable accuracy to optical colonoscopy but detection of flat lesions remains a concern.

Chapter 4. CT colonography with a limited bowel preparation is significantly better tolerated than optical colonoscopy with regard to preparation and procedure.

Chapter 5. Radiographers perform equally to radiologists in the detection of polyps but combining radiologists with radiographers does not improve CT colonography performance.

Chapter 6. CT colonography with CAD does not significantly increase sensitivity of experienced observers.

Chapter 7. In 2004, the effective dose for a complete (supine and prone) CT colonography was approximately 10.2 mSv.

Implications and future research

This thesis demonstrates that CT colonography with limited bowel preparation has the potential to be implemented in surveillance programs because it is an accurate, non-invasive and patient-friendly technique. This is important because a patient-friendly alternative to colonoscopy might increase compliance with surveillance
guidelines. However, several important limitations regarding accuracy, patient acceptance and radiation should first be resolved.

With regard to accuracy; a relatively high number of CT colonographic occult (not-visible in retrospect) or difficult-to-detect lesions are present in a surveillance population. These concern flat lesions that may be inherently more frequent in increased-risk patients or might have developed from flat polyp remnants after prior (incomplete) polypectomy. Prior colonoscopy might also result in the detection and removal of conspicuous polyps (regardless of morphology) while more difficult-to-detect lesions are not detected and remain in situ. Some investigators have therefore proposed that the use of CT colonography in surveillance populations has to be considered with caution, especially in patients who underwent polypectomy. Further research should concern the nature of these occult and difficult-to-detect lesions and focus on how to improve detection rates. Strategies on how to increase accuracy are twofold; enhance reader performance and improve technical aspects. Individual reader performance can be enhanced by training and experience. It is well known that CT colonography is a difficult exam to master with a relatively long learning curve. Extensive training and feedback should therefore be provided to radiologists that perform CT colonography. As was hypothesized in this thesis, reader performance might be improved if two observers read the examination instead of one. Our data demonstrated a slight increase in the detection of polyps (combining radiologists with radiologists, radiographers or a CAD algorithm), but this was not significant. Further research in a larger cohort is needed to establish the efficacy of a double-reading strategy. Focus should probably be on CAD as a second reader because CAD is in potential the most time-efficient and cost-effective approach. With regard to the technical aspects, newer CT scanners are able to scan with thinner (sub-millimeter) slices. This is expected to result in better conspicuity for difficult-to-detect lesions, in particular flat lesions. The use of intravenous contrast agents might improve detection rates because flat lesions may enhance and become visible. Furthermore, the development of electronic cleansing software (e.g. electronically removing tagged faecal material from the colon lumen) might help improving accuracy. With electronic cleansing, the complete colon surface is visible for evaluation as feces is removed, observers will not be distracted by tagged feces, a 3-dimensional fly-through review method can be applied and a CAD algorithm might be more efficient.
Chapter 8

With regard to patient acceptance; the extent of diarrhea associated with the limited bowel preparation should be further reduced. In our study, almost all participants (95%) experienced diarrhea as a result of the preparation and the occurrence of this side-effect was considered very burdensome by patients. Reducing the extent of diarrhea can be accomplished by decreasing the dose of laxatives or by altering the use of contrast agents. As was demonstrated in this thesis, decreasing the dose of laxatives leads to a significantly better patient tolerance. Another approach that might work is to change the amount or type of contrast agents for fecal tagging. Three types are available: ionic and non-ionic iodinated contrast and barium. Ionic iodinated contrast has a strong laxative side-effect and the need to add laxatives to the bowel preparation is probably not necessary. In fact, we no longer add any form of laxatives to the preparation with ionic contrast, and we believe this has not impaired the image quality of the examination. We have also decreased the dosage of the ionic contrast with promising results. Finally, to reduce diarrhea contrast media can be used that have none or only a small laxative side-effect. In that case, barium or non-ionic contrast agents are available. Barium is traditionally used for solid stool tagging and often administered in combination with iodinated contrast for adequate fluid tagging. When Barium or non-ionic contrast media are used, the need to add some form of laxatives is probably still required for homogeneous tagging. Focus should be on what combination and dosage of laxatives and contrast agents are optimal for a limited bowel preparation.

With regard to radiation; further efforts should be made to lower the dose for CT colonography. In 2004 we reported a median effective dose of 10.2 mSv. As was discussed previously, it is estimated that this amount of radiation will induce 1 fatal cancer in 4000 patients. If patients are scanned more than once (as with surveillance guidelines), the risk will increase proportionally. At present (2009), the use of dose reduction (dose modulation or automated current selection) and multi-detector CT scanners enable a more efficient use of dose. Therefore, updated scan protocols are needed to determine current effective doses for CT colonography. Furthermore in recent years low-dose techniques for CT colonography have been widely investigated. Several studies have reported that scanning with low tube currents (up to 10 mAs) for CT colonography is feasible. This means that effective doses for CT colonography can be in the order of 1 to 2 mSv. Such low amount of dose is widely considered acceptable for surveillance or screening.
We conclude that CT colonography is an accurate, non-invasive and patient friendly technique for patients at increased-risk for colorectal cancer. An important advantage is that patients can be prepared with a mild bowel preparation. However the high prevalence of flat and “difficult-to-detect” pathology in a surveillance population is of much concern and most likely not easily resolved. Therefore, at present we believe it is best to limit the use of CT colonography for surveillance only to patients who can or will not undergo optical colonoscopy.
Chapter 9

Samenvatting en Conclusies
Implicaties en Toekomstig Onderzoek
Samenvatting

Dit proefschrift behandelt verschillende aspecten van CT colonografie die van belang zijn voor de mogelijke toepassing van deze techniek in een populatie met een verhoogd risico op colorectaal kanker. In het eerste deel van het proefschrift (hoofdstuk 2 tot en met 4) werd de beeldkwaliteit, de diagnostische waarde en de patiënt acceptatie van CT colonografie met een beperkte darmvoorbereiding onderzocht. In de daaropvolgende hoofdstukken werd de diagnostische waarde van röntgenlaboranten (hoofdstuk 5) en van een computer aided detection (CAD) algoritme geëvalueerd (hoofdstuk 6). Tot slot, geeft het laatste onderzoek (hoofdstuk 7) een overzicht van de stralingsdoses voor CT colonografie.

In hoofdstuk 2 was onze doelstelling het bepalen van de optimale dosering van laxeremiddelen voor CT colonografie met een beperkte darmvoorbereiding met als uitkomstmaat de beeldkwaliteit en de patiëntacceptatie. Daarom hebben we vier voorbereidingen vergeleken met toenemende mate van milde laxatie in veertig patiënten. Bisacodyl en magnesium citraat werden als laxeremiddelen gebruikt. Onze resultaten toonden goede tot uitstekende beeldkwaliteit van de CT colonografie onderzoeken (37/40), ongeacht welke voorbereiding was gebruikt. Verhoging van de dosering van laxeremiddelen leidde niet tot een betere of homogener aankleuring en er was geen verbetering van de subjectieve beeldkwaliteit. Een hogere dosering van laxeremiddelen was echter wel geassocieerd met meer diarree en een hogere belasting van de voorbereiding. In onze studie resulteerde de laagste dosering van laxeremiddelen voor een goede beeldkwaliteit en minimale patiëntbelasting. Dit is belangrijk omdat de patiëntbereidheid om deel te nemen aan een surveillance programma mogelijk zal toenemen bij een milde darmvoorbereiding.

Hoofdstuk 3 gaat in op de diagnostische waarde van CT colonografie met beperkte darmvoorbereiding. Voor dit doel werden sensitiviteit en specificiteit voor de detectie van dikke darm poliepen prospectief geëvalueerd in 168 opeenvolgende patiënten met een verhoogd risico op colorectaal kanker. De referentiestandaard was colonoscopie. Twee beoordelaars (een radioloog en een fellow in CT colonografie) beoordeelden alle onderzoeken. Consensus, een double-read strategie, werd bepaald in het geval van discrepante laesies ≥ 6 mm. Tijden colonoscopie werden de resultaten van CT colonografie per segment bekend gemaakt (dit heet “segmental unblinding”). Hierdoor kon een tweede evaluatie plaatsvinden in het geval van
discrepante resultaten tussen CT colonografie en colonoscopie. Op deze manier werd de referentiestandaard verbeterd. We vonden een sensitiviteit voor CT colonografie met beperkte darmvoorbereiding van 76% en 82% voor de detectie van patiënten met poliepen ≥ 6 mm en ≥ 10 mm, respectievelijk. Specificiteit was respectievelijk 79% en 97% voor poliepen van deze grootte. Double-reading verbeterde de prestaties enigszins, maar niet significant. Colonoscopie detecteerde meer poliepen (91% van ≥ 6mm poliepen en 88% van ≥ 10 mm), dan CT colonografie, maar dit verschil was niet statistisch significant. Een belangrijke verklaring voor de iets lagere sensitiviteit voor CT colonografie was de relatief hoge prevalentie van laesies met een vlakke morfologie (24%), waarvan slechts 50% werd gevonden door de beoordelaars. Onze resultaten sluiten aan bij andere studies dat vlakke laesies relatief frequent voorkomen in een surveillance populatie. CT colonografie met beperkte darmvoorbereiding kan dus mogelijk beter presteren in een bevolkingsonderzoek (patiënten met een gemiddeld risico die nog niet gescreend zijn met colonoscopie) omdat de prevalentie van vlakke laesies lager is in deze populatie.

In hoofdstuk 4 werd de patiënt acceptatie onderzocht voor CT colonografie met een beperkte darmvoorbereiding in vergelijking tot colonoscopie. De deelnemers werd gevraagd vragenlijsten in te vullen met betrekking tot de belasting van de CT colonografie en coloscopie darmvoorbereiding en procedure. Een follow-up periode van vijf weken werd in acht genomen omdat de nadelige effecten van een test vaak temperen in de tijd en de houding op een later tijdstip beter zal aansluiten bij de voorkeur van patiënten voor toekomstig onderzoek. Patiënten werden meegedeeld dat in 20% van de CT colonografie onderzoeken alsnog een verwijzing voor colonoscopie nodig zou zijn voor poliep verwijdering. De resultaten toonden aan dat 94% van de deelnemers diarree had als bijwerking van de CT colonografie voorbereiding. Deze bijwerking werd als zeer belastend ervaren door 29% van de deelnemers. Om de patiënt acceptatie verder te optimaliseren, moet dit neveneffect worden verbeterd. Toch was de totale belasting significant lager voor de CT colonografie voorbereiding dan voor de colonoscopie voorbereiding. Bovendien hadden de deelnemers significant meer pijn en ongemak tijdens de colonoscopie procedure. Na 5 weken gaf 69% van de deelnemers een voorkeur aan voor CT colonografie. Determinanten van voorkeur waren een belastende voorbereiding en pijn tijdens de procedure. Het feit dat de CT colonografie voorbereiding en procedure significant beter werden verdragen suggereert dat deze techniek van waarde kan zijn om de naleving met surveillance richtlijnen door patiënten te verbeteren.
Een double-read strategie (twee radiologen evalueren het onderzoek in plaats van een radioloog) kan de sensitiviteit van CT colonografie verbeteren. Deze aanpak is echter tijdrovend en duur, en is waarschijnlijk niet haalbaar op een drukke radiologie afdeling. De inzet van paramedisch personeel als tweede beoordelaar is wellicht een aantrekkelijk alternatief. Eerdere haalbaarheidsonderzoeken hebben veelbelovende resultaten gerapporteerd met betrekking tot poliep detectie voor niet-radiologen. Daarom hebben we in hoofdstuk 5 de accuratesse van röntgen laboranten bepaald en vergeleken met die van radiologen in 150 patiënten. Verder hebben we onderzocht of het combineren van resultaten zou leiden tot een verhoging van de sensitiviteit. Onze data toonde aan dat de röntgen laboranten evenveel significante laesies (≥10 mm) vonden als de radiologen (sensitiviteit was 78% voor beide groepen). Specificiteit was respectievelijk 91% en 94%. Samenvoegen van de resultaten leidde niet tot een verbeterde sensitiviteit omdat alle beoordelaars dezelfde poliepen vonden en misten in dezelfde patiënten. Daarom concluderen we dat het inzetten van röntgen laboranten als beoordelaars in CT colonografie haalbaar is maar dat in dit proefschrift geen toegevoegde waarde werd gevonden met betrekking tot de detectie van significante laesies.

Een andere mogelijkheid voor een double-reading strategie is het gebruik van een computer aided detection (CAD) algoritme. Veelbelovende resultaten met betrekking tot het reduceren van fout-negatieve bevindingen (gemiste poliepen) voor minder ervaren radiologen zijn gepubliceerd. Echter de potentiële toegevoegde waarde voor de meer ervaren beoordelaar is omstreden. Bovendien zijn tot op heden de prestaties van CAD alleen onderzocht in geselecteerde onderzoeksgroepen met veel poliepen, maar niet in een klinische praktijk situatie. Daarom is in hoofdstuk 6 onderzocht of CAD in een “second-read” paradigma een verbetering geeft van de prestaties van ervaren beoordelaars. Onze data toonden een sensitiviteit van CT colonografie zonder CAD voor patiënten met laesies ≥ 6 mm en ≥ 10 mm van 80% en 64%, respectievelijk. Met CAD werd één extra patiënt met een laesie ≥ 6 mm en twee patiënten met een laesie ≥ 10 mm ontdekt, wat resulteerde in een sensitiviteit van 82% en 72%, respectievelijk. Deze kleine stijging in sensitiviteit was niet statistisch significant. Specificiteit van CAD met of zonder CAD was niet verschillend. Dus, hoewel CT colonografie met CAD een paar meer patiënten ontdekt dan CT colonografie zonder CAD, kon er geen statistisch significante verbetering van de prestaties van ervaren beoordelaars worden aangetoond in een populatie met een verhoogd risico op colorectaal kanker.
Een nadeel van CT colonografie is dat patiënten worden blootgesteld aan ioniserende straling. Omdat er geen nauwkeurige gegevens over de effectieve doses voor CT colonografie beschikbaar waren, konden de potentiële risico’s van de blootstelling aan straling voor CT colonografie tot op heden niet worden bepaald. In hoofdstuk 7 werd daarom een inventarisatie verricht van de scan parameters en effectieve doses die wereldwijd gebruikt worden voor CT colonografie. Daarnaast zijn trends in de tijd bestudeerd. In 2004 was de mediane effectieve dosis voor een compleet (rug- en buikligging) CT colonografie onderzoek 10,2 mSv. Indien deze dosis wordt toegepast op de leeftijd van 50 jaar, kan dit leiden tot één dodelijke vorm van kanker in 4000 individuen. Er werd een aanzienlijke variatie in techniek en stralingsdosis waargenomen tussen de verschillende instituten. Het gebruik van multislice scanners, die iets minder dosis-efficiënt zijn, steeg tussen 1996 en 2004, maar in deze periode bleef de mediane effectieve dosis ongeveer constant. Dit kan verklaard worden doordat lagere buisstroom (mAs) instellingen werden gebruikt. Nader onderzoek naar verdere reductie van de effectieve dosis zijn gerechtvaardigd omdat een verlaging van de dosis zal resulteren in een evenredige verlaging van het risico.

Conclusies

Hoofdstuk 2. Een beperkte darmvoorbereiding voor CT colonografie met barium en jodiumhoudend contrast vergt slechts minimale laxatie omdat het de beeldkwaliteit niet nadelig beïnvloedt, maar de patiënt acceptatie wel significant verbetert.

Hoofdstuk 3. CT colonografie met beperkte darmvoorbereiding heeft een sensitiviteit voor patiënten met een laesie ≥ 10mm die vergelijkbaar is met colonoscopie in een verhoogd risico populatie. Detectie van vlakke laesies blijft echter een probleem.

Hoofdstuk 4. De CT colonografie voorbereiding en procedure worden beter getolereerd dan colonoscopie. Als zodanig, is er een evidente voorkeur voor CT colonografie aanwezig bij surveillance patiënten.

Hoofdstuk 5. De sensitiviteit van röntgen laboranten is vergelijkbaar aan die van radiologen. Een double-read strategie met een laborant als tweede beoordelaar verbetert echter niet de sensitiviteit van CT colonografie.
Hoofdstuk 6. CT colonografie met CAD detecteerde een paar patiënten meer dan CT colonografie zonder CAD. Voor ervaren beoordelaars kon echter geen statistisch significante verbetering in poliep detectie worden aangetoond.

Hoofdstuk 7. In 2004 was de mediane effectieve dosis voor CT colonografie 10,2 mSv.

**Implicaties en toekomstig onderzoek**

Dit proefschrift toont aan dat CT colonografie met beperkte darmvoorbereiding een nauwkeurige, niet-invasieve en patiëntvriendelijke techniek is voor patiënten met een verhoogd risico op colorectaal kanker. Dit is belangrijk omdat een patiëntvriendelijk alternatief voor colonoscopie de naleving van surveillance richtlijnen door patiënten kan verbeteren. Er zijn echter een paar belangrijke beperkingen met betrekking tot accuratesse, patiëntacceptatie en straling.

Met betrekking tot de accuratesse; er is een relatief hoge prevalentie van occulte (niet zichtbaar in retrospectie) of “moeilijk-te-detecteren” laesies in een surveillance populatie. Dit betreffen vooral vlakke laesies, die enerzijds inherent vaker voorkomen in deze patiëntgroep anderzijds ontwikkeld zijn vanuit poliep restanten na een eerdere onvolledige polypectomie. Tevens kan een eerdere colonoscopie ook hebben geleid tot de opsporing en verwijdering van goed zichtbare poliepen (ongeacht morfologie), terwijl “moeilijk-te-detecteren” laesies gemist zijn en achterblijven in het colon. Sommige onderzoekers hebben daarom aangegeven dat CT colonografie bij surveillance patiënten met de nodige voorzichtigheid moet worden betracht, vooral bij patiënten met status na eerdere polypectomie. Verder onderzoek moet betrekking hebben op de aard van deze occulte en "moeilijk-te-detecteren" laesies en zich richten op het verbeteren van de detectie van deze laesies. Strategieën om de accuratesse te verbeteren zijn tweeledig; enerzijds verbeteren van de prestaties van individuele beoordelaars en anderzijds verbetering van technische prestaties. De prestatie van individuele beoordelaars kan worden verbeterd door training en ervaring. CT colonografie is een lastig onderzoek om goed onder de knie te krijgen met een relatief lange leercurve. Uitgebreide training en feedback moet derhalve gegeven worden aan radiologen. Zoals gehypothetiseerd in dit proefschrift kan de detectie eventueel ook worden verbeterd als twee beoordelaars het onderzoek beoordelen in plaats van één beoordelaar (double-read).
Onze data toonden een lichte verbetering in de detectie van poliepen als we double-read toepasten (combinatie radiologen met radiologen, laboranten of een CAD algoritme) maar dit was niet significant. Nadere studie in wellicht een groter cohort is nodig om de werkzaamheid van een double-read strategie te evalueren. Nadruk moet daarbij liggen op CAD omdat het waarschijnlijk de meest tijdsefficiënte en kosteneffectieve aanpak betreft. Met betrekking tot de technische aspecten, nieuwere CT scanners zijn in staat om te scannen met dunnere (submillimeter) plakjes. Dit zal naar verwachting resulteren in een betere zichtbaarheid van deze moeilijk vindbare laesies. Het gebruik van intraveneus contrast kan detectie verbeteren omdat vlakke laesies kunnen aankleuren. Bovendien is de ontwikkeling van de elektronische cleansing software (het elektronisch verwijderen van aangekleurd fecaal materiaal) veelbelovend. Met elektronische cleansing is de complete mucosa oppervlakte zichtbaar, beoordelaars zullen niet worden afgeleid door aangekleurde ontlasting, een 3-dimensionale “fly-through” evaluatie methode kan worden toegepast en een CAD-algoritme zal mogelijk efficiënter werken.

Met betrekking tot de patiëntacceptatie; de diarree die optreedt als bijwerking van de beperkte darmvoorbereiding voor CT colonografie zal moeten worden verminderd. In onze studie kregen nagenoeg alle deelnemers (95%) diarree als gevolg van de voorbereiding en dit werd als zeer belastend ervaren. Het reduceren van diarree kan gebeuren door verlaging van de hoeveelheid laxeermiddelen (hoofdstuk 2) of door het aanpassen van de concentratie of de keuze van contrastmiddelen. Drie soorten contrastmiddelen zijn er beschikbaar voor het aankleuren van ontlasting: barium, niet-ionische en ionische jodiumhoudend contrast. Barium en niet-ionische contrastmiddelen hebben geen of slechts een minimale laxerende bijwerking en voor deze contrastmiddelen zullen laxeermiddelen waarschijnlijk toegevoegd moeten worden voor een goede beeldkwaliteit. In tegenstelling, ionische contrastmiddelen hebben een sterker laxerend effect en het toevoegen van laxeermiddelen is daarom waarschijnlijk niet nodig. In het AMC zijn onlangs al veelbelovende resultaten behaald voor een voorbereiding zonder enige vorm van laxatie en met een halvering van de dosering contrastmiddelen. Onderzoek moet verder uitwijzen welke combinatie van laxeerk- en contrastmiddelen en in welke dosering, optimaal zijn voor een beperkte darmvoorbereiding voor CT colonografie.

Met betrekking tot straling, verdere inspanningen moeten worden geleverd om de dosis voor CT colonografie te verlagen. Een mediane effectieve dosis van 10,2 mSv,
zoals eerder besproken, zal leiden tot de inductie van 1 dodelijke kanker bij 4000 patiënten. Indien patiënten meer dan één keer worden gescand (richtlijnen surveillance), zal het risico proportioneel toenemen. Op dit moment (2009), kan de toepassing van dosisreductie (dosis modulatie of geautomatiseerde plak selectie) en multidetector CT scanners een efficiënter gebruik van dosis geven. Daarom zijn bijgewerkte scan protocollen nodig om de huidige effectieve doses voor CT colonografie te bepalen. Bovendien zijn de afgelopen jaren lage-dosis technieken voor CT colonografie uitgebreid onderzocht en toegepast. Verscheidene studies hebben gerapporteerd dat het scannen met een lage buisstroom (tot 10 mAs) voor CT colonografie werkzaam is. Dit betekent dat de effectieve dosis voor CT colonografie verlaagd kan worden tot 1 à 2 mSv. In de regel zal zulke lage doses aanvaardbaar zijn voor de surveillance of screening van patiënten.

We concluderen dat CT colonografie een nauwkeurige, niet-invasieve en patiëntvriendelijke techniek is voor patiënten met een verhoogd risico op colorectaal kanker. Een belangrijk voordeel is dat een milde darmvoorbereiding kan worden toegepast. Echter, de hoge prevalentie van vlakke en moeilijk-te-detecteren pathologie in een surveillance populatie is een belangrijk probleem dat waarschijnlijk niet snel kan worden opgelost. Daarom zijn wij van mening dat op dit moment het gebruik van CT colonografie voor surveillance het beste beperkt kan blijven tot patiënten die een colonoscopie niet kunnen of willen ondergaan.
Appendices
Appendix A

Schema darmvoorbereiding CT colonografie AMC

1 dag voor CTC
ontbijt met vezelarm dieet + 50 ml Telebrix
lunch met vezelarm dieet + 50 ml Telebrix
avondeten met vezelarm dieet + 50 ml Telebrix

Ochtend van het onderzoek
vloeibaar ontbijt

1,5 uur voorafgaand aan CTC
50 ml Telebrix

Scan Protocol CT colonografie AMC

Scanner
Philips Brilliance 64
Slice number x collimation (mm)
64 × 0.625
Tube voltage (kV)
120 kV
Tube current
40 mAs
Automatic Dose Modulation
Yes
Rotation time
0.75 sec
Pitch
0.984

Effective mAs
58 mAs
Effective dose (supine and prone)
6.5 mS
Appendix B

Patiënten Informatie AMC

Schema darmvoorbereiding/inname contrastvloeistof (Telebrix)
Voor het onderzoek is het erg belangrijk dat u zich zo goed mogelijk aan het vezelarme dieet houdt en het contrastmiddel (Telebrix) volgens schema inneemt.

Dieet
Het dieet start één dag voor het CT-onderzoek en bestaat uit vezelarme voeding. De vezelarme voeding zorgt ervoor dat het contrastmiddel zich goed verspreidt door de darminhoud.

Na de avondmaaltijd vóór het onderzoek zijn alleen vloeistoffen toegestaan zoals sappen (appelsap, heldere vruchtenmixdranken), limonade van siroop, frisdrank (ook light), water, bouillon, thee en koffie. Dit geldt totdat de CT heeft plaatsgevonden. Als u pas ’s middags een CT-colografie heeft kunt u als ontbijt vloeibare etenswaren gebruiken zoals vla, yoghurt en kwark (zonder stukjes).

Algemeen
• Het uitgangspunt van het dieet is dat vezels en vezelachtige bestanddelen in voeding beperkt worden.
• Veel voedingsmiddelen bevatten noten, zaden of grove vezels, kies niet voor deze producten maar neem een naturel variant.
• Groente en fruit bevatten veel vezels en deze zijn dus maar met mate toegestaan. Fruit in de vorm van vruchtenzappen zonder vruchtvlees en groente beperkt tot de toegestane soorten.
• Zorg ervoor voldoende te drinken (minimaal 10 – 12 glazen per dag).

Vezelrijke voedingsbestanddelen die u niet mag eten:
• Volkoren graanproducten:
  - bruin-, volkoren- en roggebrood
  - tarwe- en maïszemelen
  - muesli
  - volkoren- en meergranenpasta’s
- havermoutpap
- zilvervliesrijst

**Vezelige groenten:**
- asperges, bleekselderij, zuurkool, snijbonen, sperziebonen, prei, doperwten, peulvruchten, taugé, maïs, champignons, tomaten, rauwkost.

**Bepaalde fruit soorten:**
- onrijp fruit
- sinaasappel, grapefruit, mandarijn, ananas, mango, kiwi
- gedroogde (zuid)vruchten zoals dadels, vijgen, pruimen, krenten, rozijnen, kokos

**Noten, pinda’s en zaden:**
- alle pindasoorten
- alle nootsoorten
- sesamzaad, maanzaad, zonnebloempitten

**Overigen:**
- scherpe specerijen
- popcorn

Wat kunt u dan wel eten?

**Graanproducten**
- wit brood, beschuit, toast (naturel)
- witte rijst, pasta (bv spaghetti, macaroni)
- pannenkoeken
- custardpap, lammetjespap (rijstebloempap)

**Groenten en fruit**
- aardappelen
- gaar gekookte groenten, zoals wortelen, bloemkool, lof, andijvie en spinazie
- vers fruit mits goed rijp, geschild en ontpit zoals appel, banaan, peer

- **Alle soorten vlees, vis en kip**

- **Soepen**
  - bouillon
  - soepen met stukjes vlees/kip, soepballen, vermicelli, macaroni en rijst

- **Beleg**
  - kaas
  - vleeswaren
  - alle zoete beleg (*behalve* pindakaas, marmelade en jam met stukjes fruit)
  - eieren
  - suiker
  - vlees/kip/vis

- **Dranken**
  - vruchtensappen zonder vruchtvlees
  - limonades
  - frisdranken
  - thee en koffie
  - mineraal water
  - melk en melkproducten (vla, yoghurt (*geen* vruchtenyoghurt))
  - alcoholische dranken

- **Tussendoortjes**
  - chocolade (zonder nootjes)
  - snoep
  - ijs
  - cake (*geen* koekjes)

- **Specerijen:**
  - zout, peper, paprikapoeder, nootmuskaat, kaneel, peterselie, mosterd, ketchup, groene kruidenmixen.
Het contrastmiddel (Telebrix)

Telebrix is een jodiumhoudend contrastmiddel. Als u allergisch bent voor JODIUM of als u bekend bent met hyperthyreoïdie (een te hardwerkende schildklier), mag u dit middel niet gebruiken. Neemt u in dat geval contact op met de dienstdoende assistent Radiologie op onderstaand telefoonnummer.

U begint 1 dag voorafgaand aan het onderzoek met inname van de Telebrix:

- Gedurende één dag voorafgaand aan het onderzoek neemt u bij het ontbijt 1 flesje Telebrix à 50 ml, bij de lunch 1 flesje en bij het avondeten 1 flesje. U mag de inhoud van het flesje ook in een groot glas limonade schenken en vervolgens opdrinken (U hoeft de Telebrix niet aan te lengen met 950 ml water zoals in de bijsluiter vermeld staat!).
- Op de dag van het onderzoek neemt u 1,5 uur voor de CT-colografie de inhoud van 1 flesje Telebrix in. Omdat Telebrix vaak diarree veroorzaakt, kunt u het middel ook in het AMC innemen, waar uiteraard toiletten aanwezig zijn. U dient dan wel minimaal 1,5 uur voor de afspraak in het AMC te zijn.
- **Telebrix veroorzaakt bij veel patiënten diarree.**
- **Medicijnen** worden tijdens de darmvoorbereiding mogelijk minder goed opgenomen. Het is daarom verstandig rekening te houden met een verminderde werking van het medicijn, bijvoorbeeld in geval van de anticonceptiepil.
**Voorbereidingschema in het kort**

Hieronder staat het voorbereidingsschema nog eens beknopt weergegeven:

1 dag vóór het onderzoek:
- ontbijt met vezelarm dieet + 50 ml Telebrix
- lunch met vezelarm dieet + 50 ml Telebrix
- avondeten met vezelarm dieet + 50 ml Telebrix

ochtend van het onderzoek:
- vloeibaar ontbijt

1,5 uur voorafgaand aan de 3D-CT
- 50 ml Telebrix

Probeert u de dag van het onderzoek enkele malen naar het toilet te gaan voor ontlasting.

Voor een goede beoordeling van de dikke darm, is het belangrijk dat u zich goed aan het voorbereidingschema houdt zoals hierboven is aangegeven.

Indien u vragen heeft over het vezelarme dieet, het contrastmiddel of het effect op eventuele medicatie, kunt u ons te allen tijde telefonisch bereiken via onderstaand telefoonnummer 020-5669111, sein 59389.
Abbreviations
### List of abbreviations

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<th>Abbreviation</th>
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<tr>
<td>AMC</td>
<td>Academisch Medisch Centrum</td>
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<td>CAD</td>
<td>Computer aided detection</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CRC</td>
<td>Colorectal cancer</td>
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<td>Electronic cleansing</td>
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<td>GEE</td>
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<td>HU</td>
<td>Hounsfield units</td>
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<td>$K_p$</td>
<td>Prevalence-adjusted bias-adjusted $\kappa$ values</td>
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<td>Klean Prep</td>
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<td>OLVG</td>
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<td>Optical colonoscopy</td>
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<tr>
<td>PABAK ($K_p$)</td>
<td>Prevalence adjusted bias adjusted kappa-values</td>
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<td>PPV</td>
<td>Positive predictive value</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MPR</td>
<td>Multiplanar reformat</td>
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<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>PEG</td>
<td>Poly-ethylene glycol</td>
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<td>ROI</td>
<td>Region of interest</td>
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<td>SD</td>
<td>Standard deviation</td>
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Publications
Publications

Image quality and patient acceptance of four regimens with different amounts of mild laxatives in CT colonography

Jensch S, de Vries AH, Pot D, Peringa J, Bipat S, Florie J, van Gelder RE, Stoker J

Performance characteristics of CT colonography with a limited bowel preparation in an increased risk population

Jensch S, de Vries AH, Peringa J, Bipat S, Dekker E, Baak LC, Bartelsman JF, Heutinck A, Montauban van Swijndregt AD, Stoker J

CT colonography with a limited bowel preparation: prospective assessment of patient experience and preference in comparison to full-preparation colonoscopy

Jensch S, Bipat S, Peringa J, de Vries AH, Evelien Dekker, Lubbertus C. Baak Montauban van Swijndregt AD, Stoker J
European Radiology 2009 Jul 23 [Epub ahead of print]

Performance of radiographers in the evaluation of CT colonographic images


Effective radiation doses in CT colonography: results of an inventory among research institutions

Jensch S, van Gelder RE, Venema HW, Reitsma JB, Bossuyt PM, Lameris JS, Stoker J

Does CAD in a second read paradigm enhance the performance of experienced CT colonography readers in an population of increased risk?

MR colonography with limited bowel preparation compared with optical colonoscopy in patients at increased risk for colorectal cancer

Diagnostic Performance of Radiographers as compared to Radiologists in Magnetic Resonance Colonography
Zijta FM, Florie F, **Jensch S**, Bipat S, Nievelstein RAJ, Poulus M, Thomassen-de Graaf MA, Montauban van Swijndregt AD, Stoker J
Submitted

Incidental Extracolonic Findings at Bright Lumen MR Colonography in a Population at Increased Risk for Colorectal Carcinoma
Yusuf E, Florie J, Nio CY, **Jensch S**, Nievelstein R, Baak LC, Stoker J
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European Radiology. 2009 Feb 18. [Epub ahead of print]

MR colonography with limited bowel preparation: patient acceptance compared with that of full-preparation colonoscopy

A comparison of primary two- and three-dimensional methods to review CT colonography
Using Mannitol or Carbon Dioxide (CO2) for colonic distension in 3.0 Tesla Magnetic Resonance (MR) Colonography: a Feasibility Study
F.M. Zijta FM, Nederveen AJ, Jensch S, Florie J, Bipat S, Montauban van Swijndregt AD and Stoker J
Submitted

Frequent detection of high viraemia in HBeAg-negative South African carriers
Dankwoord
Dankwoord

Ten eerste wil ik alle patiënten die vrijwillig aan dit onderzoek hebben meegedaan bedanken. Door hen is dit proefschrift bovenal mogelijk gemaakt.

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Dankwoord

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Colonboys and girl,

(Ex-) onderzoekers van de radiologie,
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Curriculum Vitae
Curriculum Vitae

Stellingen behorend bij het proefschrift

CT Colonography as Surveillance Technique for Patients at Increased Risk for Colorectal Cancer

S. Jensch, Universiteit van Amsterdam, 16 oktober 2009

1. Een milde darmvoorbereiding leidt tot een goede beeldkwaliteit en een goede diagnostische waarde van CT colografie beelden (*dit proefschrift*)

2. Een groot voordeel van CT colografie is de mogelijkheid een milde darmvoorbereiding toe te passen omdat deze een beduidend lagere patiëntbelasting heeft dan een laxerende darmvoorbereiding (*dit proefschrift*)

3. De meest belastende bijwerking van de darmvoorbereiding met jodiumhoudend contrast is diarree (*dit proefschrift*)

4. De waarde van CT colografie in een surveillance programma is beperkt vanwege de relatief hoge prevalentie van vlakke laesies in deze patiënten populatie (*dit proefschrift*)

5. Laboranten hebben bij de beoordeling van CT colografie een vergelijkbare accuratesse voor de detectie van darmpoliepen als radiologen (*dit proefschrift*)

6. Double reading zoals gebruikelijk bij borstkanker screening is voor CT colografie waarschijnlijk niet zinvol (*dit proefschrift*)

7. Bij het evalueren van patiëntacceptatie is het van belang dat patiënten goed op de hoogte zijn van de accuraatheid van de te onderzoeken testen

8. Radiologen zijn bewuster geworden van het feit dat CT colografie met lage röntgen dosis kan worden uitgevoerd (*dit proefschrift*)

9. Het feit dat CT colografie als minder belastend wordt ervaren door de patiënt maakt deze techniek wellicht geschikter voor bevolkingsonderzoek naar dikkearmkanker dan coloscopie

10. De Tour de France win je in bed (*Joop Zoetemelk*)